Medicinrådet

Bilag til Medicinrådets anbefaling vedr. voclosporin som tillægsbehandling til lupus nefritis

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. voclosporin som tillægsbehandling til lupus nefritis
2. Forhandlingsnotat fra Amgros vedr. voclosporin som tillægsbehandling til lupus nefritis
3. Ansøgers endelige ansøgning vedr. voclosporin som tillægsbehandling til lupus nefritis

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21st January, 2024

Otsuka response to the Danish Medicine Council (DMC) Draft Assessment Report for voclosporin (Lupkynis®) treatment in combination with MMF for patients with active lupus nephritis.

Otsuka would like to thank DMC for providing the draft assessment report and hereby highlight several statements as factual inaccuracies, not consistent with research or advice from Danish clinical experts.

We acknowledge that it may not be feasible for DMC to recommend first-line use for the full indicated population. However, we struggle to understand DMC's conclusion about lack of efficacy based on the AURORA trials and do not agree that Lupkynis does not represent any clinical benefit for Danish patients.[1,2]

We ask DMC to consider voclosporin as a relevant treatment option for LN patients and recommend it's use so Danish clinical practice can be consistent with updated international guidelines, which both recommend a voclosporin-based, triple-immunotherapy regimen should be considered for patients with active LN.[3,4] In addition, to align with the updated guidelines from the Danish Society of Rheumatology where voclosporin was acknowledged as an available treatment of glomerulonephritis.[5]

The DMC state that patients in the AURORA trials are undertreated compared to Danish clinical practice and that higher response rates can be expected in Denmark with higher doses of MFF and prednisone.
The DMC assess that the patients in the Aurora studies had severe disease and are treated with lower doses than the doses that would be used in DK clinical practice. Although Otsuka agrees with the disease severity, the current wording implies there is evidence that Danish patients in general have higher doses and that the outcome with increased doses can be expected to be better than the results in the AURORA trials.[1,2]

The DMC is referring to Danish guidelines regarding the MMF dose. These state the dose *can* be increased to 3 g/day *if tolerated*. However, the point of undertreatment has not been substantiated and according to leading Danish nephrologists most patients are in fact treated with 2 g/day as few patients tolerate higher dosage due to side effects. The MMF dose in the AURORA trials are consistent with clinical practice in Denmark and Europe, which has been confirmed by both Danish and European clinical experts, as well as with recent reference trials in LN.[6-8] Further, the AURORA 1 study protocol allowed investigators to adapt MMF dose from 1-3g/day and >50% of the patients were on 2 g or less when they entered the study.[1,9]

Similarly, the steroid tapering in the AURORA 1 trial is consistent with current international guidelines. KDIGO recommend 3 tapering schemes, including the reduced dose scheme used in the AURORA 1 trial.[1,4] EULAR recommend dosing glucocorticoids, if needed, based on the type and severity of organ involvement, and should be reduced to maintenance dose of ≤5mg/day (prednisone equivalent) and, when possible, withdrawn; in patients with moderate-to-severe disease, pulses of intravenous methylprednisolone (125–1000mg/day, for 1–3 days) can be considered.[3] Previous research has also demonstrated that high doses of MMF and steroids are not necessary in all patients and may not improve outcomes. A lower dose regimen may result in better long-term safety, including a reduction in lymphoproliferative disorders, skin cancers and steroid related side effects, without compromising efficacy.[10-13, 19]

The DMC does not accurately compare the results from the AURORA 1 control arm in relation to the other recent reference trials, which all report control arm results consistent with AURORA 1.[1, 6-8] It is possible DMC has compared the results with older reference trials [14-16] which used substantially different definitions of renal response and duration. It is also possible DMC has failed to consider the severity of the patients, e.g. mean UPCR and eGFR, time since LN diagnosis, as well as distribution of patients across class and ethnicity. Otsuka agrees with DMC that the patients in the study had severe disease and we believe voclosporin will be a valuable addition for these patients as recommended by updated international guidelines.

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The DMC is implying that the studies failed to demonstrate differences on clinically relevant endpoints and sustained effect on underlying inflammation

The DMC did not acknowledge that the endpoints in AURORA are consistent with reference trials[6-8], Danish guidelines[17] and the EMA's Guideline on clinical investigations for the treatment of SLE and LN.[18] Early reduction in proteinuria, particularly within 12 months, is the best known predictor of improved long-term renal outcomes, including reduced risk of disease flares and ESRD.[1, 20-23] Voclosporin is a CNI, which are known to have two distinct activities in LN: stabilization of the podocytes and immunomodulatory effects on T-cells by reducing the transcription of genes encoding inflammatory cytokines.[23-25]

The treatment benefit of voclosporin has been observed to be higher in proliferative LN (pure class III and IV), which indicates impact on inflammatory processes. Proliferative LN is more driven by the renal inflammation than damage to the podocyte (as in membranous LN).[23,26] The AURORA 2 results also demonstrated that significantly more patients in the voclosporin group achieved 'good renal outcomes' (i.e., adequate response and no subsequent renal flares) compared to placebo group, demonstrating a clear long- term renal benefit of Voclosporin. The follow-up one month of discontinuation of voclosporin, demonstrated that proteinuria was still lower in the voclosporin-treated group than in the control group, which suggests that there is a long-lasting immunological effect.[2]

The DMC states that voclosporin has a generally more serious adverse reaction profile

In AURORA 1 the majority of treatment-related AEs were of mild or moderate intensity and the most common was eGFR decrease. Hemodynamically mediated decreases in GFR are known to be associated with CNIs and so this outcome was not unexpected. Few patients discontinued the study due to an eGFR decrease indicating that eGFR decreased were largely reversible.[1]

In the AURORA 2 follow-up study[2] over 3 years, no new or unexpected safety signals were observed and there was no evidence of chronic renal toxicity, neurotoxicity, or malignancy with long-term voclosporin treatment, compared to the know safety profile of other CNIs. The overall AE profile was stable, while frequency of AEs was reduced each year. Mean corrected eGFR was in the normal range, stable over the study period, with no statistical differences, although the slope curve declined for control group. Dose changes due to reduction in eGFR, mainly occurring in AURORA 1, reflect real-world clinical practice in terms of safety, tolerability, and efficacy. The renal efficacy was maintained also after 1 month follow-up.

When comparing the GI disorders of the AURORA 2 trial with the MMF treated patients in the ALMS study, the voclosporin treated patient experienced less GI related AEs.[2, 12, 16] A study of the long-term impact of voclosporin on the kidney at the histologic level concluded it was not associated with chronic injury.[27]

The DMC is inaccurate when stating that it is highly likely that voclosporin will have a similar profile with other CNIs as important differences have been demonstrated in a comprehensive trial program.

Voclosporin has a predictable PK/PD dose-response relationship which allows for flat-fixed dosing and no requirement for therapeutic drug monitoring as with other CNIs. Moreover, guidelines value the high-quality evidence vs other CNIs.[3,4] Voclosporin has, beside initial hypertension, no increased signal for classically CNI-attributed complications, such as diabetes, dyslipidaemia, hyperkalemia, or hypomagnesemia. Instead, lipid profiles improved in voclosporin-treated patients, and mean blood pressure, glucose, and electrolyte levels were stable and similar between the groups.[23,28]

Furthermore, the AURORA trials demonstrated that the treatment allows for a reduced corticosteroid burden and helps reduce the risk of organ damage and toxic effects associated with long-term, high-dose corticosteroids.

We ask the DMC to carefully review our feedback anchored in documented evidence and consider recommending the use in line with current international guidelines.

Note: a full reference list is provided to DMC with this response document and all referenced publications can be made available to DMC upon request.

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24.01.2024

BMC/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.02.2024
Leverandør	Otsuka Pharma Scandinavia AB
Lægemiddel	Lupkynis (voclosporin)
Ansøgt indikation	Lupkynis er indiceret i kombination med mycophenolatmofetil til behandling af voksne patienter med aktiv lupus nefritis (LN) af klasse III, IV eller V (herunder blandet klasse III/V og IV/V).
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Lupkynis (voclosporin):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Lupkynis	7,9 mg	180 stk.	6.750	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

Aftaleforhold

Da flere leverandører har udtrykt, at de kan levere Lupkynis har Amgros publiceret et udbud med tilbudsfrist den 28.02.2024.

Aftalen starter den 01.05.2024 med mulighed for prælevering så snart aftalen er underskrevet af leverandøren. Det betyder, at der kan leveres Lupkynis til den forhandlede pris umiddelbart efter den 01.04.2024.

Tabel 2: Lægemiddeludgift

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Lupkynis	7,9mg	180 stk.	23,7 mg 2 gange dagligt	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
Sverige	Ikke anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Medicinrådet

Application for the assessment of Lupkynis (voclosporin) for the treatment of lupus nephritis

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[redacted]

Colour scheme for text highlighting	
Colour of highlighted text	**Definition of highlighted text**
	Confidential information

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1. Basic information

Contact information	
Name	**Bengt Anell**
Title	Market Access Manager, Nordics and Benelux
Phone number	+46 730 644 614
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Overview of the pharmaceutical	
Proprietary name	Lupkynis
Generic name	Voclosporin
Marketing authorization holder in Denmark	Otsuka Pharmaceuticals, Netherlands B.V. Herikerbergweg 292 1101 CT, Amsterdam, the Netherlands.
ATC code	L04AD03
Pharmacotherapeutic group	Calcineurin inhibitor
Active substance(s)	Voclosporin
Pharmaceutical form(s)	Oral soft capsule
Mechanism of action	Voclosporin is an oral immunosuppressant calcineurin inhibitor (CNI). As a CNI it has a dual mechanism of action, which reduces proinflammatory T-cell mediated immune responses thereby reducing kidney inflammation, and also protects renal podocytes from damage. Specifically, CNI immunosuppressive activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens. Studies in animal models also support a non-immunological role for CNI in kidney function to stabilise actin cytoskeleton and stress fibres in podocytes leading to increased podocyte integrity in glomeruli.
Dosage regimen	• The recommended dose of voclosporin is 23.7 mg (three 7.9 mg soft capsules), twice daily [total of 47.4mg daily]. • Voclosporin can be taken with or without food. It is recommended that voclosporin is administered consistently as close to a 12-hour schedule as possible and with a minimum of 8 hours between doses. If a dose is missed, it should be taken as soon as possible within 4 hours after missing the dose; beyond the 4-hour time frame, wait until the usual scheduled time to take the next regular dose. Do not double the next dose. • Physicians should evaluate the efficacy of treatment at a time point of at least 24 weeks and make an appropriate risk-benefit analysis for the continuation of voclosporin therapy. • It is recommended to establish a baseline estimated glomerular filtration rate (eGFR) before starting treatment with voclosporin, and assess every 2 weeks for the first month, and every 4 weeks thereafter. • When co-administering voclosporin with moderate CYP3A4 inhibitors (e.g., verapamil, fluconazole, diltiazem), reduce voclosporin daily dosage to 15.8 mg in the morning and 7.9 mg in the evening
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Voclosporin is indicated in combination with mycophenolate mofetil for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (LN).
Other approved therapeutic indications	Not applicable
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Voclosporin should be used in combination with mycophenolate mofetil (1).

Overview of the pharmaceutical	
Packaging – types, sizes/number of units, and concentrations	EU Number (Invented): EU/1/22/1678/001. Strength: 7.9 mg. Form and route of Administration: Soft oral Capsule. Pack size: 180 capsules. Immediate packing: blister (alu/PVC) (2)
Orphan drug designation	No

Abbreviations: CNI = calcineurin inhibitor; eGFR = estimated glomerular filtration rate; LN = lupus nephritis

2. Abbreviations

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
ACR	American College of Rheumatology
AD	Active disease
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike's Information Criterion
AIFA	Agenzia Italiana Del Farmaco
ALMS	Aspreva Lupus Management Study
anti-dsDNA	anti-double-stranded deoxyribonucleic acid
ARB	Angiotensin receptor blocker
AZA	Azathioprine
BEL	Belimumab
BIC	Bayesian Information Criterion
CEC	Clinical Endpoints Committee
CI	Confidence interval
CHD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNI	Calcineurin inhibitor
CR	Complete response
CRR	Complete renal response
CYC	Cyclophosphamide
DIC	Deviance Information Criterion
DKK	Danish Kroner
DMC	Danish Medicines Council
DRG	Diagnosis-related group
EC-MPS	Enteric-coated mycophenolate sodium
eGFR	Estimated glomerular filtration rate
EQ-5D	EuroQol Five Dimension
ESRD	End-stage renal disease
EULAR	The European Alliance of Associations for Rheumatology
ERA-EDTA	European Renal Association–European Dialysis and Transplant Association
G-BA	Gemainsamer Bun-Desausschuss
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GDP	Gross Domestic Product
GTP	Guanosine triphosphate
HAS	Haute Autorie De Sante
HCP	Health care professional

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HD	High-dose
HD-CYC	High-dose cyclophosphamide
HR	Hazard ratio
HRQoL	Health-related Quality of life
HRU	Healthcare resource utilization
HSUV	Health state utility values
HUI	Health utilities index
ICER	Incremental cost-effectiveness ratio
IMP	Inosine monophosphate
IMPDH	Inosine 5'-monophosphate dehydrogenase enzyme
ISN/RPS	International Society of Nephrology/Renal Pathology Society
IQR	Interquartile range
ISPOR	International Society For Pharmacoeconomics And Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KDQoL	Kidney Disease Quality of Life
KOL	Key opinion leader
KSQ	Kidney Symptom Questionnaire
LD-CYC	Low-dose cyclophosphamide
LMMs	Linear Mixed-Effects Models
LN	Lupus nephritis
LS	Least squares
LYs	Life-years
MMF	Mycophenolate mofetil
MMRM	Mixed-model repeated measures
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
NMSC	Non-melanoma skin cancer
NoMA	Norwegian Medicines Agency
NPR	National Patient Registry
NR	Not reported
OR	Odds ratio
ORR	Ordinal renal response
PERR	Primary efficacy renal response
PH	Proportional hazard
PICOS	Patient intervention comparator outcome study
PISR	Post-infusion systemic reactions
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRR	Partial renal response
PSA	Probabilistic sensitivity analyses
QA	Quality assessment
QALYs	Quality-Adjusted Life-Years
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RTX	Rituximab
SAE	Serious adverse event
SAP	Statistical Analysis Plan

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SD	Standard deviation
SE	Standard error
SELENA-SLEDAI	Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index
SF-36	36-Item Short Form Survey
SG	Standard gamble
SIGN	Scottish Intercollegiate Guidelines Network
SILD	Safety of short-interval lower-dose
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	Standard of care
SSC	SLE Symptom Checklist
TAC	Tacrolimus
TB	Tuberculosis
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
TLV	Tandvårds-Och Läkemedelsförmånsverket
TTD	Time to treatment discontinuation
UPCR	Urine protein creatinine ratio
URTIs	Upper respiratory tract infections
UTIs	Urinary tract infections
VAS	Visual Analogue Scale
ZiNL	Zorginstituut Nederland

3. Tables and Figures

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4. Summary

4.1 Nature of the condition and current treatment options

Lupus nephritis (LN) is the most common serious manifestation of Systemic Lupus Erythematosus (SLE), LN is characterised by the formation of immune complex deposits within renal tissues, leading to inflammation of the kidneys, renal damage, proteinuria and impaired renal function (3, 4). In general, patients diagnosed with LN should begin immunosuppressive and anti-inflammatory therapy to decrease kidney inflammation and suppress further kidney damage. LN is an incurable, debilitating and potentially life-threatening disease that can cause permanent kidney damage (8, 10). If LN is left untreated, patients will progress through the stages of chronic kidney disease (CKD 1-5), and may even go on to develop end-stage renal disease (ESRD) i.e., CKD5 (12). The overarching goals of current LN treatment include preservation or improvement of kidney function and the prevention of chronic kidney disease (CKD) and end-stage renal disease (ESRD) (5). Overall, ESRD develops in 10–30% of patients with LN (8, 10). ESRD has particularly severe clinical consequences for patients, including high mortality rates and the need for invasive kidney replacement therapy, such as dialysis and/or kidney transplantation (12). In Denmark, the mean annual incidence rate per 100,000 is estimated to be 0.45 (95% CI 0.38–0.53); 0.20 (95% CI 0.13–0.28) for men and 0.69 (95% CI 0.57–0.83) for women (6). The overall prevalence is estimated to be 6.4 per 100,000 (95% CI 5.7–7.2) for LN (6).

Currently, the Danish Medicines Council (DMC) has not published any treatment guidelines for LN, however, the Danish Society of Nephrology (7) and the European Alliance of Associations for Rheumatology (previously European League Against Rheumatism) and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) (8) have guidelines for treating LN of which current treatment is based on cooperation across specialities. January 2023 the Danish Society of Rheumatology published an update to the Danish national treatment guidelines for the treatment of SLE. A specific LN treatment guideline was not developed. However, voclosporin was acknowledged as an available treatment of glomerulonephritis (5).

Available treatments include immunosuppressant agents such as glucocorticoid, mycophenolate mofetil (MMF), mycophenolic acid (MPA), azathioprine (AZA), cyclophosphamide, and calcineurin inhibitors (CNIs) (especially tacrolimus, but ciclosporin may be used as a CNI alternative) (9-11). The treatment approach for active LN is divided into two distinct phases, an initial treatment phase during which MMF or cyclophosphamide in combination with high doses of corticosteroids is administered to control disease activity, followed by a maintenance phase during which the doses of all drugs are reduced to improve tolerability, consolidate response, and prevent relapses (7, 8). Despite the available treatments for LN, several treatments are used off-label and associated with suboptimal response rates and renal flares after years of treatment, as well as significant toxicity and adverse effects. Furthermore, regular therapeutic drug monitoring is required with traditional calcineurin inhibitors (CNIs) (9). Therefore, there is a need for new, effective treatment options with high rates of renal response to improve LN prognosis. There is also a need for a treatment regimen that minimises (or does not require) the use of high-dose corticosteroids due to the associated adverse effects.

4.2 The technology

Voclosporin is a novel, orally administered next-generation CNI immunosuppressant with a dual mechanism of action. Voclosporin binds to calcineurin and blocks calcineurin-mediated activation of Nuclear Factor of Activated T-Cells (NFAT), a transcription factor which drives T-cell immune response. The immunosuppressant mechanism blocks T-cell-mediated immune activity (IL-2 expression, cytokine production, lymphocyte proliferation, expression of T-cell surface antigens), leading to a reduction in kidney inflammation and tissue damage. Voclosporin also stabilises the actin cytoskeleton and stress fibres in renal podocyte cells, leading to increased glomerular podocyte integrity and protection against proteinuria (12). Voclosporin has already been recommended in other European countries, including Sweden as the Swedish Dental and Pharmaceutical Benefits Agency (TLV) has recommended Voclosporin to be included in the high-cost coverage as of February 2023 (13).

4.3 Comparators

Voclosporin is anticipated to be used in accordance with its marketing authorisation; in combination with background immunosuppressive therapies (standard of care (SoC) – MMF + low dose steroid regimen (IV methylprednisolone followed by oral prednisolone) for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) LN, and therefore any patient within this classification could potentially benefit from voclosporin. Accordingly, matching placebo administrated with SoC (MMF + low dose steroid regimen (IV methylprednisolone followed by oral prednisolone)) is chosen as the comparator in the AURORA 1 and subsequent continuation study AURORA 2 to demonstrate the efficacy and safety of voclosporin, additionally MMF treatment is the mainstay of therapy for patients in Denmark, for these reasons, MMF was chosen as the main comparator for this submission. In addition, belimumab was included as a comparator based on its EMA authorisation, and seldom use in Denmark, making it a potential future comparator in the Danish clinical setting. MMF and belimumab are expected to be the treatments that are replaced by the introduction of voclosporin.

4.4 The efficacy of the pharmaceutical

The efficacy and safety of voclosporin were investigated in two pivotal trials, AURORA 1 and the extension-study AURORA 2. In the AURORA 1 trial (14), treatment with voclosporin resulted in a clinically meaningful and statistically significant higher renal response rate compared to placebo (40.8% vs 22.5%). The odds of responding were 2.65 times greater for subjects treated with voclosporin compared with placebo (OR 2.65; 95% CI: 1.64, 4.27; p<0.001) with an absolute risk reduction of 18.3%. Consistent results were observed for all planned sensitivity and supplementary analyses of the primary parameter. All pre-specified hierarchical secondary endpoints achieved statistical significance in favour of voclosporin. The treatment benefit of voclosporin was driven by its effect on UPCR; more subjects in the voclosporin arm than in the placebo arm achieved UPCR ≤0.5 mg/mg (64.8% vs 43.8%) and the time to UPCR ≤0.5 mg/mg was significantly shorter for subjects treated with voclosporin (median 169 days vs 372 days for placebo; HR 2.02; 95% CI: 1.51, 2.70; p<0.0001). These data are clinically important given that an early improvement in proteinuria is a strong predictor of positive long-term outcomes in LN. The treatment benefit of voclosporin was also observed for subjects on low-dose corticosteroids at Weeks 24 and 52.

In addition, more subjects in the voclosporin arm than the placebo arm were in renal response at the start of the AURORA 2 study (15) (52.6% vs 34.0%). Long-term efficacy was demonstrated in AURORA 2, as voclosporin + MMF achieved significantly greater CRR and PRR (secondary endpoints) vs. placebo + MMF, despite the fact that AURORA 2 was not powered to detect superior efficacy for voclosporin (15). Notably higher renal response rates were observed in the voclosporin arm than in the placebo arm at every time point, confirming the clinically meaningful benefit of continued voclosporin treatment (for up to 3 years) over placebo. The difference between the treatments was driven by reductions in UPCR to ≤0.5. A clear separation between the arms in the proportion of subjects with UPCR ≤0.5 was seen as early as three months (in AURORA 1), with rates continuing to increase and then stabilizing in both arms after approximately 18 months of treatment. Partial renal response (PRR) rates showed the same pattern as renal response with consistently higher PRR rates seen in voclosporin subjects than placebo subjects across the 3 years of treatment. Across the three years of study, a good renal outcome, based on Clinical Endpoints Committee adjudicated adequate renal response (UPCR ≤0.7) and no renal flare, was achieved by 66.4% of subjects treated with voclosporin compared with 54.0% of placebo subjects. The number of subjects experiencing a renal flare was low with no significant difference between treatments. Non-renal flares were also similar in both arms. Changes (improvements) in other efficacy parameters were generally observed within the first year of treatment (in AURORA 1) and levels then remained stable with continued treatment in AURORA 2.

To assess the relative efficacy of voclosporin vs. belimumab, a network meta-analysis (NMA) was conducted in a Bayesian framework using Monte Carlo Markov Chain, which was implemented using models developed in the probabilistic modelling language of Stan (Version 2.21.0) (16). A generalised linear model for dichotomous outcomes was applied, as presented within the DSU TSD 2 (17). Treatment effects were synthesised using the observed number of events from the known number of patients in the respective treatment arms. The results were anchored to the MMF treatment regime, as this was the common comparator. The results demonstrate that VCS+MMF is more efficacious in comparison to the belimumab regime for both complete response rate and partial response rate, which are presented in Table 1 and Table 2.

Table 1: NMA results CRR, base case

	Fixed effects			
Treatment	**Median OR**	**CrI 2.5%**	**CrI 97.5%**	**SUCRA**
MMF	*Ref*	*Ref*	*Ref*	54%
VCS+MMF	2.665	1.838	3.884	94%
BEL+MMF/CYC	1.752	1.142	2.746	79%

Abbreviations: BEL = belimumab; CrI = credible interval; CYC = Cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; SUCRA = surface under the cumulative ranking curve; VCS = voclosporin

Table 2: NMA results PRR, base case

	Fixed effects			
Treatment	**Median OR**	**CrI 2.5%**	**CrI 97.5%**	**SUCRA**
MMF	*Ref*	*Ref*	*Ref*	30%
VCS+MMF	1.249	0.800	1.964	58%
BEL+MMF/CYC	1.035	0.623	1.695	36%

Abbreviations: BEL = belimumab; CrI = credible interval; CYC = Cyclophosphamide; MMF = mycophenolate mofetil; OR = odds ratio; SUCRA = surface under the cumulative ranking curve; VCS = voclosporin

4.5 The safety of the pharmaceutical

Voclosporin was well tolerated in the study with no new or unexpected safety signals observed. Three placebo subjects died as a result of a treatment-emergent adverse event (TEAE). An additional two subjects in the placebo group and one subject in the voclosporin group died due to AEs which started more than 30 days after the last dose of study drug. A similar proportion of subjects in each arm experienced serious TEAEs (20.8% in the voclosporin arm and 21.3% in the placebo arm) or had their study treatment discontinued as a result of a TEAE (11.2% and 14.6%, respectively). The AURORA 2 continuation study evaluated the safety of continued treatment with voclosporin for up to three years. Voclosporin was well tolerated in the study with no new or unexpected safety signals observed. The overall profile of adverse events (AEs) seen in Years 2 and 3 of treatment was similar to that seen in the first year of treatment (in AURORA 1); however, the frequency of AEs reduced each year. As in AURORA 1, the most common AEs were infections, recorded in 49% and 43% of subjects in the voclosporin and placebo arms, respectively. Three placebo subjects died as a result of a TEAE. A further subject in the placebo arm died due to a serious adverse event (SAE) which started more than 30 days after the last dose of study drug. Fewer subjects in the voclosporin arm than the placebo arm experienced serious TEAEs (18.1% vs 23.0%, respectively) or had their study treatment discontinued as a result of a TEAE (9.5% vs 17.0%, respectively).

4.6 Health economic analysis

A Markov model was developed, capturing the differences in costs and health outcomes associated with the intervention, Voclosporin+MMF, and the two comparators, MMF and belimumab+MMF/CYC. A lifetime horizon defined as 99.9% of the cohort being in the dead health state and is equal to 67.5 years in the base-case), was adopted to fully capture the impact of the progression and mortality of LN. The model uses half-yearly cycles and a Danish restricted societal perspective. The model is a Markov cohort state transition model with nine health states (Figure 12), encompassing the LN-related stages of chronic kidney disease (CKD) (CKD1–4), ESRD (CKD 5), and death (the absorbing health state) for patients with LN class III, IV, and V (including mixed class III/V and IV/V). Individual patient-level data (IPD) from AURORA 1 and 2 trials were used to estimate transitions between health states for VCS+MMF and MMF alone arms for the initial 36 months. A clinical SLR was conducted to identify a randomised controlled trial (RCT) for the treatment of LN, which informed an NMA to help parameterise the comparator treatments in the model. The long-term transition was determined by identified literature and key opinion leader (KOL) expert feedback.

In the base case, LN patients treated with voclosporin+MMF accrued an additional 0.471 quality-adjusted life-years (QALYs) vs. patients treated with MMF at an additional cost of 99,736.62 Danish Kroner (DKK) (applying discount rates of 3.5%, 2.5, and 1.5%, for years <35, 36-70, 71+ respectively). This results in a base case incremental cost-effectiveness ratio (ICER) of DKK 211,530 per QALY vs. MMF. In the comparison vs. belimumab+MMF/CYC, voclosporin+MMF accrued additional 0.348 QALYs vs. patients treated with belimumab+MMF/CYC at a lower cost of DKK -190,567, meaning that voclosporin+MMF is dominating belimumab+MMF/CYC in the base-case (voclosporin+MMF is cheaper and more effective). Deterministic, probabilistic, and scenario analyses were performed. The most significant drivers of cost-effectiveness were the utility estimates for CKD 1-3a states, age, and cost inputs. There are no subgroups considered in this analysis.

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

5.1.1 Pathophysiology and clinical presentation

SLE is a chronic and complex autoimmune disease that can affect any organ in the body (3). In SLE, abnormal and persistent immune system reactions to autologous nucleic acids result in the formation of damaging deposits of immune cells and autologous cellular materials called immune complex deposits (4, 10). These immune complexes form within organ systems throughout the body (e.g., skin, joints, kidney, and central nervous system) (10). LN is the most common serious manifestation of SLE, affecting at least a third of patients (18), although this may be as high as 60% among those with Black or Hispanic family backgrounds (19-21). LN is characterised by the formation of immune complex deposits within renal tissues, leading to inflammation of the kidneys, renal damage, proteinuria and impaired renal function (3, 4). LN impacts daily activities and causes significant quality of life impairment, particularly in patients with uncontrolled active disease. LN is associated with substantial healthcare resource use and economic burden, and patients with LN and eGFR<30ml/min incur 10-year direct costs 15-fold higher than those without LN. LN severity is classified into LN class I to VI, by kidney biopsy according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system (Table 3). In some cases, biopsies may show mixed histological findings, warranting a combination of classifications (e.g., classes III + V, or class IV + V) (22). At initial LN diagnosis, the majority of patients are diagnosed with class III (10–25%), class IV (35–60%), and class V (5–30%) disease; while fewer patients are diagnosed with classes I, II, and VI (class I: 0–6%; class II: 1–20%; class VI: <5%) (21). Treatment decisions are largely based on the type and extent of renal damage (23, 24). For example, patients in classes I and II generally do not require treatment, while those in classes III, IV, and V benefit from potent immunosuppression and patients in class VI are considered for renal replacement therapy (9).

Table 3: Summary of ISN/RPS classification of LN

Pathology	Class	Class Overview
Minimal mesangial LN	Class I	Most glomeruli are healthy and unaffected
Mesangial proliferative LN	Class II	Minimal IC deposits
Focal LN	Class III	An increasing number of glomeruli are damaged relative to class I and II but >50% of glomeruli are healthy, IC deposits apparent in the outer layer/s of glomerulus tissue
Diffuse segmental (IV-S) or global (IV-G) LN	Class IV	More substantial numbers (≥50%) of glomeruli show damage, IC deposits appear in deeper layers of tissue and outer layers may show structural changes
Membranous LN	Class V	IC deposits have infiltrated extensively deep within kidney tissues, structural irregularities may be apparent
Advanced sclerosing LN	Class VI	Fewer than 10% of glomeruli are functional, extensive damage and loss of function apparent in kidney tissues

Abbreviations: IC = immune complex; ISN/RPS = International Society of Nephrology/Renal Pathology Society; IV-G = diffuse global; IV-S = diffuse segmental; LN = lupus nephritis. Source: Weening 2004 (25)

Furthermore, patients may be classified according to their level of renal function (i.e., estimated glomerular filtration rate [eGFR]). If disease remains uncontrolled, patients with LN will progress through the stages of CKD (CKD1: >90 ml/min/1.73m^2; CKD2: 60–89 ml/min/1.73m^2; CKD3: 30–59 ml/min/1.73m^2; CKD4: 15–29 ml/min/1.73m^2) to ESRD (CKD5: <15 ml/min/1.73m^2) (3, 11, 26, 27).

LN-associated renal inflammation and structural/functional damage to renal cells are caused by the production of local cytokines, chemokines and adhesion molecules, along with an ensuing influx of inflammatory cells and proinflammatory cytokines (4). T-cells play a major role in the pathogenesis and progression of LN, and contribute to renal tissue injury both directly and indirectly (28-32). T-cells amplify inflammation by producing inflammatory cytokines, and also cause renal cell damage either by direct cytotoxicity, or through activation of macrophages, natural killer cells, dendritic cells and/or nephritogenic auto-antibody producing B cells (32-34). LN is also associated with the disruption of podocyte function. Podocytes are highly specialised epithelial cells which form part of the filtration barrier in the kidneys, and are important in the regulation of glomerular filtration and regulation of protein loss (35).

Clinical presentation of LN is often subtle, and most commonly revealed by examination of the urine and blood (3). Proteinuria is the defining aspect of LN and indicates both disease activity and kidney damage. Therefore, once proteinuria is clinically apparent, kidney tissues are already inflamed and damaged (3, 9). The most common clinical signs of LN (and approximate prevalence) include proteinuria (100%), microscopic haematuria (80%), renal insufficiency (60%), nephrotic syndrome (50%), red blood cells (30%) or other cellular casts in urine (30%), and hypertension (30%) (3). Although patients with LN may experience few or no accompanying symptoms, a substantial proportion of patients may also experience skin rash across the nose and cheeks (~31%), photosensitivity (~8%), oral ulcer (~12%), arthritis (~6%), serositis (~24%), neurologic disorder (~1%), hematologic disorder (~89%), and/or immunologic disorder (~93%) (36-38).

There is no cure for LN. The overarching goal of LN treatment is to quickly reduce proteinuria and inflammation to prevent further kidney damage (3, 9). However, renal flares occur in approximately 27–66% of LN patients,(39) usually within 5 to 6 years following the start of treatment (9). The EULAR/ERA-EDTA define a renal flare as an increase in proteinuria or serum creatinine level, abnormal urinary sediment, or a reduction in creatinine clearance due to active disease (18). Renal flares can be subdivided into proteinuria or nephritic flares (39):

- Proteinuric flares – persistently increased proteinuria (>0.5–1.0 g daily) after complete response (CR), or doubling of proteinuria (to >1.0 g daily) after a partial response (PR)
- Nephritic flares – an increase or recurrence of urinary sediment with or without increased proteinuria and are usually associated with a decline in renal function

Thus, renal flares result in histological progression to severer disease (i.e., further kidney damage and decreased renal function) in 40–76% of patients, with rates of progression varying according to LN class (9, 21, 40).

5.1.2 Epidemiology

Hermansen et al. assessed the incidence and prevalence of SLE and LN (all classes) patients in Denmark using data from the Danish National Patient Registry (NPR) of 1644 incidents of SLE (among these, 233 LN) cases during 1995–2011. The overall annual incidence rate per 100,000 for SLE was 2.35 (95% CI 2.24–2.49); 0.69 (95% CI 0.60–0.78) for men and 3.96 (95% CI 3.75–4.17) for women. For LN, the mean annual incidence rate per 100,000 was estimated to be 0.45 (95% CI 0.38–0.53); 0.20 (95% CI 0.13–0.28) for men and 0.69 (95% CI 0.57–0.83) for women. The estimated overall point prevalence (December 31, 2011) per 100,000 was 45.2 (95% CI 43.3–47.4) and 79.6 (75.9–83.5) for women and 10.1 (8.8–11.5) for men. These figures were confirmed to still be valid in a Danish context by Danish clinical experts clinical experts (41). This is reported in Table 4.

Table 4: Incidence and prevalence in the past 5 years

Year	2018	2019	2021	2020	2022
Incidence in Denmark	26	26	26	26	26
Adult population in Denmark	4,615,690	4,645,697	4,666,625	4,687,050	4,721,691
Prevalence in Denmark	2086	2100	2109	2119	2134

Note: Hermansen et al. reported incidence and prevalence figures for Denmark up until 2011. For this calculation values (incidence rate and prevalence) for 2011 were used together with population values from DST. Population values are reported quarterly in DST. Q1 has been extracted for each year for consistency.
Source: DST (42), Hermansen et al. (6).

Hermansen et al. documented the demographic characteristics of the 1644 incidents of SLE (among these, 233 LN) identified from the Danish NPR (Table 5). The overall median age of SLE patients was 47 (54 for men and 46 for females). For LN, the median age was estimated to be 42 (51 for men and 41 for females). In the base case the mean age from AROURA (33.2 years) is used, but an age of 42 (in line with Hermansen et al) is tested in scenario analyses (Table 87).

Table 5: Demographic characteristics of a Danish SLE case cohort

Characteristics	SLE	SLE with Concomitant or Subsequent LN
Total, n (%)	1644 (100)	233 (14)
Female, n (%)	1409 (86)	177 (76)
Age, all, years	47 (35–58)	42 (31–56)

Age, females, years	46 (34–57)	41 (30–51)
Age, males, years	54 (42–65)	51 (35–67)
Non-ethnic Danes, n (%)	99 (6)	26 (11)

Note: Values are median (interquartile range) unless otherwise specified.
Abbreviations: LN = lupus nephritis; SLE = systemic lupus erythematosus

5.1.3 Patient populations relevant for this application

The population of interest for this submission is LN patients classified as class III, IV, and V (including mixed class III/V and IV/V). The proportion estimate is reported in multiple studies (range: 70%-83%) (43-45). The most frequently documented proportion in the patient group consisting of class III, IV, and V (including mixed class III/V and IV/V) is 83%. Danish clinical experts (41) estimated that ~80% of all Danish LN patients belong to the patient group, further supporting the 83% proportion estimate. As such, these references were used as supporting material for estimates provided in Table 6.

There are no subgroups considered in this analysis. Nor are there any subgroups of patients for whom the pharmaceutical is expected to have a different level of efficacy and/or safety compared to the entire population.

Table 6: Estimated number of patients eligible for treatment

Year	2023	2024	2025	2026	2027
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	214	223	233	242	252

Source: (41, 43, 45)

5.1.4 Clinical burden

LN is an incurable, debilitating and potentially life-threatening disease that can cause permanent kidney damage (21, 23). If LN is left untreated, patients will progress through the stages of chronic kidney disease (CKD 1-5), and may even go on to develop ESRD i.e., CKD5 (9). Overall, ESRD develops in 10–30% of patients with LN (21, 23). ESRD has particularly severe clinical consequences for patients, including high mortality rates and the need for invasive kidney replacement therapy, such as dialysis and/or kidney transplantation (9).

Progressive, uncontrolled kidney damage drives the clinical burden of LN (46-48). Despite treatment, patients remain at high risk of renal flares, which may cause further renal damage and increase the likelihood of progression of CKD stages and ESRD (39, 49). A retrospective analysis indicates that around 8% of patients with LN develop ESRD within 5 years of diagnosis (n=86; 1996–2005); while up to 20% of patients develop ESRD within three decades (n=154; 1975–2005) (50). Other studies (including a comprehensive literature review and meta-analysis) have reported even higher rates of progression to ESRD for patients with LN (10–50%) (19, 21, 23, 51, 52).

LN is associated with considerable mortality risk; however, progression to ESRD has particularly severe clinical consequences, including higher mortality rates and the need for invasive kidney replacement therapy (i.e., dialysis and/or kidney transplantation) (9). Studies assessing mortality of LN associate LN with a 6–9-fold increase in mortality risk relative to a general population, which increases to a 26-fold-greater risk if the disease progresses to ESRD (23, 46, 47). Similarly, a multi-national cohort study suggests that LN is significantly more lethal than SLE alone (hazard ratio [HR] = 2.98 [95% CI: 1.48, 5.99]; p=0.002; n=1,827) (19, 53). Although dialysis and kidney transplantation are effective in reducing mortality among patients with ESRD, most patients receive dialysis in a clinic which requires a 4–8-hour procedure at least 3 times per week until a kidney donor becomes available (2.5–3 years average waiting time) (9, 54, 55). In some cases, patients may receive dialysis at home (56). However, these patients would still be limited to the confines of their homes for extended periods of time, with duration and intensity depending on the patient's needs.

Besides disease progression and mortality, LN is linked with poor maternal and foetal outcomes (57). This is particularly important, given the majority of patients with LN are women (76%) (Table 5). LN at the time of conception, or a history of prior LN, are both significantly associated with maternal hypertension (p<0.001), while prior LN is associated with an increased risk for preeclampsia (58). High rates of preterm birth (39.4%), intrauterine growth restriction (12.7%), stillbirth (3.6%), and neonatal death (2.5%) have been reported among LN-associated pregnancies (58, 59). LN-related kidney impairment may even cause infertility due to hypothalamic-pituitary dysfunction, and manifest as menstrual irregularity (including anovulatory cycles) in women or erectile dysfunction with reduced spermatogenesis in men (60). Disease-related

pregnancy concerns are exacerbated by the use of treatments which may impair fertility and/or be harmful to a foetus (61, 62).

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

The Danish Society of Nephrology (7) and EULAR/ERA-EDTA (8) have guidelines for treating LN of which current treatment is based on cooperation across specialities. The Danish National treatment guidelines (NBV) do not include a specific guideline for LN, however, the NBV for SLE is referencing to the EULAR/ERA-EDTA for guidance on LN treatment (5). The overall aim of the treatment is CR by maintaining kidney function, minimizing symptoms and prevent flares. The treatment regimen depends on the classification of LN, which follows international criteria from the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) (2003) (63)

Initial treatment:

Class I, II: There is usually no indication for treatment for LN class I and class II as they rarely cause loss of kidney function. However, following continuous albuminuria > 0,8g/day during renin-angiotensin system blockage, short treatment with low-dose prednisolone (0.25-0.5 mg/kg/day) is considered. AZA is a possible alternative and can be supplemented in cases where the prednisolone regiment does not fit the patient.

Class III, IV: Cyclophosphamide-based or MMF-based regiments combined with adjuvant steroid treatment are considered the primary treatment of class III and IV LN patients with acute lesions and thrombotic microangiopathy and/or vasculitis.

- Starting dose of MMF is e.g., 2g/day (spanning 2-3 doses) which can be increased over 14 days to 3g/day (if tolerated).
- Cyclophosphamide is given as 500 mg IV every 14th day until a cumulative dose of 3 g (6 doses) is achieved during a 3-month period (Euro-lupus regiment).
- If signs of severe kidney affection are present, an increased IV dose of cyclophosphamide can be given (0.75-1.0 g/month for six months (NIH-regiment)).

Treatment with steroids is similar for the two regiments. IV infusion of methylprednisolone 500 mg is given for 3 days followed by oral prednisolone tablets (0.5 mg/kg/day). Clinicians intend to taper prednisolone administration to ≤10 mg by the 4th to 6th month. In case of a severe disease state, administration can start with a prednisolone dose of 0.7-1 g/kg/day. If remission is not achieved by MMF and steroid (MMF + steroid) treatment clinicians can choose to switch to cyclophosphamide + steroid administration. Plasmaphereses can be considered in case of the presence of thrombotic microangiopathy together with rapid loss of kidney function.

Class V: Class V treatment is primarily treated as the class III and class IV MMF+ steroid treatment regimen. In case of low efficacy with MMF+steroid treatment supplementing with calcineurin-inhibitor (most commonly tacrolimus) is possible.

Subsequent treatment:

When remission is achieved, MMF (e.g., 1-2g/d) administration is continued for a minimum of three years (alternatively AZA (1-2mg/kg/day)). Usually, patients experience the continued need for immunosuppression for several years with increased and decreased dosage according to their clinical progress. Clinicians will typically aim to reduce the prednisolone dose first. Some patients will relapse upon prednisolone reduction. As such, some patients will need continuous administration with prednisolone (e.g., 5-7.5mg/day) for 2-3 years.

Refractory disease:

Relapse after complete remission is primarily treated as initially. In case of relapse after partial remission, another regiment or increase in dosage is considered. Tacrolimus (0.06-0.1 mg/kg/day, S-tacrolimus level 5-7 ng/l) can be considered if remission has not been achieved by either of the initial treatment regimens (usually as MMF+steroid adjuvant). Adjuvant Rituximab administration is considered as well.

Adjuvant treatment:

Antimalaria treatment (Hydroxychloroquine 200-400 mg) is considered a standard treatment for all patients. Dosage is suggested to be reduced to half when eGFR levels are <30 ml/min.

Acetylsalicylic acid is recommended for all patients with anti-phospholipid antibodies. After thromboembolic events, anticoagulation therapy is recommended. Cholesterol-lowering drugs are recommended if S-LDL-cholesterol >2.6/l.

Possible treatment options

Current therapies for LN are non-specific and inhibit broad inflammatory pathways. As such, due to the limited targeted treatment options, several novel treatment options are emerging.
The only targeted therapy for SLE/LN is belimumab (Benlysta), a monoclonal antibody targeting soluble human B Lymphocyte Stimulator protein. Belimumab blocks the binding of soluble BLyS, a B cell survival factor, to its receptors on B cells and inhibits B cell survival and differentiation into immunoglobulin-producing plasma cells. Belimumab is authorised in the EU since July 2011 (first published EPAR – 2012) as add-on therapy in adult patients with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy. Benlysta has recently been indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active LN. Anifrolumab (first published EPAR – 2022) is a human IgG1κ monoclonal antibody directed against subunit 1 of the type I interferon receptor. Anifrolumab inhibits the binding of type I interferon to IFNAR1 blocking the biological activity of type I IFNs. The constant domain of the IgG heavy chain on anifrolumab was intentionally modified to eliminate FcγRI, FcγRIIA and FcγRIIB, FcγRIIIA and C1q binding. These mutations also eliminate the potential for antibody-dependent cell cytotoxicity and complement-dependent cytotoxicity. The EMA has considered that Anifrolumab can be used as an add-on for the treatment of patients with SLE. However, it is not approved for the treatment of active LN.

Belimumab was included as a comparator based on its EMA authorisation, and seldom use in Denmark, making it a potential future comparator in the Danish clinical setting.

2023 update

January 2023 the Danish Society of Rheumatology (7) published an update to the Danish national treatment guidelines for the treatment of SLE (64). A specific LN treatment guideline was not developed. However, voclosporin was acknowledged as an available treatment of glomerulonephritis (64).

In addition, voclosporin for the treatment of adult patients with active SLE class III, IV, or V nephritis (including mixed classes III/V and IV/V), in combination with MMF was included in the high-cost coverage as of February 2023 by TLV (13).

5.2.2 Choice of comparator(s)

Voclosporin is anticipated to be used in accordance with its marketing authorisation; in combination with background immunosuppressive therapies (SoC – MMF + low dose steroid regimen (IV methylprednisolone followed by oral prednisolone) for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) LN. Accordingly, matching placebo administrated with SoC (MMF + low dose steroid regiment (IV methylprednisolone followed by oral prednisolone)) is chosen as the comparator in the AURORA and subsequent continuation study AURORA 2 to demonstrate the efficacy and safety of voclosporin.

The basis treatment regimen in Danish clinical practice for patients with active LN class III, IV and V are MMF alongside with prednisolone (MMF + steroids). Patients receive a starting dose of 2g/day MMF which can be increased over 14 days to 3g/day (if tolerated). In addition, patients receive IV infusion of 500 mg methylprednisolone for 3 days followed by an oral prednisolone tablet (0.5 mg/kg/day). Clinicians intend to taper prednisolone administration to ≤10 mg by the 4th to 6th month. In the pivotal phase 3 study (AURORA 1) and follow-on phase 3 long-term continuation study (AURORA 2), subjects

received MMF (2 g/day[1], with the ability to increase to 3 g/day, if necessary) throughout the study. In addition, subjects were given IV methylprednisolone (a total of 1 g (0.5 g for subjects weighing <45 kg)) over days 1 and 2 followed by oral prednisone at a dose of 25 mg/day (20 mg/day if the subject weighed <45 kg) on day 3 which was then tapered down in 5 mg increments according to a tapering schedule, with the aim of reaching 2.5 mg/day by the end of week 16 (~4th month).

While the dose of MMF used in the studies is comparable to that in Danish clinical practice for the patient group (2-3 g/day), the dose and tapering regimen for corticosteroids differed. It is hypothesized that the reduced steroid dose regimen in the AURORA studies demonstrates that voclosporin is effective at treating LN, even given the reduced steroid exposure, and all other things being equal. The comparators are described in Table 7 and Table 8.

5.2.3 Description of the comparator(s)

Table 7: Information on the comparator: MMF

Generic name(s) (ATC-code)	Mycophenolate mofetil (L04AA06) + methylprednisolone (D10AA02) + prednisolone (H02AB06)
Mode of action	**Mycophenolate mofetil:** The active metabolite of mycophenolate, mycophenolic acid, prevents T-cell and B-cell proliferation and the production of cytotoxic T-cells and antibodies. Lymphocyte and monocyte adhesion to endothelial cells of blood vessels that are normally part of inflammation is prevented via the glycosylation of cell adhesion molecules by mycophenolic acid (MPA). MPA inhibits de novo purine biosynthesis (that promotes immune cell proliferation) by inhibiting inosine 5'-monophosphate dehydrogenase enzyme (IMPDH), with a preferential inhibition of IMPDH II. IMPDH normally transforms inosine monophosphate (IMP) to xanthine monophosphate, a metabolite contributing to the production of guanosine triphosphate (GTP). GTP is an important molecule for the synthesis of ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and protein. As a result of the above cascade of effects, mycophenolate mofetil (MMF) reduces de-novo production of guanosine nucleotides, interfering with the synthesis of DNA, RNA, and protein required for immune cell production. Further contributing to the above anti-inflammatory effects, MMF depletes tetrahydrobiopterin, causing the decreased function of inducible nitric oxide synthase enzyme, in turn decreasing the production of peroxynitrite, a molecule that promotes inflammation (65) **Methylprednisolone:** The short-term effects of corticosteroids are decreased vasodilation and permeability of capillaries, as well as decreased leukocyte migration to sites of inflammation. Corticosteroids binding to the glucocorticoid receptor mediates changes in gene expression that lead to multiple downstream effects over hours to days. Glucocorticoids inhibit neutrophil apoptosis and migration; they inhibit phospholipase A2, which decreases the formation of arachidonic acid derivatives; they inhibit NF-Kappa B and other inflammatory transcription factors; they promote anti-inflammatory genes like interleukin-10. Lower doses of corticosteroids provide an anti-inflammatory effect, while higher doses are immunosuppressive. High doses of glucocorticoids for an extended period bind to the mineralocorticoid receptor, raising sodium levels and decreasing potassium levels. (65) **Prednisolone:** The short-term effects of corticosteroids are decreased vasodilation and permeability of capillaries, as well as decreased leukocyte migration to sites of inflammation. Corticosteroids binding to the glucocorticoid receptor mediates

[1] For subjects who were not already taking prescribed MMF prior to randomization, the dosing of MMF started 1 g/day for the first week, increasing to 2 g/day for the second and subsequent weeks.

	changes in gene expression that lead to multiple downstream effects over hours to days. Glucocorticoids inhibit neutrophil apoptosis and migration; they inhibit phospholipase A2, which decreases the formation of arachidonic acid derivatives; they inhibit NF-Kappa B and other inflammatory transcription factors; they promote anti-inflammatory genes like interleukin-10. Lower doses of corticosteroids provide an anti-inflammatory effect, while higher doses are immunosuppressive. High doses of glucocorticoids for an extended period bind to the mineralocorticoid receptor, raising sodium levels and decreasing potassium levels. (65)
Pharmaceutical form/Method of administration	**Mycophenolate mofetil:** Tablet for oral administration **Methylprednisolone:** Powder for concentrate for solution for infusion. **Prednisolone:** Tablet for oral administration
Posology/Dosing	Starting dose of MMF is e.g., 2g/day (spanning 2-3 doses) which is increased over 14 days to 3g/day (if tolerated). IV infusion of methylprednisolone 500 mg is given for 3 days together with an oral prednisolone tablet (0.5 mg/kg/day). Clinicians intend to taper prednisolone administration to ≤10 mg by the 4th to 6th month. In case of a severe disease state, administration can start with prednisolone dose of 0.7-1 g/kg/day (8).
Should the pharmaceutical be administered with other medicines?	No
Treatment duration/criteria for the end of treatment	**Duration of treatment** (8)**:** *Induction:* MMF is administered for 3-6 months together with 3 days of treatment with IV methylprednisolone followed by oral prednisolone 0.5 mg/kg/d. *Post-remission:* MMF is administered (e.g., 1-2 g/day) for a minimum of 3 years. Alternatively, azathioprine (1-2 mg/kg/day) can be administered instead. Tapering of oral prednisolone starts from week 4. In case of flares when prednisolone is tapered some patients will continue with prednisolone 5-7.5 mg/d for 2-3 years **Criteria for end of treatment** Discontinuation by physician's choice based on patient's health condition and course of the disease
Necessary monitoring, both during administration and during the treatment period	Monitoring every 2-4 weeks during the first 2-4 months depending on the response of treatment. Lifelong monitoring every 3-6 months will almost always be necessary. (8). Renal function should be monitored every 14th day during the first month of treatment and subsequently every 1-3 months after 3 months of treatment. (8).
Need for diagnostics or other tests (i.e., companion diagnostics)	• Complete blood count (including serum albumin, eGFR) • Kidney biopsy • Urinalysis (includes GFR, serum albumin, proteinuria, and urinary sediment) • Anti-dsDNA and C3, C4 level monitoring for the confirmation of the SLE diagnosis These tests are usually required for all patients with LN and are not specific to treatment with MMF alone (9)
Packaging	**Mycophenolate mofetil:** 150 tablets of 500mg (per pack) **Methylprednisolone:** 1 vial of 500mg **Prednisolone:** 100 tablets of 25 mg (per pack) 100 tablets of 5 mg (per pack)

Abbreviations: DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; GTP = guanosine triphosphate; IMP = inosine monophosphate; IMPDH = inosine 5'-monophosphate dehydrogenase enzyme; LN = lupus nephritis; MMF = mycophenolate mofetil; MPA = mycophenolic acid; NF = nuclear factor; RNA = ribonucleic acid; SLE = systemic lupus erythematosus

Source: (66)

Table 8: Information on the comparator: Belimumab

Generic name(s) (ATC-code)	Belimumab (L04AA26)
Mode of action	Belimumab is an intravenous or subcutaneous immunosuppressant for the adjunctive treatment of SLE. More specifically, it is a fully human recombinant IgG1λ monoclonal antibody produced from a recombinant NS0 cell line stably transfected with the belimumab heavy chain and light chain genes. It is the first biological treatment approved for the indication of SLE. Concomitant use with live or inactivated vaccines must be avoided. Belimumab consists of 2 heavy chains, and 2 light chains of the lambda subclass. Each heavy chain contains 452 amino acid residues and each light chain contains 214 amino acid residues. There are 3 post-translational modifications: a conserved N-linked glycosylation on the CH2 domain at Asn 303 of the heavy chain, the conversion of the N-terminal glutamine residue of the heavy chain into pyroglutamate, and the loss of C-terminal lysine residue of the heavy chain.
Pharmaceutical form/Method of administration	The diluted solution (syringe) should be administered by intravenous infusion over a period of 1 hour.. Pre-filled pens are to be administered subcutaneous.
Posology/Dosing	In patients initiating therapy with belimumab for active LN, the recommended dosage regimen is a 400 mg dose (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter. In patients continuing therapy with belimumab for active LN, the recommended dosage is 200 mg once weekly.
Should the pharmaceutical be administered with other medicines?	Belimumab should be used in combination with corticosteroids and mycophenolate or cyclophosphamide for induction, or mycophenolate or azathioprine for maintenance
Treatment duration/criteria for end of treatment	**Discontinuation:** Discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment. Physicians should assess the risk of depression and suicide considering the patient's medical history and current psychiatric status before treatment with belimumab and continue to monitor patients during treatment. Physicians should advise patients to contact their health care provider about new or worsening psychiatric symptoms. In patients who experience symptoms (depression, suicidal ideation and behaviour including suicide) treatment discontinuation should be considered.
Necessary monitoring, both during administration and during the treatment period	The patient's condition should be evaluated continuously. Belimumab should be administered by healthcare providers prepared to manage anaphylaxis. Belimumab should be administered by healthcare providers prepared to manage infusion reactions. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. Healthcare providers should be aware of the risk of hypersensitivity reactions, which may present as infusion reactions, and monitor patients closely. Belimumab should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of Benlysta with other agents. **Vital Signs Monitoring** There were no specific guidelines in the medication guide from the manufacturer for vital signs monitoring. It is reasonable and prudent, however, to obtain vital signs (patient temperature, blood pressure and pulse) upon arrival, after the start of Benlysta, upon discontinuing infusion, and before the patient departs the facility. If the patient has a

	prior history of an acute infusion reaction, monitor vitals every 10 minutes for 30 minutes and for 30 minutes after infusion.
Need for diagnostics or other tests (i.e., companion diagnostics)	• Complete blood count • Kidney biopsy • Urinalysis (includes eGFR, serum albumin, proteinuria, and urinary sediment) • Anti-dsDNA and C3, C4 level monitoring for the confirmation of SLE diagnosis These tests are usually required for all patients with LN.
Packaging	Belimumab 200 mg solution for injection in pre-filled pen. Belimumab 200 mg solution for injection in pre-filled syringe.

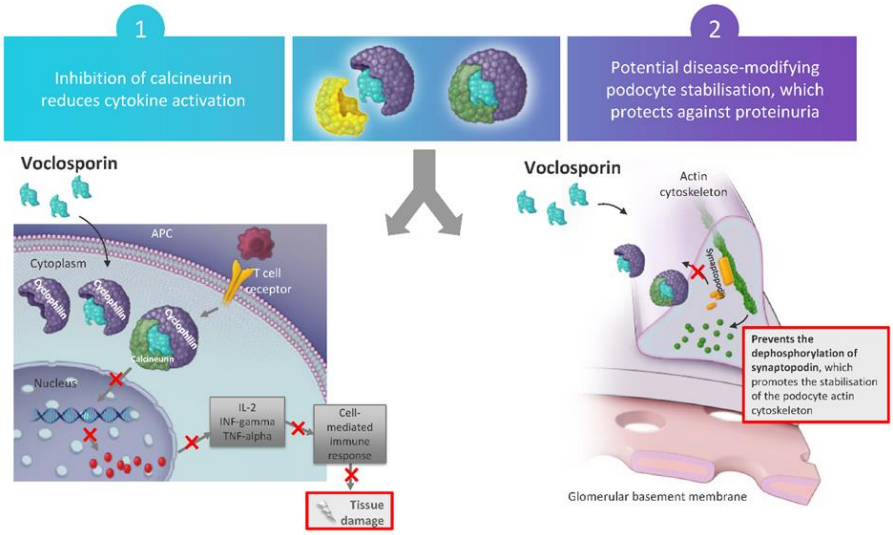
Abbreviations: anti-dsDNA = anti-double-stranded deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; LN = lupus nephritis; SLE = systemic lupus erythematosus
Source: (67)

5.3 The intervention

Voclosporin is a novel orally administered next-generation CNI immunosuppressant with a dual mechanism of action which reduces proinflammatory T-cell mediated immune responses linked to kidney inflammation (1) and protects renal podocytes from damage (Figure 1) (14). Specifically, voclosporin binds to calcineurin and blocks calcineurin-mediated activation of NFAT, a transcription factor which drives T-cell immune response (1, 68-71). CNI immunosuppressive activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens (1). In addition, studies in animal models indicate that voclosporin stabilises actin cytoskeleton and stress fibres in renal podocytes, leading to increased podocyte integrity in glomeruli (1). Podocytes are specialised epithelial cells that are a key component of the glomerular filtration barrier, and their cytoskeletal integrity is critical to ensure healthy kidney function (69-72).

Voclosporin is structurally similar to cyclosporin A but incorporates a modification to a functional group on amino acid-1 of the molecule (73). This modification changes both how voclosporin binds to calcineurin and its metabolic profile, leading to a four-fold increase in immunosuppressive potency compared to cyclosporin A and fewer CNI-associated side effects due to the rapid elimination of voclosporin metabolites (73). In addition, the combination of increased potency and decreased metabolite exposure gives voclosporin a more predictable pharmacokinetic and pharmacodynamic profile compared to currently used CNIs, eliminating the need for intensive therapeutic monitoring (73-76). A summary of the technology being appraised, voclosporin, is provided in Table 9.

Figure 1: Voclosporin mechanism of action



Abbreviations: APC = antigen-presenting cell; IL = interleukin; INF = interferon; TNF = tumour necrosis factor

Source: R.B. Huizinga et al. 2017 presentation (77).

Table 9: The Intervention (Voclosporin)

Voclosporin	
Generic name, brand name, ATC-code	Voclosporin, Lupkynis, L04AD03
Method of administration	Oral (soft capsule)
Dosing	• The recommended dose of voclosporin is 23.7 mg (three 7.9 mg soft capsules), twice daily. • Voclosporin can be taken with or without food. It is recommended that voclosporin is administered, consistently as close to a 12-hour schedule as possible, and with a minimum of 8 hours between doses. If a dose is missed, it should be taken as soon as possible within 4 hours after missing the dose; beyond the 4-hour time frame, wait until the usual scheduled time to take the next regular dose. Do not double the next dose. • When co-administering voclosporin with moderate CYP3A4 inhibitors (e.g., verapamil, fluconazole, diltiazem), reduce voclosporin daily dosage to 15.8 mg in the morning and 7.9 mg in the evening. • Renal toxicity: As with other calcineurin-inhibitors, adverse reactions of acute worsening of renal function or estimated glomerular filtration rate (eGFR) decreases have been seen in patients treated with voclosporin. In the first four weeks of treatment with voclosporin, haemodynamic reductions in eGFR have been observed. This can be managed by dose adjustments. Regular monitoring of eGFR levels is recommended. Contraindications: Hypersensitivity to the active substance or to any of the excipients [Arginine hydrochloride, Histidine, Histidine monohydrochloride, Polysorbate 80, Sodium chloride, Water (for injection)] o Co-administration of voclosporin with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin). o Ethanol o Vitamin E polyethylene glycol succinate (tocofersolan) o Polysorbate 40 o Medium-chain triglycerides o Gelatin o Sorbitol sorbitan solution o Glycerin o Purified water o Titanium dioxide o Iron oxide, red o Iron oxide, yellow
Should the pharmaceutical be administered with other medicines?	• Voclosporin should be used in combination with mycophenolate mofetil (MMF).
Necessary monitoring, both during administration and during the treatment period	• Physicians should evaluate the efficacy of treatment at a timepoint of at least 24 weeks and make an appropriate risk-benefit analysis for continuation of voclosporin therapy.
Need for diagnostics or other tests (i.e., companion diagnostics)	• It is recommended to establish a baseline eGFR before starting treatment with voclosporin, and assess every 2 weeks for the first month, and every 4 weeks thereafter. • Blood pressure monitoring every two weeks for the first month.
Treatment duration/criteria for end of treatment	• 36 months • Dosing/treatment should be modified/discontinued based on eGFR: o eGFR assessment every two weeks for the first month, and every four weeks thereafter. o Dose adjustments are required for those individuals whose eGFR is confirmed to be reduced and below 60 mL/min/173m^2. If eGFR remains ≥ 60mL/min/173m^2 no dose modification is required. o Confirmed eGFR decrease from baseline by>20% and <30%, voclosporin dose should be reduced by 7.9 mg capsule twice daily. eGFR reassessment within two weeks; if eGFR has not recovered, reduce the dose further to 7.9 mg twice daily. o Confirmed eGFR decrease from baseline by ≥30%, treatment should be discontinued. Restart voclosporin upon eGFR recovery at a lower dose and increase as tolerated based on renal function. o Confirmed eGFR decrease from baseline by ≤ 20%, maintain current dose and monitor

	It is recommended that patients requiring a reduction in dose are reassessed for eGFR recovery within 2 weeks. For patients that had a decrease in dose due to eGFR reduction, increase the dose by 7.9 mg twice daily for each eGFR measurement ≥ 80% of baseline should be considered. The starting dose should not be exceeded.

Abbreviations: eGFR = estimated glomerular filtration rate; MMF = mycophenolate mofetil
Source: (1)

The introduction of the voclosporin will allow a further treatment option for patients with LN, whether that be to be used first line or later when current treatment has failed.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

6.1.1 Global SLR

A full overview of the SLR methods undertaken for this submission is provided in Appendix A Literature search for efficacy and safety of intervention and comparator(s). As per Danish Medicines Council (DMC) guidelines, each SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (78) and the Cochrane Handbook for Systematic Reviews of Interventions. Systematic searches were conducted on 1st June 2021 (Parent SLR), and later repeated on 24 January 2022 (SLR update) to identify RCTs that evaluated the efficacy and safety of active treatments in patients with active LN.

Parent SLR

Database searches were conducted on June 1, 2021. A total of 3279 publications were identified from the databases. After the removal of duplicates, the titles and abstracts of 2935 publications were screened for eligibility. After 2539 publications were excluded based on title and abstract screening, 396 full-text publications were assessed for eligibility based on pre-specified criteria (Table 96: PICOS inclusion/Exclusion Criteria). A total of 238 publications were excluded after the full-text screening. Reasons for exclusion were due to the ineligibility of population (n=38), intervention (n=7), comparators (n=2), outcomes (n=11), study designs (n=149), duplicates (n=27) and non-English (n=4). A total of 107 clinical trials without results were included but not extracted therefore not a part of the final synthesis. Hand searches of 62 conference abstracts yielded one publication(79) for data synthesis which linked to primary publication (80). Overall, a total of 52 publications reporting on 41 unique trials were included in this SLR.

SLR update

Database searches were conducted on January 24, 2022. A total of 211 publications were identified from the databases. After 180 publications were excluded based on title and abstract screening, 31 full-text publications were assessed for eligibility based on pre-specified criteria (Table 96: PICOS inclusion/Exclusion Criteria). A total of 13 publications were excluded after full-text screening. Reasons for exclusion were due to the ineligibility of population (n=2) and duplicates (n=11). A total of 13 clinical trials without results were included but not extracted [RCTs without results/ RCT protocols (n = 7), Secondary analysis of RCT data (n = 4), Open-label extension studies (n = 2)] and were therefore not a part of the final synthesis. Zero conference abstracts were identified in the hand searches. Overall, a total of 5 publications were included in the first SLR update - two publications linked to two studies (AURORA and NOBILIY) from the parent SLR, with the remaining three publications representing three unique studies. A total of 57 publications reporting on 44 unique trials were identified from the databases. All the trials were prospective and randomised, either phase II, III or IV. The sample size of these trials ranged from 9 to 484. Most were open-label (n=22). Only 12 were double-blinded trials, and the rest (n=10) did not report this. Three trials had a cross-over study design (81-83). Trial location varied: there were 11 multinational studies (82, 84-96); ten studies from China (97-107); six studies from the US (81, 108-112); two each from Thailand (113, 114), Hong Kong (115, 116), and Italy (117-119); and one each from India (120), Saudi Arabia (121), Czech Republic (Cyclofa-Lune) (92, 93), Netherlands (DUTCH LN) (122-124), Malaysia (125) and Egypt (126) and Bangladesh (127).

Geographical scope was not reported in four trials (80, 128-133). Most of the studies (n=25) assessed induction treatment except one (89), and the others were not reported.

6.1.2 Danish Relevance

MMF + (cortico)steroids

In this section, only studies investigating the efficacy and safety of treatments recommended in Denmark are reported. Danish clinical practice for treatment of patients with active LN (class III, IV or V (including mixed class III/V and IV/V)) recommends a regimen consisting of MMF in combination with IV methylprednisolone followed by an oral prednisolone tablet. In the pivotal phase 3 study (AURORA 1), follow-on phase 3 long-term continuation study (AURORA 2), and the supporting phase 2 (AURA-LV) the efficacy and safety of placebo + MMF in combination with IV methylprednisolone followed by oral prednisolone tablet is assessed. As such, in accordance with the DMC guidance, if a head-to-head study with a comparator relevant to Danish clinical practice exists, the literature search can be omitted (134).

Belimumab

Currently, belimumab is the only approved add-on therapy in LN ((67). In the absence of a head-to-head trial comparing voclosporin to belimumab, the evidence of the global SLR was reviewed and studies that could inform an indirect comparison of belimumab were selected.

6.2 List of relevant studies

Table 10: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
A secondary analysis of the belimumab International Study in Lupus Nephritis trial examined the effects of belimumab on kidney outcomes and preservation of kidney function in patients with lupus nephritis, Rovin BH, et al., Kidney Int. 2022 (135) Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis, Furie et al., The New England Journal of Medicine, 2020 (80)	Efficacy and Safety of Belimumab in Patients With Active Lupus Nephritis (**BLISS-LN**)	NCT01639339	**Start:** July 12, 2012 **Completion:** March 12, 2020

Note: For detailed information about the included study, refer to Appendix B-C.

7. Efficacy and safety

The efficacy and safety of voclosporin have been evaluated in the pivotal Phase 3 study (AURORA 1: AUR-VCS-2016-01 [NCT03021499]), as well as a follow-on Phase 3 long-term continuation study (AURORA 2: AUR-VCS-2016-02 [NCT03597464]). In addition, data is provided from a Phase 2b study (AURA-LV; AUR-VCS-2012-01 [NCT02141672]).

7.1 Efficacy and safety of voclosporin + MMF and low-dose corticosteroid (SoC) compared to placebo + MMF and low-dose corticosteroid (SoC) for patients with active LN (class III, IV or V (including mixed class III/V and IV/V)

7.1.1 Relevant studies

The efficacy and safety of voclosporin have been evaluated in a comprehensive clinical trial programme. The results of the AURORA 1 Phase 3 and AURORA 2 Phase 3 long-term continuation trials constitute the primary source of clinical evidence for this submission along with supporting data from the AURA-LV Phase 2 study. A summary of methodology for AURORA 1 (Section 7.1.1.1), AURORA 2 (Section 7.1.1.1.1.7) and AURA-LV (7.1.1.3) is provided, along with supporting efficacy and safety data for each trial. Full in-detail description of main characteristics/methodology (Appendix B Main characteristics of included studies), population baseline characteristics (Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety), table of efficacy and safety (with definition, validity and clinical relevance)

(Appendix D Efficacy and safety results per study), as well as safety data (Appendix E Safety data for intervention and comparator(s)) for all included studies, are available in appendices B-E

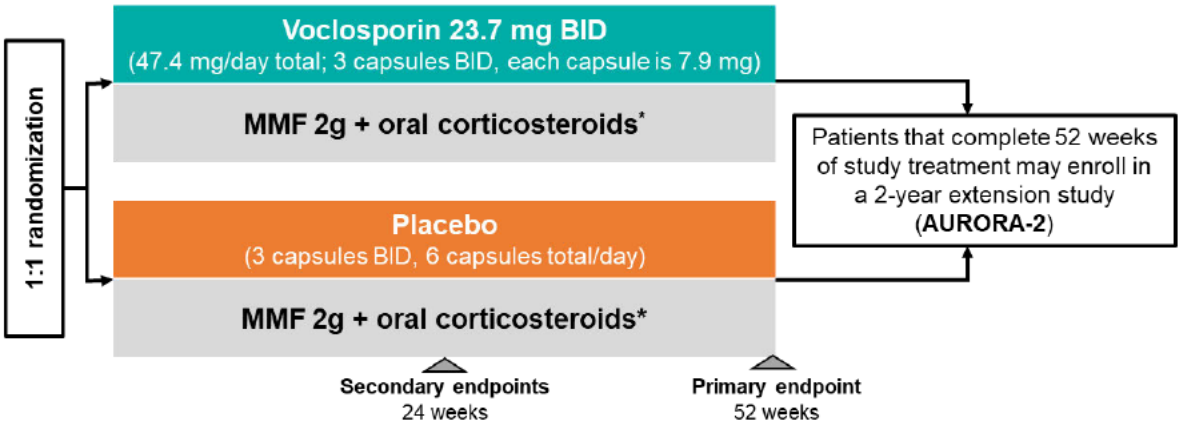
Across each trial, the terms "complete remission", "complete renal remission", "renal response" and "CRR" have been used interchangeably but share the same definition. Similarly, "partial remission", "partial response" and "partial renal response" have also been used interchangeably but share the same definition. For the purposes of this submission, the outcomes are henceforth referred to as "CRR" and "PRR" for consistency across all three trials.

7.1.1.1 AURORA 1 phase 3 study

AURORA 1 is a Phase 3, multicentre, double-blind, placebo-controlled, randomised trial that compared the efficacy and safety of voclosporin vs. placebo, each in combination with MMF and low-dose oral corticosteroids for the treatment of patients with active LN (14). In each treatment arm, over a period of 52 weeks, the primary objective was to assess efficacy in achieving CRR, while the secondary objective was to assess safety and tolerability of therapy in patients with active LN (136).

An overview of AURORA 1 trial design is presented in Figure 2, accompanied by a summary of the methodology in Table 11. A detailed description of the methodology and main characteristics is presented in Appendix B Main characteristics of included studies as well as baseline characteristics in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

Figure 2: Trial design: AURORA 1 (AUR-VCS-2016-01; NCT03021499)



Note: *Oral corticosteroids were tapered per protocol
Abbreviations: BID = twice-daily; MMF = mycophenolate mofetil
Source: Rovin et al., 2021 (14)

Table 11: Summary of methodology for AURORA 1 (AUR-VCS-2016-01; NCT03021499)

Study name	A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Orelvo (voclosporin) (23.7 mg Twice Daily) with Placebo in Achieving Renal Response in Subjects with Active Lupus Nephritis	
Study design	Phase 3, 52-week, randomised, double-blind, parallel-group, placebo-controlled, two-arm, multicentre study	
Sample size (n)	357	
Patient population(s)	Comparator	Intervention
	178	179
Intervention(s)	Voclosporin 23.7 mg BID plus MMF 1g BID and low-dose corticosteroid*	
Comparator(s)	Placebo BID plus MMF 1g BID and low-dose corticosteroid*	
Follow-up period	52 weeks	
Key eligibility criteria	Inclusion criteria	Exclusion criteria
	Key inclusion criteria: Diagnosis of SLE (per American College of Rheumatology criteria) with active LN (by kidney biopsy), and confirmation of class III, IV, V (alone or in combination with class III or IV) LN† with (UPCR of ≥1.5 mg/mg for class III and IV LN or ≥ 2 mg/mg if pure class V) ‡	**Key exclusion criteria:** eGFR ≤45 ml/min/1.73 m2 at screening • Patient required renal dialysis at screening or during the study period • Previous or planned kidney transplant during the study treatment period

	•Age 18 to 75 (or legal age of consent if >18 years) •Patient required high-dose corticosteroids and immunosuppressive therapy • Women of childbearing potential were not pregnant, and using effective contraception unless abstinent	• Patients taking or requiring any medications prohibited in the study protocol • Hypersensitivity or contraindication to MMF, MPA, CsA, corticosteroids, or any components of these drug products • Had a current or medical history of: o Malignancy within 5 years of screening with exception of BCC and SCC treated by complete excision§ o Congenital or acquired immunodeficiency o Clinically significant drug or alcohol abuse within 2 years prior to screening o Lymphoproliferative disease or previous total lymphoid irradiation o Severe viral infection (e.g., cytomegalovirus, hepatitis B virus, hepatitis C virus) within 3 months of screening; or known human immunodeficiency virus infection o Active tuberculosis or known history of tuberculosis/evidence of old tuberculosis if not taking prophylaxis with isoniazid • Other known clinically significant active medical conditions° • Overlapping autoimmune conditions which may affect study assessments/ outcomes • Vaccines using live organisms, virus, or bacteria during screening or study treatment • Patients who were pregnant, breastfeeding or not using adequate contraceptive precautions if of childbearing potential • Participation in another clinical study within 4 weeks prior to screening and/or receipt of investigational drugs within 4 weeks or 5 half-lives prior to screening • Previous treatment with voclosporin in a clinical study
Primary endpoint(s)	Complete renal response at Week 52 as adjudicated by the Clinical Endpoints Committee Complete renal response based on the following parameters: • UPCR of ≤0.5 mg/mg, and • eGFR ≥60 mL/min/1.73 m2 or no confirmed decrease from baseline in eGFR of >20%, and • Received no rescue medication for LN, and • Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44-52, just prior to the renal response assessment.	
Secondary endpoint(s)	**Hierarchical Key Secondary Endpoints:** • Time to UPCR of ≤0.5 mg/mg, • Partial renal response, defined as ≥50% reduction from baseline in UPCR, at Weeks 24 and 52 • Time to 50% reduction in UPCR from baseline • Complete renal response at Week 24 (based on definition of primary endpoint) **Other Secondary Endpoints:** • Duration of UPCR ≤0.5 mg/mg • Proportion of subjects experiencing a confirmed >30% decrease from baseline in eGFR at each time point • Change from baseline in UPCR at each time point • Change from baseline in urine protein, serum creatinine and eGFR • Change from baseline in immunology parameters (C3, C4 and anti-dsDNA) at Weeks 24 and 52 • Renal response with low-dose steroids (defined as renal response in the presence of corticosteroids of ≤2.5 mg/day between Weeks 16 to 24 and Weeks 44 to 52)	
Baseline characteristics	Baseline characteristics are presented in detail in Abbreviations: AE = adverse event; AESI = adverse events of special interest; CRR = complete renal response; CYC = cyclophosphamide; eGFR = estimated glomerular filtration rate; GCP = Good Clinical Practice; MMF = mycophenolate mofetil; ORR = ordinal renal response; PERR = primary efficacy renal response; PRR = partial renal response; SAE = serious adverse event; SLE = systemic lupus erythematosus; uPCR = urine protein creatinine ratio Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.	
Predefined subgroups	Complete renal response at Week 52 by: • Age • Gender	

- Race
- Biopsy class
- Region
- Ethnicity
- MMF use at screening and maximum MMF dose

Used in the HE model?	Yes

Note: *IV methylprednisolone (0.5 g/day for patients ≥ 45 kg, or 0.25 g/day for patients < 45 kg) once daily on days 1 and 2; followed by the commencement of oral prednisone (25 mg/day for patients ≥ 45 kg, or 20 mg/day for patients < 45 kg) on day 3. Oral prednisone was then rapidly tapered to a dose of 2.5 mg/day at Week 16, according to a protocol-specified tapering schedule. Any subsequent dose adjustments were made per investigator's discretion; †According to kidney biopsy within 2 years of screening; ‡Doubling or greater increase in UPCR in the 6 months before screening was required in patients who had a kidney biopsy > 6 months before screening; § Patients with cervical dysplasia that was cervical intraepithelial neoplasia 1 but had been treated with conization or loop electrosurgical excision procedure and had a normal repeat Papanicolaou test were Allowed; ° Severe cardiovascular disease, liver dysfunction, chronic obstructive pulmonary disease or asthma requiring steroids, bone marrow insufficiency unrelated to SLE, active bleeding disorders, or infection requiring antibiotics. A complete list of all trial endpoints and their definitions are reported in Appendix D Efficacy and safety results per study.
Abbreviations: anti-dsDNA = anti-double-stranded deoxyribonucleic acid; BCC = basal cell carcinoma; BID = twice-daily; CsA = ciclosporin; eGFR = estimated glomerular filtration rate; IV = intravenous; LN = lupus nephritis; MMF = mycophenolate mofetil; MPA = mycophenolic acid; SCC = squamous cell carcinoma; SLE = systemic lupus erythematosus; UPCR = urine protein creatinine ratio

7.1.1.1.1 Efficacy and safety

AURORA 1 assessed the efficacy and safety of voclosporin compared with placebo in achieving complete renal response after 52 weeks of therapy in patients with active LN. A total of 357 eligible patients were randomised into two groups with well-balanced demographic characteristics: 178 in the placebo arm and 179 in the voclosporin arm. The study met its primary objective, demonstrating that treatment with voclosporin results in a clinically meaningful and statistically significant higher renal response rate compared to placebo.

7.1.1.1.1.1 Complete Renal Response at Week 52 (primary endpoint)

In AURORA 1, significantly more patients treated with voclosporin than with placebo achieved a CRR at Week 52 (73 (40.8%) vs 40 (22.5%) patients; OR 2.65; (95% CI 1.6, 4.3); p<0.0001) (14). The absolute difference between groups for achieving a CRR was 18% in favour of voclosporin; therefore, the number-needed-to-treat with voclosporin is 6 individuals with active LN (14).

Logistic regression analyses for each individual component of response (UPCR ≤0.5 mg/mg, eGFR success, no rescue medication, no withdrawal prior to assessment and not more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days during the 8 weeks prior to assessment) showed that UPCR ≤0.5 mg/mg was the only significant factor in the observed difference in renal response between the two treatment arms (odd ratios for comparisons from Month 6 to 36 ranging between 2.49 and 1.66; p values of 0.002 to 0.071) (Table 12).

Table 12: AURORA 1 Summary of CRR (primary endpoint) and composites of CRR

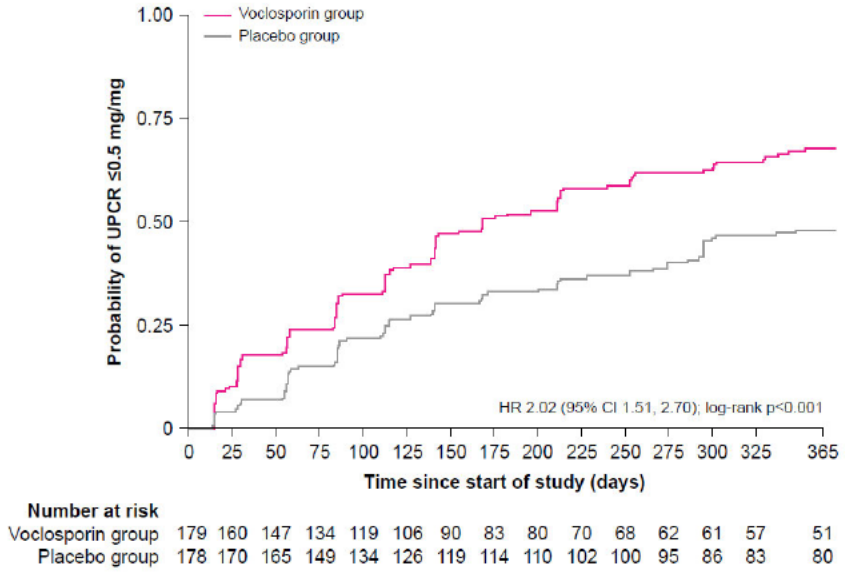
	Patients, n (%)		OR (95% CI)	p-value
	Voclosporin n=179	Placebo n=178		
Primary endpoint: CRR at 52 weeks	73 (40.8)	40 (22.5)	2.65 (1.6, 4.3)	<0.0001
Composites of CRR*				
UPCR ≤ 0.5 mg/mg*	81 (45.2)	41 (23.0)	3.11 (1.9, 5.0)	<0.001
eGFR ≥ 60, eGFR < 60 with no confirmed decrease of > 20%, or eGFR < 60 with confirmed decrease of > 20% but with no disease-related or treatment-related eGFR associated AE present at time of assessment*	147 (82.1)	135 (75.8)	1.50 (0.9, 2.5)	0.129
Received no rescue medication for LN*	163 (91.1)	154 (86.5)	1.62 (0.8, 3.2)	0.164
Did not receive > 10 mg/day prednisone for ≥ 3 consecutive days or for ≥ 7 days in total during Weeks 44 through 52*	156 (87.2)	152 (85.4)	1.26 (0.7, 2.3)	0.465

Note: The binary endpoint analyses were conducted on the ITT population using a logistic regression model with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region, and response (Yes/No) at as the response variables (135).
Footnote: * Based on logistic regression analysis for each individual component of CRR.
Abbreviations: AE = adverse event; CI = confidence interval; CRR = complete renal response; eGFR = estimated glomerular filtration rate; LN = lupus nephritis; OR = odds ratio; UPCR = urine protein creatinine ratio
Source: Otsuka 2020 (136); Rovin et al., 2021 (14)

7.1.1.1.1.2 Time to UPCR of ≤0.5 mg/mg (secondary endpoint)

More patients in the voclosporin arm achieved UPCR ≤0.5 mg/mg vs. the placebo arm, (64.8% vs 43.8%) and the time to UPCR ≤0.5 mg/mg was also significantly shorter with voclosporin (median time: 169 days vs 372 days; HR 2.0; (95% CI: 1.5, 2.7) ; p<0.001; Figure 3) (14).

Figure 3: AURORA 1 Probability of UPCR of ≤0.5 mg/mg



Note: Time-to-event was estimated using Kaplan-Meier methodology and analysed by comparing the survivor function between treatment arms. A Cox's proportional hazards model was performed to assess the significance of the differences between treatment arms. The model included terms for treatment, baseline UPCR, biopsy class, and MMF use at baseline.
Abbreviations: CI = confidence interval; HR = hazard ratio; UPCR = urine protein creatinine ratio; Percentiles are Kaplan-Meier estimates.
Source: Rovin et al., 2021 (14)

7.1.1.1.1.3 Partial Renal Response at Weeks 24 and 52 (secondary endpoint)

Consistent with the results for renal response, more patients in the voclosporin arm achieved a PRR (defined as a 50% reduction from baseline in UPCR) at Week 24 and Week 52 (Table 13). In both arms, PRR was achieved by Week 24 in the majority of patients who responded. The response rate of approximately 50% in the placebo arm demonstrates that the MMF and steroid regimen used in the study is effective in reducing UPCR; however, a greater number of patients responded in the voclosporin arm.

Table 13: PRR at Weeks 24 and 52

	Voclosporin n=179	Placebo n=178	OR (95% CI)	p-value
PRR at 24 weeks, n (%)	126 (70)	89 (50)	2.43 (1.56, 3.79)	< 0.001
PRR at 52 weeks, n (%)	125 (70)	92 (52)	2.26 (1.45, 3.51)	< 0.001

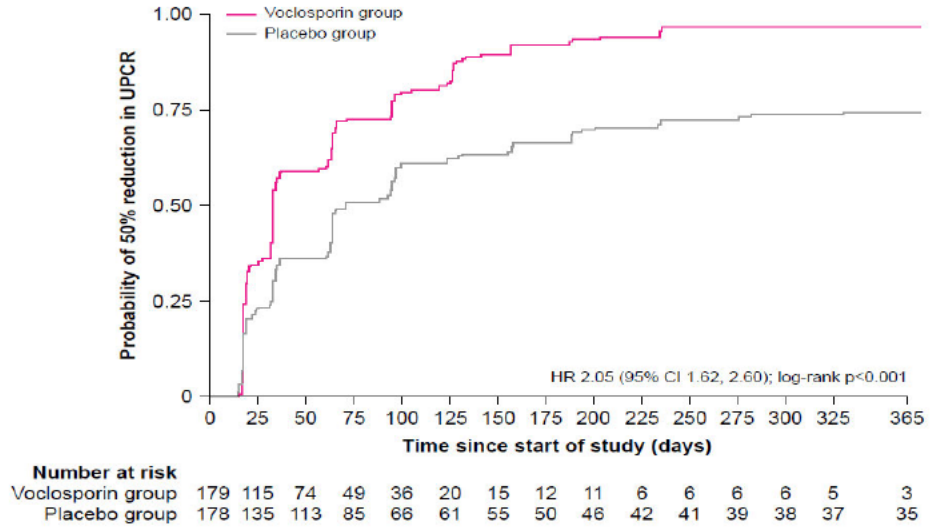
Note: The binary endpoint analyses were conducted on the ITT population using a logistic regression model with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region, and response (Yes/No) at as the response variables (135).
Abbreviations: CI = confidence interval; OR = odds ratio; PRR = partial renal response

7.1.1.1.1.4 Time to 50% Reduction in UPCR (secondary endpoint)

A 50% reduction in UPCR from baseline at any time during the study was achieved by 96.6% of patients treated with voclosporin compared with 75.8% of patients receiving placebo. The time taken to reach a 50% reduction in UPCR was significantly shorter for the voclosporin arm than the placebo arm (HR 2.05; 95% CI: 1.6, 2.6; p<0.001). Median time to 50% reduction in UPCR was 29 days for voclosporin vs. 63 days for placebo. Similar results were seen when using the lowest available pre-dose UPCR measurement as baseline (14). Consistent with the time to UPCR ≤0.5 mg/mg, the difference between the two treatment arms in the time to 50% reduction in UPCR was apparent within the first month of treatment and was sustained throughout the study (Figure 4). The Kaplan-Meier curve shows that a small number of patients in the

placebo arm achieved a 50% reduction in UPCR late in the study (beyond Day 350). However, most patients in the voclosporin arm achieved this response earlier; 6 and 38 patients were classed as still "at risk" beyond Day 300 in the voclosporin arm and the placebo arm, respectively. Significantly greater reductions from baseline in UPCR were achieved in the voclosporin arm compared with the placebo arm at every time point.

Figure 4: AURORA 1: Probability of ≥ 50% Reduction from Baseline in UPCR



Note: Time-to-event was estimated using Kaplan-Meier methodology and analysed by comparing the survivor function between treatment arms. A Cox's proportional hazards model was performed to assess the significance of the differences between treatment arms. The model included terms for treatment, baseline UPCR, biopsy class, and MMF use at baseline.
Abbreviations: CI = confidence interval; HR = hazard ratio; UPCR = urine protein creatinine ratio.
Source: Rovin et al., 2021 (14)

7.1.1.1.1.5 Disease activity (secondary endpoint)

Changes from baseline in disease activity were measured using the Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) instrument (136). The SELENA-SLEDAI instrument objectively measures disease activity within the past 10 days by scoring 24 different disease activity descriptors (137). Higher scores indicate a greater degree of disease activity, and the maximum theoretical score is 105 (all predictors are present). Improvements (i.e., decreases from baseline) in mean SELENA-SLEDAI index scores were observed in both treatment groups. Although numerically greater decreases from baseline were seen with voclosporin, there was no statistically significant difference between voclosporin and placebo (Table 14).

Table 14: Change in SELENA-SLEDAI Index Score from baseline

Visit (n/n)	Mean difference (95% CI)		Mean difference vs placebo (95% CI)	p-value
	Voclosporin n=179	Placebo n=178		
Week 24 (167/172)	-4.5 (-5.4, -3.7)	-4.1 (-5.0, -3.2)	-0.5 (-1.6, 0.6)	0.375
Week 52 (150/160)	-6.0 (-6.7, -5.2)	-5.5 (-6.3, -4.7)	-0.5 (-1.4, 0.4)	0.277

Note: SELENA-SLEDAI score was analysed using a mixed effect model repeated measures analysis with treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region, and baseline UPCR included as covariates in the model.
Abbreviations: CI = confidence interval; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index
Source: Otsuka 2020 (136)

7.1.1.1.1.6 Patient-reported outcomes

Improvements (i.e., increases) in mean scores from baseline were seen in both the voclosporin and the placebo arm for the HRQoL assessments 36-Item Short Form Survey (SF-36) and for the health-related domains of the LupusPRO assessment

(136). Smaller changes were seen in both arms for the non-health-related domains of the LupusPRO assessment. There was no significant difference in the degree of improvement between the two treatments.

7.1.1.1.1.7 Subgroup analyses

Methodology and statistical analysis

The primary endpoint of CRR at Week 52 was analysed for the following pre-specified subgroups (136):

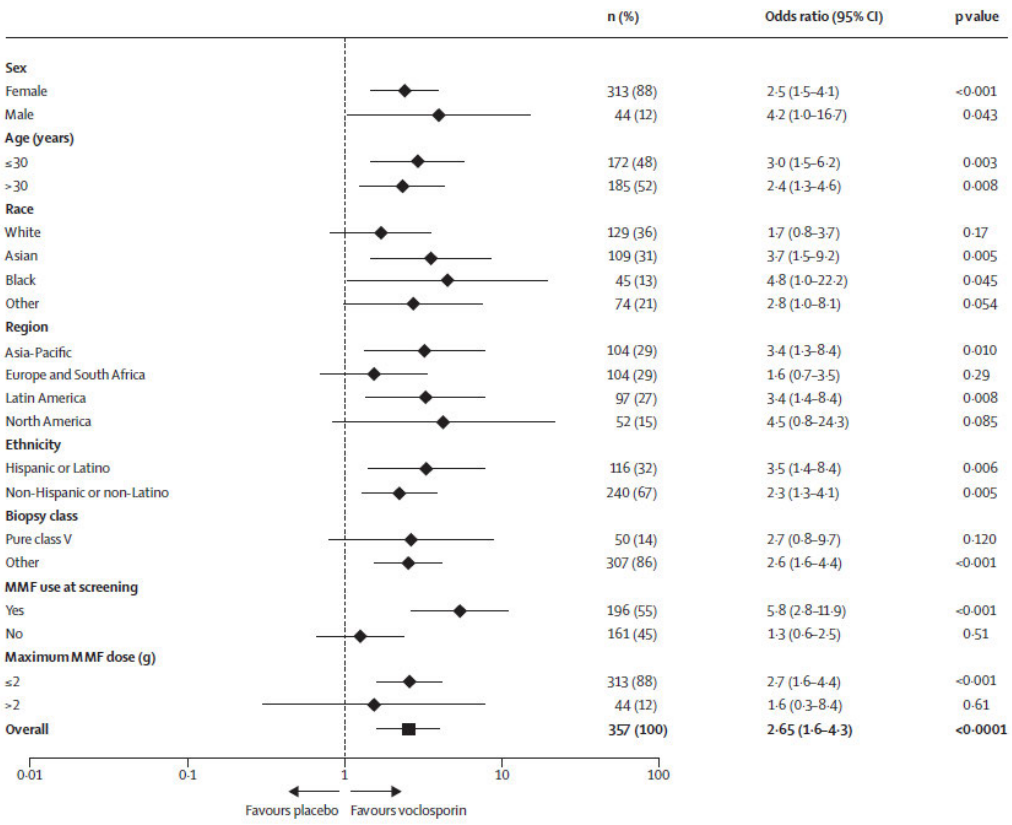
- Age (≤30 vs >30 years)
- Gender (male, female)
- Race (White, Asian, other)
- Biopsy class (class V, other)
- Region (Asia-Pacific, Europe and South Africa, Latin America, North America)
- Ethnicity (Hispanic or Latino and Non-Hispanic or non-Latino)
- MMF use at screening (yes, no)
- Maximum MMF dose (≤2 g vs >2 g)

Prespecified covariate analyses were done using a logistic regression model. An interaction between the subgroup and treatment group was added to the model, and a p-value for the main effect of the covariate in question along with the p-value for the interaction between treatment and covariate were reported (136):

Results of subgroup analyses

The treatment benefit of voclosporin was seen in all pre-specified subgroups (136) (Figure 5) . Although the study was not powered to detect a significant difference between the two treatments in the individual subgroups, statistically significant results were observed for many subgroups, confirming the positive effect of voclosporin in achieving renal response. Where the results were not statistically significant (White, pure Class V, Europe + South Africa, North America, no MMF at screening and maximum MMF dose >2 g), the odds ratios still favoured voclosporin over placebo (136).

Figure 5 Aurora 1 - predefined subgroup forest plot



Abbreviations: Ci = confidence interval; MMF = mycophenolate
Source: Otsuka 2020 (136)

7.1.1.1.1.8 Adverse events

Overall and serious AEs occurred at similar frequencies in both treatment groups, and most AEs were of mild or moderate intensity (Table 15) (14). The most frequent type of AE in both groups was infections and infestations, which is expected in this immunocompromised patient population (136).

Table 15: AURORA 1: summary of AEs

	TEAEs		Treatment-related TEAEs	
	Voclosporin (n=178)	Placebo (n=178)	Voclosporin (n=178)	Placebo (n=178)
AEs, n (%)	162 (91.0)	158 (88.8)	80 (44.9)	45 (25.3)
Serious	37 (20.8)	38 (21.3)	8 (4.5)	8 (4.5)
Leading to discontinuation	20 (11.2)	26 (14.6)	NR	NR
Leading to death	0	3 (1.7)	0	0

Abbreviations: AE = adverse event; n = number of patients; NR = not reported; TEAE = treatment-emergent adverse event
Source: Otsuka 2020 (136)

Commonly reported adverse events

Approximately 90% of patients in both arms experienced at least one TEAE (voclosporin arm: 162 (91.0%); placebo arm: 158 (88.8%) (Table 16). The most common TEAEs in both groups were Infections and Infestations, reported by 64.6% of patients in the voclosporin arm and 56.7% of patients in the placebo arm. The most frequent infections in both arms were upper respiratory tract infections (URTIs) and urinary tract infections (UTIs). The majority of infections were of mild or moderate intensity; severe infections (predominantly pneumonia), were recorded in 10 patients (5.6%) in the voclosporin arm and 7 patients (3.9%) in the placebo arm (136). Known side effects of MMF use include diarrhoea, nausea, vomiting and dyspepsia. Gastrointestinal Disorders were the second most common TEAEs. More gastrointestinal events were recorded in patients in the voclosporin arm than in the placebo arm (46.6% vs 34.3%), particularly diarrhoea and abdominal pain/upper abdominal pain (136).

Known adverse effects of CNIs, such as diabetes, kidney dysfunction and hypertension, were also of particular interest in this study (14, 136). New onset diabetes did not occur in any voclosporin-treated patients and in 1 placebo-treated patient (14), the incidence of investigator-reported serious renal dysfunction was low and similar between treatment groups (voclosporin, 3%; placebo, 2%) (14), and overall, there was no significant difference in mean blood pressure between the treatment groups (14). Treatment-related TEAEs were reported in 44.9% and 25.3% of patients in the voclosporin and placebo arms, respectively. The majority of treatment-related TEAEs were of mild or moderate intensity, with severe events recorded in 12 patients (6.7%) in the voclosporin arm and two patients (1.1%) in the placebo arm. The most common treatment-related TEAE was glomerular filtration rate (GFR) decreased (24.2% vs 8.2%, respectively) (136). Hemodynamically mediated decreases in GFR are known to be associated with CNIs and so this outcome was not unexpected. Vascular disorders (predominantly hypertension) and renal and urinary disorders were also considered treatment-related in a greater proportion of patients in the voclosporin arm than in the placebo arm (hypertension: 7.3% vs 1.7%, respectively; renal and urinary disorders: 4.4% vs 1.7%, respectively) (136).

Table 16: AURORA 1 - Most common TEAEs (occurring in ≥ 4% of patients in any group)

System organ class (Preferred term)	Voclosporin, n=178	Placebo, n=178
Any TEAE, n (%)	162 (91.0)	158 (88.8)
Infections and infestations	115 (64.6)	101 (56.7)
Upper respiratory tract infection	31 (17.4)	26 (14.6)
Viral upper respiratory tract infection	20 (11.2)	18 (10.1)
Urinary tract infection	19 (10.7)	13 (7.3)
Herpes zoster	14 (7.9)	9 (5.1)
Influenza	12 (6.7)	10 (5.6)
Gastroenteritis	9 (5.1)	10 (5.6)
Pneumonia	9 (5.1)	11 (6.2)
Bronchitis	3 (1.7)	10 (5.6)

Pharyngitis	3 (1.7)	9 (5.1)
Gastrointestinal disorders	83 (46.6)	61 (34.3)
Diarrhoea	34 (19.1)	22 (12.4)
Abdominal pain upper	13 (7.3)	1 (0.6)
Abdominal pain	10 (5.6)	2 (1.1)
Nausea	10 (5.6)	17 (9.6)
Dyspepsia	10 (5.6)	3 (1.7)
Vomiting	5 (2.8)	12 (6.7)
Investigations and infestations	60 (33.7)	31 (17.4)
GFR decreased	43 (24.2)	15 (8.4)
Nervous system disorders	47 (26.4)	27 (15.2)
Headache	30 (16.9)	11 (6.2)
Skin and subcutaneous tissue disorders	42 (23.6)	31 (17.4)
Alopecia	10 (5.6)	5 (2.8)
Musculoskeletal and connective tissue disorders	40 (22.5)	46 (25.8)
Systemic lupus erythematosus	8 (4.5)	10 (5.6)
Arthralgia	8 (4.5)	17 (9.6)
Vascular disorders	38 (21.3)	23 (12.9)
Hypertension	36 (20.2)	15 (8.4)
General disorders and administration site conditions	36 (20.2)	32 (18.0)
Oedema peripheral	11 (6.2)	11 (6.2)
Blood and lymphatic system disorders	35 (19.7)	29 (16.3)
Anaemia	21 (11.8)	10 (5.6)
Neutropenia	8 (4.5)	6 (3.4)
Leukopenia	7 (3.9)	10 (5.6)
Respiratory, thoracic, and mediastinal disorders	26 (14.6)	17 (9.6)
Cough	13 (7.3)	3 (1.7)
Renal and urinary disorders	26 (14.6)	37 (20.8)
Renal impairment	13 (7.3)	6 (3.4)
Lupus nephritis	2 (1.1)	12 (6.7)
Proteinuria	0 (0.0)	8 (4.5)
Metabolism and nutritional disorders	25 (14.0)	37 (20.8)
Hypokalaemia	3 (1.7)	10 (5.6)

Abbreviations: GFR = glomerular filtration rate; TEAE = treatment-emergent adverse event
Source: Otsuka 2020 (136); Rovin et al., 2021 (14)

Serious adverse events

A similar proportion of patients in each arm experienced serious TEAEs (voclosporin arm: 37 [20.8%]; placebo arm: 38 [21.3%]) (14),(136). The most common serious TEAEs (reported in ≥2 patients in any treatment group) are summarised in Table 17. Serious treatment-related TEAEs were observed in the same number of patients in each treatment group (voclosporin arm: 8 (4.5%); placebo arm: 8 (4.5%)) (136). Serious treatment-related TEAEs are summarised in Table 18

Abbreviations: TEAE = treatment-emergent adverse event
Source: Otsuka 2020 (136)

Table 17: AURORA 1 - Common TEAEs

System organ class (Preferred term)	Voclosporin n=178	Placebo n=178
Any serious TEAE, n (%)	37 (20.8)	38 (21.3)
Infections and infestations	18 (10.1)	20 (11.2)
Pneumonia	7 (3.9)	8 (4.5)
Gastroenteritis	3 (1.7)	0 (0.0)
Urinary tract infection	2 (1.1)	1 (0.6)
Pyelonephritis acute	1 (0.6)	1 (0.6)
Upper respiratory tract infection	1 (0.6)	1 (0.6)
Bronchitis	0 (0.0	3 (1.7)
Renal and urinary disorders	8 (4.5)	8 (4.5)
Acute kidney injury	4 (2.2)	2 (1.1)
Renal impairment	2 (1.1)	1 (0.6)
Lupus nephritis	1 (0.6)	4 (2.2)
Renal failure	1 (0.6)	1 (0.6)

Blood and lymphatic system disorders	4 (2.2)	0 (0.0)
Anaemia	3 (1.7)	0 (0.0)
Vascular disorders	4 (2.2)	3 (1.7)
Hypertension	3 (1.7)	1 (0.6)
Hypertensive crisis	1 (0.6)	2 (1.1)
Musculoskeletal and connective tissue disorders	3 (1.7)	4 (2.2)
Systemic lupus erythematosus	3 (1.7)	3 (1.7)
Investigations	2 (1.1)	1 (0.6)
Glomerular filtration rate decreased	1 (0.6)	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	1 (0.6)	2 (1.1)
Pleural effusion	1 (0.6)	1 (0.6)
General disorders and administration site conditions	1 (0.6)	1 (0.6)
Generalised oedema	1 (0.6)	1 (0.6)

Note: *including cysts and polyps
Abbreviations: TEAE = treatment-emergent adverse event
Source: Otsuka 2020 (136)

Table 18: AURORA 1 - Serious treatment-related TEAEs

System organ class (Preferred term)	Voclosporin n=178	Placebo n=178
Any serious treatment-related TEAE, n (%)	8 (4.5)	8 (4.5)
Infections and infestations	4 (2.2)	6 (3.4)
Pneumonia	1 (0.6)	2 (1.2)
Upper respiratory tract infection	1 (0.6)	1 (0.6)
Acute sinusitis	0 (0.0)	1 (0.6)
Lung abscess	0 (0.0)	1 (0.6)
Pyeloneprhritis acute	0 (0.0)	1 (0.6)
Bronchitis	1 (0.6)	0 (0.0)
Herpes zoster disseminated	1 (0.6)	0 (0.0)
Pyelonephritis	1 (0.6)	0 (0.0)
Renal and urinary disorders	2 (1.2)	1 (0.6)
Renal impairment	1 (0.6)	1 (0.6)
Acute kidney injury	1 (0.6)	0 (0.0)
Vascular disorders	2 (1.2)	0 (0.0)
Hypertension	2 (1.2)	0 (0.0)
Blood and lymphatic system disorders	1 (0.6)	0 (0.0)
Anaemia	1 (0.6)	0 (0.0)
Neoplasms benign, malignant and unspecified*	1 (0.6)	0 (0.0)
Schwannoma	1 (0.6)	0 (0.0)

Note: *including cysts and polyps
Abbreviations: TEAE = treatment-emergent adverse event
Source: Otsuka 2020 (136)

Deaths

Mortality was lower in the voclosporin group of this study (Table 15). Three placebo-treated patients died as a result of TEAEs (pneumonia; pneumonia and septic shock; LN). An additional two patients in the placebo group and one patient in the voclosporin group died due to AEs that started more than 30 days after the last dose of study drug. None of the events leading to death was considered by the investigators to be related to the study treatment (136).

Adverse events leading to treatment discontinuation

A similar proportion of patients in the voclosporin and placebo arm had their study treatment discontinued as a result of a TEAE; 20 patients (11.2%) in the voclosporin arm and 26 patients (14.6%) in the placebo arm had their study drug discontinued as a result of a TEAE, most commonly this was due to Renal and Urinary Disorders (136). A summary of the most common TEAEs leading to treatment discontinuation is presented in Table 19.

Table 19: AURORA 1 - Most common TEAEs leading to treatment discontinuation (in ≥2% of patients in any group)

System organ class (Preferred term)	Voclosporin n=178	Placebo n=178
Any TEAE leading to permanent study drug discontinuation, n (%)	20 (11.2)	26 (14.6)

Renal and urinary disorders	8 (4.5)	15 (8.4)
Renal impairment	4 (2.2)	4 (2.2)
Lupus nephritis	2 (1.1)	5 (2.8)
Proteinuria	0 (0.0)	4 (2.2)
Investigations	4 (2.2)	4 (2.2)
Glomerular filtration rate decreased	3 (1.7)	4 (2.2
Infections and infestations	3 (1.7)	4 (2.2)
Pneumonia	1 (0.6)	2 (1.1)
Vascular disorders	2 (1.1)	0 (0.0)
Hypertension	2 (1.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (0.6)	2 (1.1)
Systemic lupus erythematosus	1 (0.6)	2 (1.1)

Abbreviations: TEAE = treatment-emergent adverse event
Source: Otsuka 2020 (136)

Adverse events leading to dose interruption or modification

More patients in the voclosporin arm (80 patients (44.9%)) than in the placebo arm (47 patients (26.4%)) had their dose of the study drug modified as a result of a TEAE (136). As expected for a CNI, the most common TEAE leading to dose modification was GFR decreased (reported for 40 patients (22.5%) in the voclosporin arm and 11 patients [6.2%] in the placebo arm (136). However, only 3 patients in the voclosporin arm and 4 in the placebo arm had their treatment permanently discontinued as a result of decreased GFR (Table 19). Serious TEAEs resulting in study drug dose modifications were reported for 19 patients (10.7%) in the voclosporin arm and 15 patients (8.4%) in the placebo arm; these were predominantly infections (in 11 voclosporin patients (6.2%) and 10 placebo patients (5.6%)). A summary of the most common TEAEs leading to dose modification is summarised in Table 20.

Table 20: AURORA 1 - Most common TEAEs leading to dose modification (in ≥2% of patients in any group)

System organ class (Preferred term)	Voclosporin n=178	Placebo n=178
Any TEAE leading to dose modification, n (%)	80 (44.9)	47 (26.4)
Investigations	43 (24.2)	11 (6.2)
Glomerular filtration rate decreased	40 (22.5)	11 (6.2)
Infections and infestations	23 (12.9)	24 (13.5)
Gastroenteritis	5 (2.8)	2 (1.1)
Herpes zoster	5 (2.8)	1 (0.6)
Upper respiratory tract infection	4 (2.2)	3 (1.7)
Pneumonia	4 (2.2)	5 (2.8)
Bacterial diarrhoea	2 (1.1)	1 (0.6)
Viral upper respiratory tract infection	1 (0.6)	2 (1.1)
Bronchitis	0 (0.0)	3 (1.7)
Influenza	0 (0.0)	2 (1.1)
Gastrointestinal disorders	10 (5.6)	7 (3.9)
Diarrhoea	3 (1.7)	2 (1.1)
Nausea	3 (1.7)	1 (0.6)
Gastritis	2 (1.1)	0 (0.0)
Renal and urinary disorders	9 (5.1)	3 (1.7)
Renal impairment	7 (3.9)	1 (0.6)
Blood and lymphatic system disorders	5 (2.8)	1 (0.6)
Leukopenia	2 (1.1)	1 (0.6)
Anaemia	2 (1.1)	0 (0.0)
Neutropenia	2 (1.1)	0 (0.0)
Nervous system disorders	5 (2.8)	1 (0.6)
Headache	2 (1.1)	0 (0.0)
Migraine	2 (1.1)	0 (0.0)
Vascular disorders	4 (2.2)	0 (0.0)
Hypertension	3 (1.7)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (1.1)	2 (1.1)
Systemic lupus erythematosus	2 (1.1)	2 (1.1)

Abbreviations: TEAE = treatment-emergent adverse event
Source: Otsuka 2020 (136)

Adverse events of special interest

The commonly known adverse effects of the CNIs ciclosporin and tacrolimus include kidney dysfunction, hypertension, electrolyte disturbances, tremor, and diabetes. Therefore, these events were of particular interest in this study (136). Hypertension occurred at a higher incidence in the voclosporin arm (20.2% vs 8.4% for placebo) (136). Consistent with the protocol guidance to maintain normal blood pressure through the use of antihypertensives, more patients in the voclosporin arm than the placebo arm were prescribed calcium channel blockers (33% vs 21%) and beta-blockers (18% vs 11%) during the study; a similar proportion of patients in each arm (32% and 30%, respectively) were treated with diuretics. The majority of hypertension events were mild or moderate. Overall, there was no significant difference in mean blood pressure between the treatment groups.

No voclosporin-treated patients recorded TEAEs of diabetes or hyperglycaemia (vs one of each event in the placebo arm) (14). A total of 18 (10%) patients in each treatment group had a confirmed eGFR decrease (prespecified as a > 30% decrease from baseline) at any time throughout the study. Only 2% of patients in each treatment group discontinued study drug due to eGFR decrease, which suggests that the eGFR decreases were largely reversible in both treatment groups (14). Incidence of investigator-reported serious renal dysfunction was low and similar between treatment groups (voclosporin, 3%; placebo, 2%). Mean systolic blood pressure increased by 3.9 mmHg in the voclosporin group at week 2 and returned to baseline levels by week 8.

AURORA 1 safety conclusions

Voclosporin was well tolerated in the AURORA 1 study with no new or unexpected safety signals observed (136). Three placebo patients died as a result of TEAEs. An additional two patients in the placebo group and one patient in the voclosporin group died due to AEs which started more than 30 days after the last dose of study drug. A similar proportion of patients in each arm experienced serious TEAEs (20.8% in the voclosporin arm and 21.3% in the placebo arm) or had their study treatment discontinued as a result of a TEAE (11.2% and 14.6%, respectively).

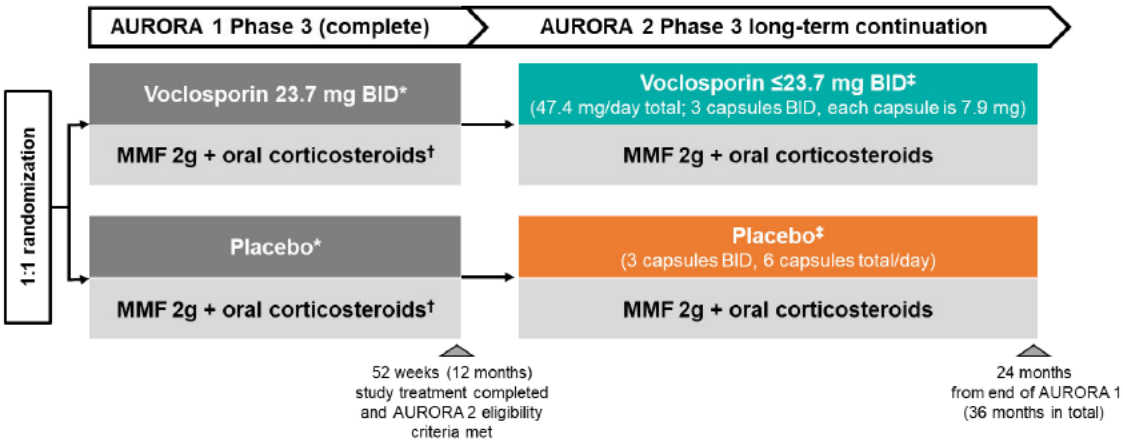
The safety profile of voclosporin was comparable with that of the placebo on a background of MMF and low-dose steroids in this 52-week trial. The AEs observed in both treatment groups were as expected for the population and treatment regimen (14).

7.1.1.2 AURORA 2 Phase 3 long-term continuation study

AURORA 2 is a Phase 3, multicentre, double-blind, placebo-controlled, randomised, 24-month long-term continuation study to the AURORA 1 study. Patients who completed 52 weeks of study drug treatment in the AURORA 1 study and met eligibility criteria were allowed to continue long-term treatment as part of the AURORA 2 study.

The primary objective of AURORA 2 was to assess the long-term safety and tolerability of voclosporin compared to placebo for up to an additional 24 months following completion of treatment in the AURORA 1 study in patients with LN. All patients will continue to receive background therapy of MMF and oral corticosteroids, if applicable, starting at the same dose as at the end of the AURORA 1 study. The secondary objective was to assess the long-term efficacy of voclosporin compared to placebo for up to an additional 24 months following completion of treatment in the AURORA 1 study in patients with LN.

Figure 6: Trial design - AURORA 2



Note: *Patients in the voclosporin arm were randomised to receive 47.4 mg/day total; 3 capsules BID (each capsule is 7.9 mg), while patients in the placebo arm received 3 placebo capsules BID (i.e., 6 capsules total per day); †Oral corticosteroids were tapered per protocol; ‡Target doses are presented; however, patients enrolled onto AURORA 2 are initiated on the same dose of study treatment, MMF, and oral corticosteroids as received at the end of the AURORA 1 study

Abbreviations: BID = twice-daily; MMF = mycophenolate mofetil

Source: Otsuka et al., 2018;(138) Rovin et al., 2021(14, 138)

Table 21: Trial design - AURORA 2

Study name		Aurinia Renal Response in Lupus with Voclosporin (AURORA 2)
Study design		Phase 3 long-term continuation, multicentre, double-blind, placebo-controlled, randomised trial
Sample size (n)		216 patients
Patient population(s)	Comparator 116	Intervention 100
Intervention(s)		Oral voclosporin 23.7 mg BID plus MMF 1g BID and low-dose corticosteroid (oral prednisone 2.5 mg/day)
Comparator(s)		Oral placebo BID plus MMF 1g BID and low-dose corticosteroid* (oral prednisone 2.5 mg/day)
Follow-up period		24 months (from end of AURORA 1 (36 months in total))
• Inclusion: Completed 52 weeks of treatment with study drug in AURORA 1, including patients who had a temporary interruption and successfully restarted study drug during AURORA 1		• Exclusion: Patient requires or expected to require renal dialysis or kidney transplant during study period
Primary endpoint(s)		AEs and routine biochemical and haematological assessments
Secondary endpoint(s)		• CRR at Week 24 • PRR • Renal and extra-renal flares • SELENA-SLEDAI score change from AURORA 1 baseline • UPCR, eGFR, urine protein, and serum creatinine change from AURORA 1 baseline • HRQoL (SF-36) change from AURORA 1 baseline
Baseline characteristics		Baseline characteristics are presented in detail in Abbreviations: AE = adverse event; AESI = adverse events of special interest; CRR = complete renal response; CYC = cyclophosphamide; eGFR = estimated glomerular filtration rate; GCP = Good Clinical Practice; MMF = mycophenolate mofetil; ORR = ordinal renal response; PERR = primary efficacy renal response; PRR = partial renal response; SAE = serious adverse event; SLE = systemic lupus erythematosus; uPCR = urine protein creatinine ratio Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.
Used in the health economic model?		Yes

Abbreviations: AE = adverse event; BID = twice-daily; CRR = complete renal response; eGFR = estimated glomerular filtration rate; HRQoL = health-related quality of life; MMF = mycophenolate mofetil; PRR = partial renal response; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index; SF-36 = 36-Item Short Form Survey; UPCR = urine protein creatinine ratio

7.1.1.2.1 Efficacy and safety

AURORA 2 assessed the long-term safety, tolerability and efficacy of voclosporin compared with placebo for an additional 24 months following completion of treatment in the AURORA 1 study. A total of 216 eligible patients were analysed according to the treatment they were randomised to in the AURORA 1 study (n=100 in the placebo arm; n=116 in the voclosporin arm) (15). AURORA 2 results reflected similar findings to AURORA 1, demonstrating favourable efficacy of voclosporin compared with placebo and a tolerable safety profile (15).

7.1.1.2.1.1 Complete renal response (secondary endpoint)

At months 18, 24, 30 and 36 during AURORA 2, the proportion of patients achieving CRR was higher in the voclosporin arm compared with the placebo arm (Table 22) (15). Despite the study not being powered to measure statistical significance, a significant and clinically meaningful difference ($p<0.05$) from placebo was observed at every time point except the 36-month assessment ($p=0.051$) (15). In particular, voclosporin demonstrated significantly greater CRR than placebo at month 18 (63.8% vs 46.0%; OR 2.19 (95% CI 1.25–3.83); $p=0.006$), month 24 (56.0% vs 43.0%; OR 1.81 (95% CI 1.04–3.16); $p=0.035$), and month 30 (59.5% vs 42.0%; OR 2.24 (95% CI 1.28–3.92); $p=0.005$) (15).

Table 22: CRR at months 18 to 36

	Patients, n (%)		OR (95% CI)	p-value
	Voclosporin n=116	Placebo n=100		
CRR at 18 months	74 (63.8)	46 (46.0)	2.19 (1.25, 3.83)	0.006
CRR at 24 months	65 (56.0)	43 (43.0)	1.81 (1.04, 3.16)	0.035
CRR at 30 months	69 (59.5)	42 (42.0)	2.24 (1.28, 3.92)	0.005
CRR at 36 months	59 (50.9)	39 (39.0)	1.74 (1.00, 3.03)	0.051

Note: The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region. Subjects who withdrew from the study prior to the visit assessments and thus provide insufficient visit data were defined as non-responders.
Abbreviations: CI = confidence interval; CRR = complete renal response; OR = odds ratio
Source: AURORA 2 CSR (15)

7.1.1.2.1.2 Partial renal response (secondary endpoint)

A greater proportion of patients in the voclosporin arm also experienced PRR compared with patients in the placebo arm across all time points (defined as a 50% reduction from baseline in UPCR) (Table 23) (15). As observed in AURORA 1, the high response rate in the placebo arm demonstrates that the MMF and steroid regimen used in the study is effective in reducing UPCR (15). Despite this, voclosporin demonstrated significantly greater PRR than placebo at month 18 (82.8% vs 68.0%; OR 2.50 (95% CI 1.28–4.88); $p=0.008$), month 24 (77.6% vs 58.0%; OR 2.68 (95% CI 1.46–4.91); $p=0.001$), and month 30 (73.3% vs 61.0%; OR 1.86 (95% CI 1.03–3.34); $p=0.040$) (15).

Table 23: PRR at months 18 to 36

	Voclosporin n=116	Placebo n=100	OR (95% CI)	p-value
PRR at 18 months, n (%)	96 (82.8)	68 (68.0)	2.50 (1.28, 4.88)	0.008
PRR at 24 months, n (%)	90 (77.6)	58 (58.0)	2.68 (1.46, 4.91)	0.001
PRR at 30 months, n (%)	85 (73.3)	61 (61.0)	1.86 (1.03, 3.34)	0.040
PRR at 36 months, n (%)	86 (74.1)	69 (69.0)	1.39 (0.75, 2.58)	0.290

Note: The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region. Subjects who withdrew from the study prior to the visit assessments and thus provide insufficient visit data were defined as non-responders.
Abbreviations: CI = confidence interval; OR = odds ratio; PRR = partial renal response
Source: AURORA 2 CSR(15)

7.1.1.2.1.3 Renal flares (secondary endpoint)

To be considered to have experienced a renal flare, patients must first achieve an adequate renal response (15). Over the three-year course of the study, a greater proportion of patients in the voclosporin arm were considered to have an adequate

renal response than those in the placebo arm (87.1% vs. 73.0%, respectively) (15). Among these patients, a slightly lower proportion of patients experienced a renal flare in the voclosporin arm compared to the placebo arm (23.8% vs 26.0%, respectively) (Table 24). Although a statistically significant difference could not be demonstrated between treatment arms, this may in part be due to the fact that AURORA 2 was not powered to demonstrate a significant difference in renal flare rates and few renal flare events were observed in either arm over the three year treatment period (15).

When analysed on a year-by-year basis throughout the study period, the greatest difference in renal flare rate was observed during the first year of treatment; with fewer patients experiencing renal flares in the voclosporin arm compared with the placebo arm (6.5% vs 14.5%, respectively; OR 0.35 (95% CI 0.11–1.07); p=0.066) (15). In years two and three of treatment, renal flares were similar between the voclosporin and placebo arms (Table 24) (15).

Table 24: Patients with adequate response and renal flares over the three-year AURORA 1 and AURORA 2 study period

		Voclosporin n (%) n=116	Placebo n (%) n=100	OR (95% CI)	p-value
Overall (AURORA 1 baseline [Month 0] to Month 36)	Patients with adequate response*	101 (87.1)	73 (73.0)	0.85 (0.42, 1.73)	0.662
	Patients with renal flares	24 (23.8)	19 (26.0)		
Year 1 (Months 0–12)	Patients with adequate response	93 (80.2)	62 (62.0)	0.35 (0.11, 1.07)	0.066
	Patients with renal flares	6 (6.5)	9 (14.5)		
Year 2 (Months 12–24)	Patients with adequate response	98 (84.5)	68 (68.0)	1.00 (0.38, 2.64)	0.995
	Patients with renal flares	12 (12.2)	8 (11.8)		
Year 3 (Months 24–36)	Patients with adequate response	101 (87.1)	73 (73.0)		
	Patients with renal flares	12 (11.9)	6 (8.2)	1.43 (0.50, 4.08)	0.504

Note: The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region.
Footnote: *A CEC adjudicated the response status of each patient, percentages for patients who responded are based on AURORA 2 population; percentages for patients with renal flares are based on the number of patients who responded prior to visit.
Abbreviations: CEC = Clinical Endpoints Committee; CI = confidence interval; OR = odds ratio
Source: AURORA 2 CSR (15)

Due to the low number of patients with renal flares, a further analysis was conducted to assess and identify patients with sustained 'good renal outcomes' (i.e., those who achieved adequate response and did not experience renal flare). Significantly more patients in the voclosporin arm benefited from a good renal outcome than those in the placebo arm (66.4% vs 54.0%; OR 0.56 [95% CI 0.32–0.99]; p=0.045), demonstrating a clear-long-term renal benefit of voclosporin treatment (Table 25) (15).

Table 25: Patients with good renal outcomes* over the three-year AURORA 1 and AURORA 2 study period

	Placebo n (%) n=100	Voclosporin n (%) n=116	OR (Placebo vs. Voclosporin) (95% CI)	p-value
Overall (AURORA 1 baseline [Month 0] to Month 36)	54 (54.0)	77 (66.4)	0.56 (0.32, 0.99)	0.045
Year 1 (Months 0–12)	53 (53.0)	87 (75.0)	0.33 (0.18, 0.60)	<0.001
Year 2 (Months 12–24)	60 (60.0)	86 (74.1)	0.49 (0.27, 0.88)	0.017
Year 3 (Months 24–36)	67 (67.0)	89 (76.7)	0.58 (0.31, 1.07)	0.079

Note: The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region.
Footnote: *Good renal outcome is defined as adequate response and without flare.
Abbreviations: CI = confidence interval; OR = odds ratio
Source: AURORA 2 CSR (15)

7.1.1.2.1.4 Extra-renal flares (secondary endpoint)

Independent of renal response status, patients could experience non-renal ("extra-renal") flares at any point during the AURORA trials (15). During the three-year study period, 14.0% of patients in the placebo arm and 18.1% of patients in the

voclosporin arm were considered to have extra-renal flares (OR 1.33 (95% CI 0.63–2.81; p=0.448)) (Table 26). As with other efficacy endpoints, AURORA 2 was not powered to demonstrate a significant difference in extra-renal flares and there were notably few occurrences of extra-renal flares in the AURORA 2 study population (as is typically the case in patients with LN) (15).

Table 26: Patients with extra-renal flares over the three-year AURORA 1 and AURORA 2 study period

	Voclosporin n (%) n=116	Placebo n (%) n=100	OR (95% CI)	p-value
Overall (AURORA 1 baseline [Month 0] to Month 36)	21 (18.1)	14 (14.0)	1.33 (0.63, 2.81)	0.448
Year 1 (Months 0–12)	11 (9.5)	10 (10.0)	0.91 (0.36, 2.30)	0.847
Year 2 (Months 12–24)	4 (3.4)	6 (6.0)	0.54 (0.14, 2.05)	0.367
Year 3 (Months 24–36)	8 (6.9)	2 (2.0)	3.13 (0.80, 12.21)	0.100

Note: The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region.
Abbreviations: CI = confidence interval; OR = odds ratio
Source: AURORA 2 CSR (15)

7.1.1.2.1.5 Disease activity (secondary endpoint)

Disease activity, as measured via the SELENA-SLEDAI score was higher in the voclosporin arm (mean: 12.9, median: 12.0) than in the placebo arm (mean: 11.4, median: 10.0) (15). Improvements from AURORA 1 baseline were seen in both arms during AURORA 2, demonstrating improvements in SLE symptoms. The greatest improvements were observed in year 1 of treatment, however, there was no significant difference between the treatment arms (15).

7.1.1.2.1.6 Change in UPCR from baseline

At the start of AURORA 1, baseline mean UPCR levels were balanced between the two treatment arms (3.87 mg/mg in the placebo arm and 3.94 mg/mg in the voclosporin arm) (15). At the end of AURORA 1 (Month 12), the mean UPCR was 0.86 in the voclosporin arm compared with 1.47 in the placebo arm. At the follow-up visit, UPCR in the voclosporin arm showed a decrease of 3.02 from baseline compared with a decrease of 2.42 in the placebo arm (15) (Appendix P) .

The mixed-model repeated measures (MMRM) analysis confirmed that statistically significantly greater reductions from baseline in UPCR were achieved in the voclosporin arm compared with the placebo arm at Months 18, 24 and 30 but not Month 36 (15). During AURORA 2 (from Month 12) there was little change in UPCR in either treatment arm. Mean UPCR values at Month 12 were lower in the voclosporin arm (0.86 mg/mg) than in the placebo arm (1.47 mg/mg) as a result of the benefit derived from 12 months of treatment with voclosporin (15). There was no demonstrable difference between the two arms in the change from Month 12 at visits through to Month 36, showing that the difference observed at Month 12 is sustained for further 2 years with continued treatment with voclosporin (15).

7.1.1.2.1.7 Change in urine protein, serum creatinine and eGFR from baseline

Urine protein decreased across the 3 years of observation during the AURORA 1 and AURORA 2 studies (15). There was a greater decrease in mean urine protein observed in patients receiving voclosporin compared with placebo, which was consistent with UPCR findings (15). The MMRM analysis confirmed a statistically significantly greater mean decrease for voclosporin treatment compared to placebo at most time points (15) (Appendix Q .

Mean serum creatinine levels at baseline prior to the start of treatment in AURORA 1 were within the normal range and similar in both treatment arms (placebo: 0.829 mg/dL, voclosporin: 0.850 mg/dL) (15). Over the first 15 months of treatment, small increases (i.e., within normal range) in mean levels were observed in the voclosporin arm while levels in the placebo arm decreased slightly (15). This resulted in statistically significant differences between the treatment arms up to Month 15 in the MMRM analysis but not from Month 18 onwards (15). During AURORA 2, mean corrected eGFR values were similar in both arms prior to the start of study treatment in AURORA 1 (79.0 mL/min/1.73m2 in the voclosporin arm and 78.7 mL/min/1.73m2 in the placebo arm) (15). Over the first 3 months of treatment, the mean corrected eGFR was stable in the voclosporin arm while the mean value in the placebo arm showed a small increase. The small difference

between the arms remained through to Month 27, after which the mean eGFR value increased slightly in the voclosporin arm and started to decline in the placebo arm (15).

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7.1.1.2.1.8 Patient-reported outcomes

Improvements (i.e., increases) in mean scores from baseline were seen in both the voclosporin and the placebo arm for all domains of the SF-36 assessment, with no significant difference in the total mean scores observed between the two treatments (15) (Table 27).

Table 27 SF-36 change from baseline (Week 12, Week 24, Week 52)

Visit (n/n)	Placebo (N = 178) LS Mean (95% CI)	Voclosporin (N = 179) LS Mean (95% CI)	LS Mean Difference vs. Placebo (95% CI)	p-value
Week 12 **(170/171)**	5.03 (2.86, 7.20)	5.35 (3.19, 7.52)	0.32 (-2.18, 2.82)	0.799
Week 24 **(167/171)**	7.11 (4.80, 9.42)	6.64 (4.34, 8.93)	-0.47 (-3.21, 2.26)	0.733
Week 52 **(151/160)**	10.81 (8.37, 13.25)	10.44 (8.04, 12.83)	-0.37 (-3.29, 2.54)	0.801

Note: Results are based on a Mixed Effect Model Repeated Measures analysis with Change from baseline at each visit as the response variable, while treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region and baseline immunology result are included effects in the model.
Abbreviations: LS, least square

7.1.1.2.1.9 Adverse events (Primary endpoint)

The primary objective of the AURORA 2 study was to evaluate the long-term safety and tolerability of continued treatment with voclosporin for up to three years (15). During the study, voclosporin was well tolerated with no new or unexpected safety signals observed. The overall profile of AEs seen in the second and third years of treatment was similar to that seen in the first year (AURORA 1), although the frequency of AEs reduced each year. TEAEs reported during AURORA 2 are presented in Table 28 (15).

Table 28: Summary of TEAEs reported in AURORA 2

	Voclosporin (n=116)		Placebo (n=100)	
	Patients n (%)	Events n	Patients n (%)	Events n
Any TEAE	100 (86.2)	488	80 (80.0)	291
Treatment-Related TEAE	28 (24.1)	46	21 (21.0)	34
Serious TEAE	21 (18.1)	22	23 (23.0)	34
Treatment-Related Serious TEAE	1 (0.9)	1	2 (2.0)	2
TEAE Leading to Voclosporin/Placebo Discontinuation	11 (9.5)	11	17 (17.0)	18
TEAE Leading to Death	0 (0.0)	0	3 (3.0)	3
Treatment-Related TEAE Leading to Death	0 (0.0)	0	0 (0.0)	0
Disease-Related TEAE	50 (43.1)	93	34 (34.0)	69
Disease-Related Serious TEAE	7 (6.0)	7	11 (11.0)	14

Abbreviations: TEAE = treatment-emergent adverse event
Source: AURORA 2 CSR (15)

Commonly reported adverse events

The most commonly reported AEs in AURORA 2 were infections and were consistent with findings from the AURORA 1 study (15). Infections were reported by 49% of patients in the voclosporin arm and 43% of patients in the placebo arm (Table 29). Given the study population was immunosuppressed, an expected wide variety of infections were reported; with the most frequent infections in the voclosporin arm being UTIs, URTIs, and viral URTIs. Coronavirus infections and herpes zoster were more common in the placebo arm (15). Most infections were of mild or moderate intensity, with only three patients in each study arm recording severe infections (viral URTI, coronavirus and breast abscess in the voclosporin arm; three events of coronavirus in the placebo arm) (15).

Table 29: Summary of TEAEs reported by ≥3% of patients in either arm (AURORA 2)

	Voclosporin n=116		Placebo n=100	
System Organ Class **Preferred term**	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**
Any TEAE	100 (86.2)	488	80 (80.0)	291
Infections and infestations	57 (49.1)	132	43 (43.0)	82
Urinary tract infection	15 (12.9)	24	8 (8.0)	10
Upper respiratory tract infection	10 (8.6)	12	3 (3.0)	6
Viral upper respiratory tract infection	10 (8.6)	10	4 (4.0)	6
Coronavirus infection	7 (6.0)	8	12 (12.0)	14
Gastroenteritis	6 (5.2)	7	3 (3.0)	3
Bronchitis	5 (4.3)	5	4 (4.0)	4
Gingivitis	4 (3.4)	5	0	0
Herpes zoster	4 (3.4)	4	7 (7.0)	7
Gastrointestinal disorders	28 (24.1)	50	15 (15.0)	25
Diarrhoea	10 (8.6)	15	5 (5.0)	5
Nausea	3 (2.6)	3	5 (5.0)	6
Musculoskeletal and connective tissue disorders	27 (23.3)	37	23 (23.0)	33
Arthralgia	7 (6.0)	7	4 (4.0)	5
Systemic lupus erythematosus	6 (5.2)	6	9 (9.0)	12
Arthritis	4 (3.4)	5	2 (2.0)	2
Osteonecrosis	1 (0.9)	1	3 (3.0)	3
Investigations	24 (20.7)	35	16 (16.0)	20
Glomerular filtration rate decreased	12 (10.3)	15	5 (5.0)	5
Neutrophil count decreased	2 (1.7)	2	3 (3.0)	3
Skin and subcutaneous tissue disorders	21 (18.1)	34	9 (9.0)	10
Alopecia	5 (4.3)	5	2 (2.0)	2

Dermatitis	4 (3.4)	4	0	0
Renal and urinary disorders	21 (18.1)	25	10 (10.0)	14
Lupus nephritis	10 (8.6)	11	4 (4.0)	4
Proteinuria	4 (3.4)	6	1 (1.0)	2
Renal impairment	4 (3.4)	4	2 (2.0)	2
Blood and lymphatic system disorders	16 (13.8)	23	9 (9.0)	14
Anaemia	7 (6.0)	7	0	0
Neutropenia	6 (5.2)	8	5 (5.0)	5
Injury, poisoning and procedural complications	15 (12.9)	21	9 (9.0)	11
Ligament sprain	4 (3.4)	5	1 (1.0)	2
Tooth fracture	4 (3.4)	4	0	0
General disorders and administration site	14 (12.1)	22	13	15
Oedema peripheral	4 (3.4)	4	8 (8.0)	9
Nervous system disorders	14 (12.1)	22	8 (8.0)	10
Headache	8 (6.9)	12	5 (5.0)	6
Metabolism and nutrition disorders	12 (10.3)	16	8 (8.0)	9
Vascular disorders	10 (8.6)	11	13 (13.0)	13
Hypertension	10 (8.6)	10	7 (7.0)	7
Respiratory, thoracic and mediastinal disorders	9 (7.8)	13	6 (6.0)	10
Cough	3 (2.6)	3	4 (4.0)	5
Eye disorders	9 (7.8)	12	6 (6.0)	8
Dry eye	4 (3.4)	4	1 (1.0)	1
Psychiatric disorders	5 (4.3)	6	4 (4.0)	6
Reproductive system and breast disorders	5 (4.3)	6	3 (3.0)	3
Cardiac disorders	4 (3.4)	7	3 (3.0)	3
Hepatobiliary disorders	4 (3.4)	5	2 (2.0)	2

Abbreviations: TEAE = treatment-emergent adverse event
Source: AURORA 2 CSR (15)

Serious adverse events

There were more SAEs in the placebo arm than in the voclosporin arm during AURORA 2 (23 patients (23.0%) vs. 21 patients (18.1%)) (15). Infections were the most frequently reported SAE, with the predominant cause being coronavirus infections; reported by five patients in the placebo arm (5.0%) and two patients (1.7%) in the voclosporin arm (Table 30) (15). The AURORA 2 investigators considered only three SAEs to be related to study treatment, namely disseminated tuberculosis and hypertension in placebo-treated patients and URTI in a voclosporin-treated patient (15). More patients in the placebo arm than the voclosporin arm experienced SAEs that were considered to be related to their disease, most commonly worsening LN (3.0% vs. 1.7% respectively), SLE flare (3.0% vs. 0.9%) and osteonecrosis (2.0% vs. 0%). One patient in the voclosporin arm recorded an SAE of decreased GFR (15).

Table 30: Summary of serious TEAEs occurring in >1% of patients in either treatment arm (AURORA 2)

	Voclosporin n=116		Placebo n=100	
System Organ Class **Preferred term**	**Patients** **n (%)**	**Events** **n**	**Patients** **n (%)**	**Events** **n**
Any serious TEAE	21 (18.1)	22	23 (23.0)	34
Infections and infestations	8 (6.9)	9	8 (8.0)	10
Coronavirus infection	2 (1.7)	2	5 (5.0)	5
Urinary tract infection	2 (1.7)	2	0	0
Pneumonia viral	0	0	2 (2.0)	2
Disseminated tuberculosis	0	0	1 (1.0)	1
Renal and Urinary Disorders	2 (1.7)	2	5 (5.0)	5
Lupus nephritis	2 (1.7)	2	3 (3.0)	3
Musculoskeletal and connective tissue disorders	1 (0.9)	1	6 (6.0)	8
Systemic lupus erythematosus				
Osteonecrosis	1 (0.9)	1	3 (3.0)	3
	0	0	2 (2.0)	2

Abbreviations: TEAE = treatment-emergent adverse event
Source: AURORA 2 CSR (15)

Deaths

Four patients died during the study, all of whom were in the placebo arm. Three were due to SARS-CoV-2 coronavirus infection, one was due to a pulmonary embolism (15). Three events were treatment-emergent (TE) and none of the events was considered by the study investigators to be related to study treatment. In the case of pulmonary embolism, the investigator considered it to be related to LN disease (15).

Adverse events leading to treatment discontinuation

More patients in the placebo arm than in the voclosporin arm (17 (17.0%) vs. 11 (9.5%), respectively) had their study treatment discontinued permanently as a consequence of an AE (Table 31) (15). The most common AEs leading to treatment discontinuation were worsening LN (3.0% vs. 4.3%), decreased GFR (3.0% vs. 0.9%), SLE flare (2.0% vs. 0.9%) and renal impairment (1.0% vs. 1.7%) in the placebo and voclosporin arms, respectively. Infections caused five patients in the placebo arm to stop treatment and one patient in the voclosporin arm (15).

Table 31: TEAEs leading to discontinuation of voclosporin or placebo

	Voclosporin (n=116)		Placebo (n=100)	
System Organ Class **Preferred term**	**Patients** **n (%)**	**Events** **n**	**Patients** **n (%)**	**Events** **n**

Any TEAE Leading to Permanent Voclosporin/Placebo Discontinuation	11 (9.5)	11	17 (17.0)	18
Renal and urinary disorders	7 (6.0)	7	6 (6.0)	6
Lupus nephritis	5 (4.3)	5	3 (3.0)	3
Renal impairment	2 (1.7)	2	1 (1.0)	1
Nephrotic syndrome	0 (0.0)	0	2 (2.0)	2
Infections and infestations	1 (0.9)	1	5 (5.0)	5
Lymph node tuberculosis	1 (0.9)	1	0 (0.0)	0
Coronavirus infection	0 (0.0)	0	2 (2.0)	2
Disseminated tuberculosis	0 (0.0)	0	1 (1.0)	1
Pulmonary tuberculosis	0 (0.0)	0	1 (1.0)	1
Sinobronchitis	0 (0.0)	0	1 (1.0)	1
Investigation	1 (0.9)	1	4 (4.0)	4
Glomerular filtration rate decreased	1 (0.9)	1	3 (3.0)	3
Electrocardiogram QT prolonged	0 (0.0)	0	1 (1.0)	1
Musculoskeletal and connective tissue disorders	1 (0.9)	1	2 (2.0)	2
Systemic lupus erythematosus	1 (0.9)	1	2 (2.0)	2
Vascular disorders	1 (0.9)	1	1 (1.0)	1
Hypertension	1 (0.9)	1	1 (1.0)	1

Abbreviations: TEAE = treatment-emergent adverse event

Source: AURORA 2 CSR (15)

Adverse events leading to dose interruption or modification

More doses of study drug were modified in the voclosporin arm than in the placebo arm (this includes increases, decreases or interruptions) due to an AE (15). The most frequently reported type of TEAE leading to these dose modifications was infections, reported in 12.0% of placebo-treated patients and 13.8% of voclosporin-treated patients (Table 32) (15). Specifically, in voclosporin-treated patients, the most common AE leading to dose modification were decreases in eGFR (11 patients (9.5%) in the voclosporin arm vs. 2 patients (2.0%) in the placebo arm) (15).

Table 32: TEAEs leading to dose modification of voclosporin or placebo

	Voclosporin (n=116)		Placebo (n=100)	
System Organ Class **Preferred Term**	Patients n (%)	Events n	Patients n (%)	Events n
Any TEAE Leading to Dose Modification	35 (30.2)	50	19 (19.0)	29
Infections and infestations	16 (13.8)	22	12 12.0)	17
Coronavirus infection	5 (4.3)	6	4 (4.0)	4
Urinary tract infection	2 (1.7)	4	1 (1.0)	1
Herpes zoster	2 (1.7)	2	5 (5.0)	5
Upper respiratory tract infection	2 (1.7)	2	0 (0.0)	0
Investigations	11 (9.5)	14	4 (4.0)	4
Decreased GFR	11 (9.5)	14	2 (2.0)	2
Renal and urinary disorders	3 (2.6)	3	2 (2.0)	2
Renal impairment	2 (1.7)	2	1 (1.0)	1
Urinary tract infection	2 (1.7)	4	1 (1.0)	1
Blood and lymphatic system disorders	2 (1.7)	2	1 (1.0)	1
Gastrointestinal disorders	2 (1.7)	2	1 (1.0)	1

Abbreviations: GFR = glomerular filtration rate; TEAE = treatment-emergent adverse event

Source: AURORA 2 CSR (15)

Adverse events of special interest

AEs of particular interest in the AURORA studies were hypertension, kidney dysfunction, electrolyte disturbances, tremor and diabetes (15). Similar to AURORA 1, during AURORA 2 hypertension occurred at a higher incidence in the voclosporin arm (8.6%) compared with the placebo arm (7.0%) (15). As per the protocol guidance to maintain normal blood pressure through the use of antihypertensives, more patients in the voclosporin arm than the placebo arm were prescribed calcium channel blockers (16.4% vs. 15.0%, respectively) during AURORA 2 (15). More patients in the placebo arm than in the voclosporin arm were prescribed beta blockers (10.0% vs. 5.2%, respectively). More patients in the placebo arm were treated with diuretics than in the voclosporin arm (19.0% vs. 12.1%, respectively). The majority of

hypertension events were mild or moderate – only one case of severe hypertension was reported in a placebo-treated patient (15).

Various renal disorders were reported during AURORA 2, consistently more frequently in the voclosporin arm compared with the placebo arm. LN was reported in 8.6% vs. 4.0% (voclosporin vs. placebo, respectively); proteinuria was reported in 3.4% vs. 1.0% (voclosporin vs. placebo, respectively); and renal impairments were reported in 3.4% and 2.0% of voclosporin- and placebo-treated patients, respectively (15). No electrolyte imbalances, tremors or diabetes were reported in AURORA 2 (15).

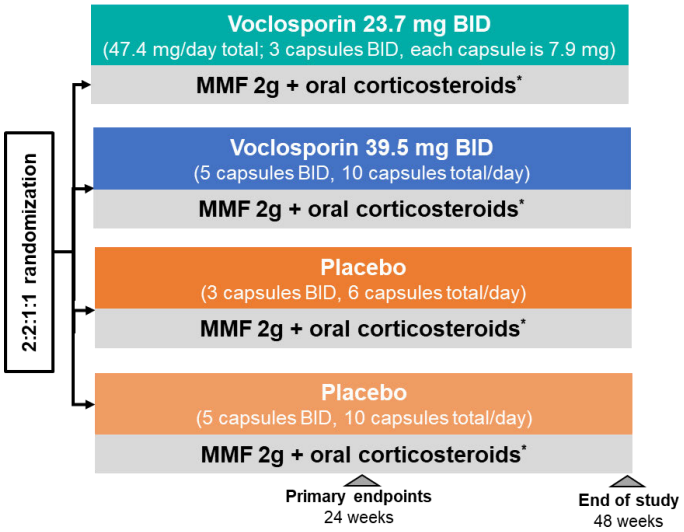
AURORA 2 safety conclusions

Across three years of follow-up, the addition of voclosporin to MMF and low-dose corticosteroids demonstrated acceptable safety and tolerability with sustained efficacy. The resulting risk/benefit profile is favourable for patients with LN (15). The profile of AEs reported in AURORA 2 was consistent with AURORA 1; however, incidence reduced with each year of continued treatment with voclosporin, further demonstrating tolerability in this population (15). In contrast to known safety risks with other CNIs, there was no evidence suggestive of renal toxicity, neurotoxicity or malignancy with long-term treatment with voclosporin (15).

7.1.1.3 AURA-LV Phase 2 study

AURA-LV is a Phase 2, multicentre, double-blind, placebo-controlled, randomised trial of 2 doses of voclosporin vs. placebo added to MMF and rapidly tapered low-dose oral corticosteroids for the treatment of patients with active LN (73). The primary objective of AURA-LV was to evaluate whether voclosporin added to background therapy was more effective in inducing CRR at 24 weeks compared to background therapy alone in patients with active LN. Secondary objectives were to evaluate the efficacy, safety, and tolerability of voclosporin compared with placebo after 48 weeks of treatment. An overview of the AURA-LV trial design is presented in Figure 7 accompanied by a summary of the methodology in the appendix in Table 106.

Figure 7: AURA-LV - Trial Design (AUR-VCS-2012-01; NCT02141672)



Note: *Oral corticosteroids were tapered per protocol.
Abbreviations: BID = twice daily; MMF = mycophenolate mofetil
Source: Rovin et al., 2019 (73)

7.1.1.3.1 Efficacy and safety

7.1.1.3.1.1 Complete Renal Response at Week 24 (primary endpoint)

At Week 24, CRR was achieved by a higher proportion of patients in both the low-dose (32.6%) and high-dose (27.3%) voclosporin groups compared to the placebo group (19.3%). CRR at Week 24 was significantly improved in patients treated with low-dose voclosporin compared to patients in the placebo group (OR=2.03; (95% CI: 1.01, 4.05); p=0.045) (73).

7.1.1.3.1.2 Complete Renal Response at Week 48 (secondary endpoint)

At Week 48, CRR was achieved by a higher proportion of patients in both the low-dose (49.4%) and high-dose (39.8%) voclosporin groups compared to the placebo group (23.9%), with an increased separation between the treatment and control arms compared to Week 24. CRR was increased in both the voclosporin groups compared to the placebo: i.e., patients treated with low-dose voclosporin had triple the odds of achieving CRR at Week 48 compared to patients in the placebo group (OR=3.21; (95% CI: 1.68, 6.13); p<0.001), and patients treated with high-dose voclosporin had double the odds of achieving CRR compared to patients in the placebo group (OR=2.10; (95% CI: 1.09, 4.02); p=0.026) (73).

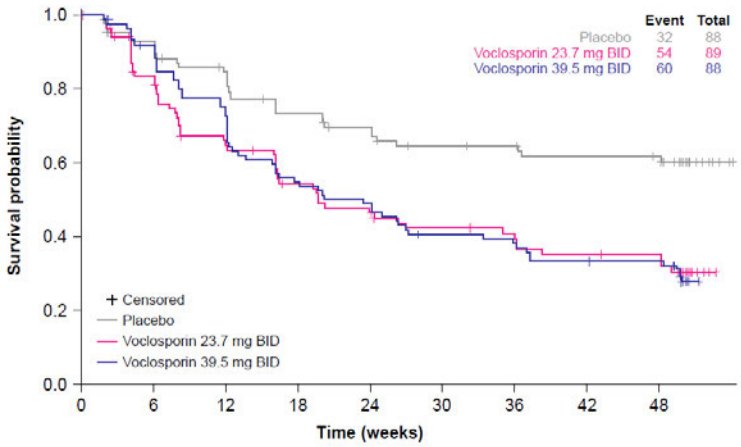
7.1.1.3.1.3 Partial renal response at Week 24 and Week 48 (secondary endpoint)

At Week 24, PRR was achieved by a higher proportion of patients in both the low-dose (69.7%) and high-dose (65.9%) voclosporin groups compared to the placebo group (49.4%) (139). Low-dose or high-dose voclosporin had double the odds of achieving PRR at Week 24 compared to patients in the placebo group (OR 2.33; p=0.007 and OR=2.03; p=0.024, respectively). Results were similar at Week 48, with even higher odds demonstrated for the high-dose voclosporin group vs. placebo (OR 2.68; p=0.002) (139).

7.1.1.3.1.4 Time to Complete Renal Response (secondary endpoint)

CRR occurred statistically significantly earlier in patients treated with either low-dose or high-dose voclosporin compared to placebo (HR 2.26 and 2.25, respectively). The median time to CRR was 19.7 weeks in the low-dose voclosporin group and 23.4 weeks in the high-dose voclosporin group. Median time to CRR could not be determined for the placebo group (Figure 8) (139).

Figure 8: AURA-LV - Analysis of Time to CRR



Abbreviations: BID = twice daily
Source: Otsuka 2018 (139)

7.1.1.3.1.5 Time to Partial Renal Response, Sustained Partial Renal Response and Sustained Early Partial Renal Response (secondary endpoint)

PRR occurred significantly earlier in patients treated with either low-dose or high-dose voclosporin compared to placebo (HR 1.63 (p=0.005) and HR 1.74 (p=0.002), respectively). The median time to PRR was 4.3 and 4.4 weeks in the low-dose and high-dose voclosporin groups, respectively, compared to 6.6 weeks in the placebo group (73, 139). Compared to placebo, sustained PRR occurred significantly earlier in patients treated with either low-dose voclosporin (HR=2.03; p<0.001) or high-dose voclosporin (HR=1.81; p=0.004) (139). The median time to sustained PRR was 26.9 weeks in the placebo group, compared to 6.3 weeks in the low-dose voclosporin group and 8.1 weeks in the high-dose voclosporin group (139).

Sustained early PRR was achieved by a higher proportion of patients in both the low-dose (67.4%) and high-dose (65.9%) voclosporin groups compared to the placebo group (41.4%) (139). Both voclosporin dose groups demonstrated significantly increased odds of achieving sustained early PRR compared to patients in the placebo group. The patients treated with low-dose voclosporin had an OR of 2.93 compared to those treated with placebo (p<0.001) and the patients treated with high-dose voclosporin had an OR of 2.74 compared to those treated with placebo (p=0.021) (139). Compared to placebo, time to sustained early PRR occurred significantly earlier in patients treated with either low-dose voclosporin (HR=2.21; p<0.001) or high-dose voclosporin (HR=1.87; p=0.004) (139). The median time to sustained early PRR was 6.3 weeks in the low-dose voclosporin group and 8.1 weeks in the high-dose voclosporin group. Median time to CRR could not be determined for the placebo group (139).

7.1.1.3.1.6 Disease activity

Mean SELENA-SLEDAI scores improved (i.e., decreased) in all 3 treatment groups. Changes from baseline in mean SELENA-SLEDAI scores were significantly greater for both the low-dose and high-dose voclosporin groups compared with placebo at Week 24 (p=0.003 for both comparisons) and at Week 48 (p<0.001 for both comparisons; Table 33) (139).

Table 33: AURA-LV - Mean Change from Baseline in SELENA-SLEDAI Scores at Week 24 and Week 48

	Voclosporin (low-dose)* n=74 at Week 24 n=77 at Week 48	Voclosporin (high-dose)† n=82 at Week 24 n=82 at Week 48	Placebo n=76 at Week 24 n=79 at Week 48
Week 24	-6.3‡	-7.1‡	-4.5
Week 48	-7.9‡	-8.3‡	-5.3

Note: *23.7 mg BID; †39.5 mg BID; ‡Significant difference compared with placebo (p<0.05) in ANCOVA for the change from baseline
Abbreviations: ANCOVA = analysis of covariance; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index
Note: a decrease in SELENA-SLEDAI score indicates improvement
Source: Otsuka 2018 (139)

7.1.1.3.1.7 Subgroup analyses

The subgroup analyses are presented in Appendix M Subgroup analyses for AURA-LV

7.1.1.3.1.8 Adverse events

TEAEs and treatment-related TEAEs were more common in the voclosporin groups (low-dose and high-dose) compared with placebo (TEAEs: 92.1%, 96.6%, and 85.2%, respectively; treatment-related TEAEs: 50.6%, 62.5%, and 17.0%, respectively) (73). The frequency of patients with TEAEs and treatment-related TEAEs is summarised in Table 34.

Table 34: AURA-LV - Summary of AEs

	TEAEs			Treatment-related TEAEs		
	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)
AEs, n (%)	82 (92.1)	85 (96.6)	75 (85.2)	45 (50.6)	55 (62.5)	15 (17.0)
Grade ≥3	-	-	-	-	-	-
Serious	25 (28.1)	22 (25.0)	14 (15.9)	4 (4.5)	7 (8.0)	1 (1.1)
Leading to discontinuation	16 (18.0)	14 (15.9)	9 (10.2)	11 (12.4)	8 (9.1)	2 (2.3)
Leading to death	10 (11.2)	2 (2.3)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)

Note: *23.7 mg BID; †39.5 mg BID
Abbreviations: AE = adverse event; BID = twice daily; TEAE = treatment-emergent adverse event
Source: Otsuka 2018 (139)

Details on safety are presented in the Appendix E Safety data for intervention and comparator(s) AURA-LV.

Safety conclusions

When compared with the tolerability profile of voclosporin from studies in other therapeutic areas, no new or unexpected safety signals were observed with the use of voclosporin in LN; voclosporin was generally well-tolerated over a 48-week period (139). The overall safety profile was consistent with the expectations for the class of drug, the patient population, and concomitant therapies. Treatment compliance was high in all groups (≥97.6%), including placebo. As would be expected in a population with active LN treated for 48 weeks, most patients reported at least one TEAE during the study (i.e., 85.2%, 92.1%, and 96.6%) in the placebo, low-dose voclosporin, and high-dose voclosporin groups, respectively) (139). The majority of TEAEs in all three groups were mild or moderate in severity. Severe TEAEs were more frequent in the low-dose voclosporin (23.6%) group compared to either the placebo (15.9%) or high-dose voclosporin (13.6%) group. As expected for patients with highly disordered immune systems treated with immunosuppressants, the highest incidence of TEAEs in all three treatment groups was Infections and Infestations, reported for 53.4%, 58.4%, and 65.9% of patients in the placebo, low-dose voclosporin, and high-dose voclosporin groups, respectively.

The overall incidence of treatment-related TEAEs increased with increasing the dose of voclosporin (139). The incidence of treatment-related TEAEs and serious TEAEs were higher in both the low-dose and high-dose voclosporin treatment groups compared to the placebo group. TEAEs leading to study drug discontinuation were reported more frequently for voclosporin-treated patients. The majority of TEAEs and serious TEAEs occurred in the first half of the study. In general, the reduction in TEAEs over time may be reflective of improvement/stabilisation in disease status with treatment, reductions in steroid dosing, and early withdrawals of the most severe patients (139). The frequency of deaths was higher in the low-dose voclosporin treatment group (10 patients(11.2%) compared to either the high-dose voclosporin (2 patients (2.3%)) or placebo (1 (1.1%) patient) treatment group (139). Analysis of the patients who died confirmed that these patients had more severe LN disease. Three additional deaths in the placebo group were reported after study completion. When these deaths are included, the overall incidence of deaths is more balanced, with deaths reported for 4 (4.5%) patients in the placebo group compared to an overall death rate of 12 (6.7%) patients in the voclosporin-treated patients.

7.2 Comparative analyses of efficacy and safety

No head-to-head studies are available that directly compare the efficacy of voclosporin + MMF and belimumab + MMF in the treatment of active LN patients (class III, IV, and V (including mixed class III/V and IV/V). Following the global SLRs discussed in section 6.1.1, a global NMA was carried out to identify relevant clinical trials to be used for the comparative clinical efficacy of voclosporin + MMF and belimumab + MMF in the treatment of active LN patients based on evidence from RCTs. In alignment with the scope of the submission, this section reports on voclosporin + MMF relative efficacy vs. belimumab + MMF for the outcomes of interest. For full results on the relative efficacy of voclosporin + MMF vs. all other comparators please see [redacted]

In this section, the methods used to run the global NMA are briefly presented. Presented below are the outcomes analysed in the NMA. **Efficacy:** Complete renal response, PRR. **Safety:** TRAEs, SAEs, Infections, Major/serious/server infections, Gastrointestinal disorders. Of these, complete renal response and PRR were of interest for efficacy for the comparison for the scope of the submission. For safety, TEAEs event rates and a comparison are presented in Table 52.

Statistical methods for the NMA

A standard Bayesian NMA is conducted using the aggregate data of AURORA-1 and BLISS-LN, this is performed as a supplementary analysis to the primary analysis. The Bayesian NMA is conducted using Monte Carlo Markov Chain and implemented using models developed in the probabilistic modelling language of Stan (Version 2.21.0). (16). A generalized linear model for dichotomous outcomes was applied, as presented within the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2. (17). Treatment effects were synthesized using the observed number of events from the known number of patients in the respective treatment arms. The data were assumed to come from a binomial likelihood. Therefore, the binomial model with a logit link was used to model the log odds of the outcome on a given treatment, in a specified trial via an effect (fixed or random). As recommended, a noninformative prior was assigned for the treatment effect, in both fixed and random effects models, $N(0, 100^2)$. Due to the low number of trials included, the heterogeneity parameter in the random effects becomes increasingly more difficult to estimate. Therefore, the random effects model makes use of an informative prior for the between-study heterogeneity parameter. The prior used for the analysis is obtained from Table IV in Turner et al. (2015) and represents a log-normal distribution with a mean of -2.93 and a standard deviation of 1.58 LN (-2.93, 1.582). The setting is based on a subjective outcome, as renal response is subject to meeting certain criteria. Under this informative prior, 95% of the prior density lies between 0 and 1.18. Please note, for PRR we only have one trial per treatment comparison, so the fixed effect model only has been implemented as effectively there is no between study variation between the pairwise comparisons.

In the Monte Carlo simulation, 4 simulation chains with a minimum of 10,000 iterations (including 5,000 burn-in) were used to summarize the posterior distribution. The number of samples was deemed appropriate for model convergence. Convergence was then assessed in accordance with NICE DUS TSD 2; by examining diagnostic autocorrelation, trace, and density plots as well as the recommended statistics such as the Gelman-Ruben Rhat, and whether the Monte Carlo standard errors are ≤5% of the posterior deviation of the parameters of interest (17).

Detailed results and plots for the consistency checks are provided in [redacted]

Differences between trials

Trial designs and patient population across included studies were found to be comparable across all included studies in the NMA. Study similarity was assessed for heterogeneity according to the population, intervention, comparator, outcome, and study design framework which is detailed in [redacted] along with tables with baseline patient characteristics, a summary of outcome definitions and background corticosteroid use.

Results from the comparative analysis

The network of evidence has been identified as a connected network of evidence as voclosporin plus MMF and belimumab plus SoC are both compared to MMF (SoC). However, it must be noted that the comparator arm of the BLISS-LN trial does include a proportion of patients (26%) who received cyclophosphamide, while the other 74% received MMF. For the outcome of CRR, both the phase 2 (AURA-LV) and phase 3 (AURORA-1) RCTs contribute evidence for the comparison of voclosporin versus MMF. For the outcome of PRR, only AURORA-1 contributes evidence to the network. This is because the proportion of partial responders, defined as those achieving a PRR independent from CRR, was derived via the individual patient data analysis that was used to inform the transition probabilities in the cost-effectiveness analysis, which focused on AURORA 1 as this was the Phase 3 study. **Fejl! Henvisningskilde ikke fundet.** A and B represents the network of evidence for CRR and PRR, respectively.

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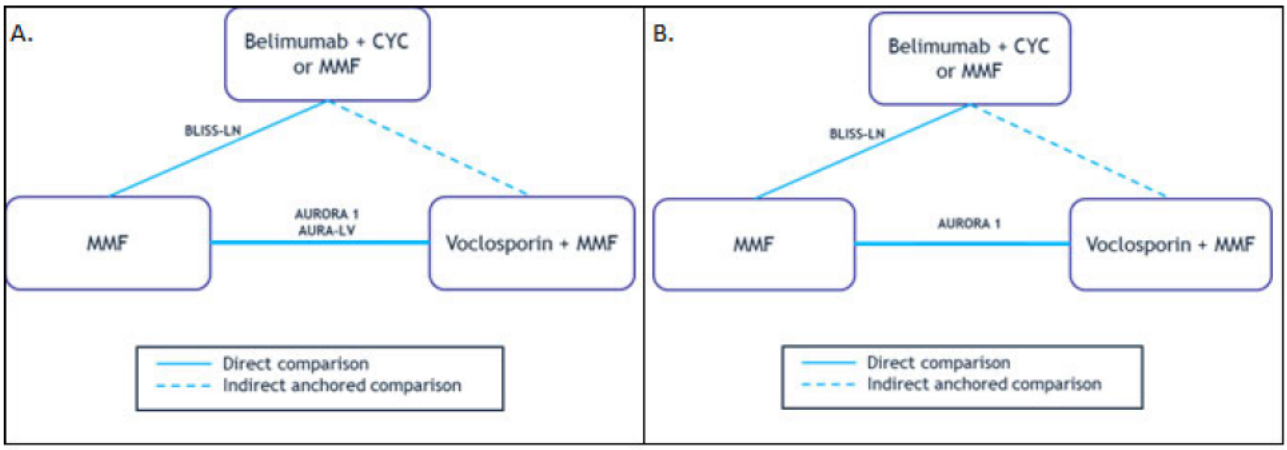
Figure 9: NMA network diagram: A represents the network for CRR – B represent the network for PRR



Abbreviations: CYC, Cyclophosphamide; MMF, Mycophenolate mofetil

Complete renal response

In Table 35, the results of the fixed effect (FE) and random effect (RE) models are presented, the DIC values between the two models are similar and the residual deviance is marginally higher for the RE model, however no meaningful differences are observed. The results demonstrate there is a high probability (>= 95%) that VCS+MMF and BEL+MMF/CYC are more efficacious in comparison to MMF, in terms of CRR; demonstrated by both tails of the CrI around the point OR being > 1 (Figure 10). Ranking the treatments according to the surface below the cumulative ranking curve (SUCRA) VCS+MMF received a very high value (95%), followed by BEL+MMF/CYC (54%).

The pairwise results for all treatment comparisons for the FE model are presented in Table 36 . The pairwise comparisons demonstrated that VCS+MMF is similar in efficacy to that of BEL+MMF/CYC as no significant differences are observed.

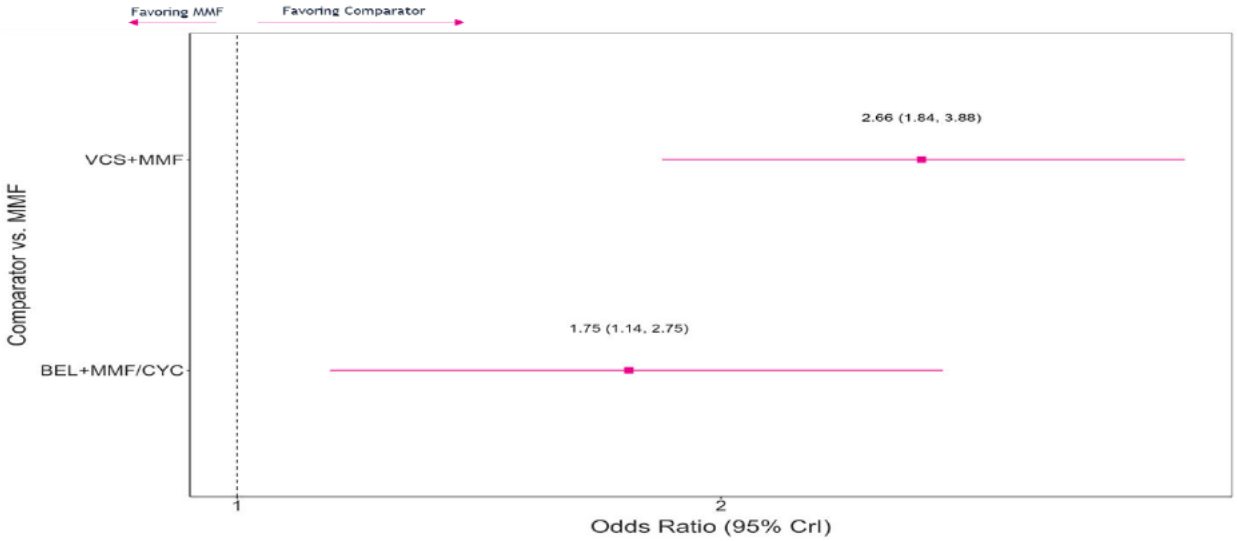
Table 35: NMA results CRR, base case

	Fixed effects				Random effects			
Treatment	Median OR	CrI 2.5%	CrI 97.5%	SUCRA	Median OR	CrI 2.5%	CrI 97.5%	SUCRA
MMF	-	-	-	0%	-	-	-	1%
VCS+MMF	2.66	1.84	3.88	96%	2.67	1.75	4.25	95%
BEL+MMF/CYC	1.75	1.14	2.75	54%	1.75	1.01	3.00	54%
Model Selection Statistics		FE	RE					
Residual deviance		5.60	5.66					
pD		5.00	5.20					
DIC		10.61	10.86					

Note: Results are the median ORs and 95% CrI in the row defining treatment (comparator) compared with the ORs in the column defining treatment (reference). Values > 1 are in favor of the comparator (row defining treatment), while those < 1 are in favor of the reference treatment.

Abbreviations: MMF, Mycophenolate mofetil; VCS, Voclosporin; CYC, Cyclophosphamide; BEL, Belimumab

Figure 10: Forest plot for posterior median ORs and 95% CrI, for complete renal response – fixed effect



Abbreviations: BEL = belimumab; CYC = cyclophosphamide; MMF = mycophenolate mofetil; VCS = voclosporin.

Table 36 Pairwise NMA results, posterior median and 95% CrI - CRR, base case – Fixed effect

	Reference		
Comparator	MMF	VCS+MMF	BEL+MMF/CYC
MMF	1.00 (1.00, 1.00)	0.38 (0.26, 0.54)	0.57 (0.36, 0.88)
VCS+MMF	2.66 (1.84, 3.88)	1.00 (1.00, 1.00)	1.52 (0.85, 2.69)
BEL+MMF/CYC	1.75 (1.14, 2.75)	0.66 (0.37, 1.18)	1.00 (1.00, 1.00)

Note: Results are the median ORs and 95% CrI in the row defining treatment (comparator) compared with the ORs in the column defining treatment (reference). Values > 1 are in favor of the comparator (row defining treatment), while those < 1 are in favour of the reference treatment.
Abbreviations: MMF, Mycophenolate mofetil; VCS, Voclosporin; CYC, Cyclophosphamide; BEL, Belimumab

Partial renal response

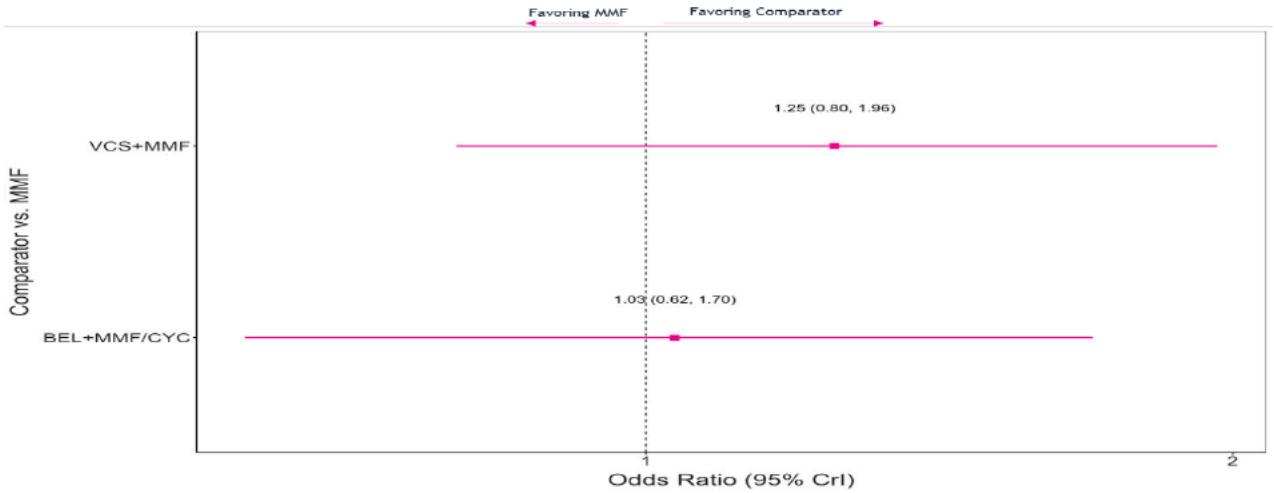
In Table 37, the results of only the FE model is presented, the FE model is preferred as there is only one trial per treatment comparison and is therefore used for inference. The results demonstrate that VCS+MMF and BEL+MMF/CYC are similar to MMF in achieving PRR independently to CRR, as the CrI includes 1.00 which is the line of no difference. According to the SUCRA values, the best value is high for VCS+MMF (78%), followed by BEL+MMF/CYC (42%).

Table 37: NMA results partial renal response, base case

	Fixed effects			
Treatment	Median OR	CrI 2.5%	CrI 97.5%	SUCRA
MMF	-	-	-	31%
VCS+MMF	1.25	0.80	1.96	78%
BEL+MMF/CYC	1.03	0.62	1.7	42%
Model Selection Statistics		FE		
Residual deviance		4.04		
pD		4.04		
DIC		8.08		

Note: Results are the median ORs and 95% CrI in the row defining treatment (comparator) compared with the ORs in the column defining treatment (reference). Values > 1 are in favour of the comparator (row defining treatment), while those < 1 are in favour of the reference treatment.
Abbreviations: MMF, Mycophenolate mofetil; VCS, Voclosporin; CYC, Cyclophosphamide; BEL, Belimumab

Figure 11: Forest plot for posterior median ORs and 95% CrI, for partial renal response



Note: Results are presented in descending order from highest to lowest. A higher odds ratio is preferred for CRR; therefore, the best performing treatment vs MMF is at the top. A comparator with an OR greater than one gives preference to the comparator, while an OR less than one gives preference to MMF.

Table 38: Pairwise NMA results, posterior median and 95% CrI - CRR, base case FE

	Reference		
Comparator	MMF	VCS+MMF	BEL+MMF/CYC
MMF	1.00(1.00, 1.00)	0.80 (0.51, 1.25)	0.97 (0.59, 1.61)
VCS+MMF	1.25 (0.80, 1.96)	1.00 (1.00, 1.00)	1.21 (0.62, 2.40)
BEL+MMF/CYC	1.03 (0.62, 1.70)	0.83 (0.42, 1.61)	1.00 (1.00, 1.00)

Note: Results are the median ORs and 95% CrI in the row defining treatment (comparator) compared with the ORs in the column defining treatment (reference). Values > 1 are in favor of the comparator (row defining treatment), while those < 1 are in favor of the reference treatment
Abbreviations: MMF, Mycophenolate mofetil; VCS, Voclosporin; CYC, Cyclophosphamide; BEL, Belimumab

8. Health economic analysis

A cost-utility analysis was utilised per the DMC guidelines (140) as the intervention is expected to impact the HRQoL and survival of LN patients. The analysis was based on a cohort Markov state transition model.

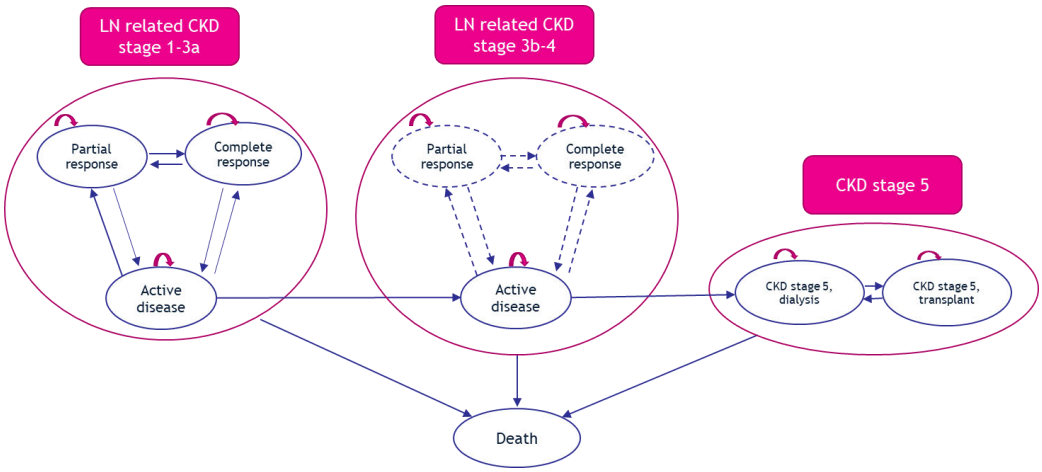
8.1 Model

8.1.1 Model structure

The clinical pathway depicted in section 5 has been translated into a cohort Markov state transition model with nine health states. In the absence of any published DMC or NICE technology appraisals for the treatment of patients with LN, the cost-utility model structure was based on previously published models identified by SLR and targeted literature review outlined in 8.1.1.1, data availability from the AURORA 1 and AURORA 2 trials, and the known clinical pathway of patients with LN supported by KOL expert feedback. Figure 12 illustrates the model structure. The model is a cohort state transition model with nine health states, encompassing the LN-related stages of CKD (CKD1–4), ESRD (CKD 5), and death (the absorbing health state):

- Complete Response with CKD stages 1-3a (CR CKD 1-3a)
- Partial Response with CKD stages 1-3a (PR CKD 1-3a)
- Active Disease with CKD stages 1-3a (AD CKD 1-3a)
- Complete Response with CKD stages 3b-4 (CR CKD 3b-4)
- Partial Response with CKD stages 3b-4 (PR CKD 3b-4)
- Active Disease with CKD stages 3b-4 (AD CKD 3b-4)
- CKD stage 5, dialysis (dialysis)
- CKD stage 5, after kidney transplant (transplant)
- Death (absorbing health state)

Figure 12: Model schematic for the Markov model



Note: Dashed lines indicate the health states not used in the model due to lack of data. However, the transition to these states can be applied in the model. Transition to the all-cause death state can occur in all health states.
Abbreviations: CKD = chronic kidney disease; LN = lupus nephritis

All patients enter the model in the AD CKD 1-3a health state. From the AD CKD 1-3a health state patients can either:

i) die
ii) have a complete response and transition to CR CKD 1-3a,
iii) have a PR and transition to PR CKD 1-3a,
iv) remain in AD CKD 1-3a
v) have worsening eGFR and transition to AD CKD 3b-4.

As stated previously eGFR levels are sensitive to multiple factors. Therefore, when using the patient-level data from the AURORA trials it was necessary to take into account only the consistent and confirmed eGFR changes over time as a proxy for changes to CR to treatment.

The treatment pathway is defined by CKD stage. When patients begin receiving treatment, the model assumes that they have most of their kidney function remaining, i.e., CKD stage 1-3a, but are in an active disease state (all patients enter the model in this state). Over time, they will either have a response, and go to one of the two response health states for CKD stages 1-3a, or they will remain in active disease, with kidney function worsening. This will result in patients transitioning to the later advanced CKD stage 3b-4. Due to lack of data, In the base case, patients can only transition to CKD stage 5 from AD CKD 3b-4. Once in CKD stage 5, also known as ESRD, patients begin dialysis and await kidney transplantation. Due to limited follow-up in the latest AURORA 2 data cut, it was not possible to estimate transition probabilities for LN patients with more advanced CKD beyond CKD stages 1-3a. Therefore, literature sources and KOL feedback were used for the transitions between AD CKD 1-3a and AD CKD 3b-4, and all transitions in CKD 3b-4 and CKD stage 5.

8.1.1.1 Development of the economic health economic model

There are currently not any published DMC or NICE technology appraisals for the treatment of patients with LN, and instead published literature was used for model structure inspiration. The model structure was based on previous LN models, with consideration of the limitations of previous cost-effectiveness models in LN, the treatment pathway of patients with LN, data available from the AURORA 1 and 2 trials, and KOL expert feedback (141). The model structure was validated by Danish KOLs (142). An SLR and a targeted literature review to identify economic evaluations of voclosporin and other comparators for the treatment of adult patients with LN. The SLR identified four published cost-effectiveness models (143-146) for LN, which were supplemented by an additional cost-effectiveness model (147) identified within targeted literature searches. An overview of the five cost-effectiveness models is provided in the appendix in Table 103. Further details of the economic SLR, targeted searches, and identified economic evaluations are detailed in Appendix H – Literature search for HRQoL data.

Markov and mixed decision tree-Markov models were most commonly employed over a lifetime horizon, with largely consistent health states that included AD, CR, PR, ESRD, kidney transplant, post-kidney transplant and death. Response definitions varied, with one model using eGFR to determine response, and all other models included at least serum creatine levels and UPCR (21, 143-145, 147). Prior models did not model LN through LN class progression for two key reasons. First, data on progression is limited due to biopsies not being repeated to confirm LN class. Second, the natural history of LN is not 'sequential' through the LN classes; specifically, LN class 5 patients have different pathophysiology to class 3/4 LN (21). A number of costing models did focus on modelling the LN patient using eGFR levels only as opposed to combined UPCR and eGFR levels as only registry eGFR data were available to estimate these costs over time. However, eGFR levels can vary over time for multiple reasons which may or may not be related to CR to treatment. Based on clinical guidelines CR is confirmed using multiple biomarkers such as kidney function (confirmed eGFR measures), proteinuria and UPCR level; as was the case in the AURORA trial.

A lifetime horizon was the commonly assumed time horizon. The models commonly adopted an initial six-month cycle followed by a long-term one-year cycle length. Treatment stages such as induction, maintenance and post-maintenance were often modelled; although the time a patient spent on treatment within each of these stages varied. All models included health state-specific utilities, while some models included utility increments or decrements to account for differences between treatments.

These LN model structures were discussed with external KOLs(141), who concluded that the health states (AD, CR, PR, ESRD and Death) included in previous economic models were relevant for modelling LN; with CR and PR response definitions from the AURORA trial considered suitable for assessing response over time in the model. However, a key limitation of previous economic models for LN is that they did not fully capture the LN disease pathway. Specifically, the cumulative impact of renal flares over time was not captured by modelling LN progression through the advanced CKD

stages prior to reaching ESRD. KOL expert feedback (141) indicated that it would be relevant to model advanced CKD stages; as when modelling an LN patient's kidney deterioration there are different costs, outcomes and mortality rates associated with the early (CKD 1-3a) vs. advanced (CKD 3b-4) stages prior to reaching CKD 5. Therefore, with consideration of the limitations of previous cost-effectiveness models in LN and KOL expert feedback, a Markov cohort state transition model was developed to incorporate all stages of CKD and accurately model LN patient progression over a lifetime horizon.

A key limitation of previous economic models for LN was that they did not fully capture the LN disease pathway. Specifically, the cumulative impact of renal flares over time was not captured by modelling LN progression through the advanced CKD stages prior to reaching ESRD. KOL expert feedback indicated that it would be relevant to model advanced CKD stages; as when modelling an LN patient's kidney deterioration there are different costs, outcomes and mortality rates associated with the early (CKD 1-3a) vs. advanced (CKD 3b-4) stages prior to reaching CKD 5. Renal flares are partly captured in the model by both active disease (AD) states, as whenever a patient returns to AD after having been in a response state, they are experiencing a renal flare. While the model is Markovian and therefore cannot track how often one or multiple patients have experienced renal flares, the cumulative impact of renal flares is captured by allowing patients to progress through CKD stages. In particular, a patient cannot experience a worsening of kidney function (as captured by CKD stage) without having spent a cycle in an AD state.

8.1.1.2 Model characteristics

Table 39 provides an overview of the key model characteristics.

Table 39: Overview - Key model characteristics

Model Elements	Description
Model Design	• Markov model, cost-utility in line with DMC guidance
Perspective	• The model considers a Danish restrictive societal perspective, consistent with the guidelines presented by the DMC. This includes All relevant hospital-related costs, costs covered by public health services, treatment-related costs incurred by the patient and municipal costs should be included. Relevant transport costs and time spent in connection with treatment for both patients and relatives (including informal care) (140).
Target Population	• Patients with active LN class III, IV, III/V, IV/V and V LN
Treatment Intervention	• Voclosporin + mycophenolate mofetil (VCS + MMF)
Treatment Comparators	• Mycophenolate mofetil (MMF) plus corticosteroids • Belimumab + MMF/CYC (BEL + MMF/CYC)
Time Horizon	• Lifetime (67.5 years for the base-case), with the option to consider reduced time horizons
Cycle length	• 6 months

Outcomes of Interest	• Costs by category
	  ◦ Drug acquisition
	  ◦ Drug administration
	  ◦ Subsequent treatment
	  ◦ Background therapy
	  ◦ Resource use
	  ◦ Patient time
	  ◦ Transportation
	  ◦ Patient time
	  ◦ Adverse event
	• Life-years (LYs) and quality-adjusted life-years (QALYs)
	• Incremental costs, LYs and QALYs
	• Cost per LY/QALY gained

Year of Cost & Currency	• 2022, Danish Kroner (DKK)
Annual Discount Rate	• A discount rate of 3.5% until year 35, 2.5% in years 36-70, and 1.5% beyond year 70 was applied to costs, as defined by the Danish Ministry of Finance and in the DMC guidelines (140, 148).

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Sensitivity Analysis	•	One-way deterministic sensitivity analyses (Section 8.7.1)
	•	Scenario analyses (Section 8.7.1.3)
	•	Probabilistic sensitivity analyses (Section 8.7.2)

Abbreviations: BEL = belimumab; CYC = cyclophosphamide; DKK = Danish Kroner; DMC = Danish Medicines Council; LN = lupus nephritis; LYs = life-years; MMF = mycophenolate mofetil; QALY = quality-adjusted life-years; VCS = voclosporin

8.1.2 Patient population

In accordance with the anticipated marketing authorisation, the cost-effectiveness analysis evaluates the cost-effectiveness of voclosporin in combination with background immunosuppressive therapies for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) LN. This population reflects the use of voclosporin in the pivotal studies, AURORA 1 and AURORA 2.

8.1.3 Perspective, time horizon, and cycle length

The model considers a Danish restrictive societal perspective, consistent with the guidelines presented by the DMC (140). A lifetime horizon was selected to ensure the full impact of treatment in terms of cost and health outcomes are captured. Lifetime was defined as 99.9% of the cohort being in the dead health state and is equal to 67.5 years in the base-case. As such, the time horizon for the analysis should be long enough to catch all significant differences in effects and costs between the alternatives and an extension of the time horizon would not affect the results. The model enables the option to consider reduced time horizons. The cycle length of the CEM is 6 months and half-cycle correction has been applied to account for events not occurring at the beginning or end of every cycle. This has been deemed to be an appropriate length based on disease progression, given EULAR/ERA-EDTA (149) and BSR (150) guidelines recommending SLE patients with LN being assessed minimally every 6 months and verified by clinical experts to adequately capture progression over time.

8.1.4 Discounting

Discount rates of 3.5% until year 35, 2.5% from year 36 to 70, and 1.5% beyond year 70 were applied to costs, as defined by the Danish Ministry of Finance and in the DMC guidelines (140, 148). A discount rate of 0% was explored as a scenario analysis in section 8.7.1.3.

8.1.5 Intervention and comparators

In the AURORA trial, VCS+MMF was compared to MMF alone. Both treatment arms had background treatment including corticosteroids. Comparators were identified based on the clinical SLR and NMA (see separate SLR and NMA reports for details) and included relevant comparators from the scope of the Danish context and the treatment guidelines in Europe. The identified comparators included within the CEM are presented in Table 40.

Table 40: Included treatment regimens

Treatment	Rationale for inclusion in the model
Voclosporin + Mycophenolate mofetil	Intervention of interest
Mycophenolate mofetil (MMF)	The CEA will include MMF as a comparator, as this is the active comparator in the AURORA 1 and 2 trials.
Belimumab + MMF/CYC (BEL + MMF/CYC)	The CEA will include Benlysta (belimumab) as a comparator, as this is the only currently approved add-on therapy in LN (67), and due to the similar study characteristics between the Lupkynis and Benlysta trials.

Abbreviations: BEL = belimumab; CEA = cost-effectiveness analysis; CYC = cyclophosphamide; MMF = mycophenolate mofetil; LN= lupus nephritis

8.1.6 Approach to modelling efficacy

Individual patient-level data (IPD) from AURORA 1 and 2 trials were used to estimate transitions between health states for VCS+MMF and MMF alone arms. A clinical SLR was conducted to identify a RCT for the treatment of LN, which informed an NMA to help parameterise the comparator treatments in the model. The application of long-term transition is presented in section 8.3 with the relevant sources found in the literature and validated with KOLs.

8.1.7 Model features and assumptions

Table 41 provides an overview of model features and assumptions which should be considered when assessing the results.

Table 41: Key model features and assumptions

Model input	Feature	Rationale
Transition to CKD 3b-4	Does not occur in the first three years	Reflecting AURORA 1 and 2 data
TTD curves	TTD extrapolations based on combined AURORA 1 and AURORA 2 trial data were used to estimate VCS + MMF and MMF discontinuation over a 36-month treatment period.	Log-logistic curves were fitted to Kaplan-Meier discontinuation data collected across the 36-month treatment period of AURORA 1 and AURORA 2, to estimate a parametric fit that informs treatment discontinuation over the 36-month treatment period.
	It is assumed that no other treatments were discontinued in the base-case. Belimumab can BEL + MMF/CYC TTD can be set equal to VCS+MMF or MMF TTD	No TTD data was available for treatments which were not investigated within the AURORA trials.
Length of treatment	36 months for all regimens with subsequent treatment options.	Voclosporin+MMF and MMF alone were used for 36 months per AURORA 1 and AURORA 2 trials' initial treatment duration. The rest was assumed to have a similar treatment duration.
Treatment waning	A treatment waning effect is applied to all treatments following treatment discontinuation and maintained for the outstanding duration of the lifetime horizon. Upon discontinuation of VCS + MMF, patient health state transition probabilities wane to an average (i.e., midpoint) of those recorded within the AURORA 2 trial at Months 30 and 36 for the VCS + MMF arm, and those recorded at Months 30 and 36 months for the MMF alone arm. Similarly, for all other treatments, long-term health state transition probabilities wane to an average of those derived from indirect treatment comparison data and those recorded at months 30 and 36 months for the MMF alone arm in AURORA 2.	Treatment waning effect is applied to account for a partial treatment effect, sustained beyond the treatment period, The loss of treatment effect is unlikely to occur instantaneously following treatment discontinuation. In line with EULAR/ERA-EDTA and KDIGO guidelines; patients with lupus nephritis (LN) that respond to initial treatment may progress to a subsequent therapy to maintain response (9, 11) and a Phase 3 study has indicated that maintenance of response can depend on the regimen in which an initial response was obtained (151, 152). Therefore, it would not be appropriate for patients distributed across response states to behave homogeneously (i.e., all patients having the same transitions after 36 months) and fully wane immediately.
Patient response for CKD 1-3b	It is assumed that patients in the AURORA 1 and AURORA 2 trials are reflective of LN patients with CKD 1-3a	Patient-level response and TTD data from AURORA 1 and AURORA 2 trials were used to inform transition probabilities in the CKD 1-3a health state. AURORA trial patients were assumed to reflect CKD 1-3a on the basis of confirmed eGFR levels, in line with KDIGO-guideline published eGFR CKD thresholds.
	It is assumed that only consistent and confirmed eGFR changes over time were reflective of patient response status and CKD progression	CKD progression was modelled based on confirmed and irreversible eGFR changes as opposed to transient, reversible changes in eGFR levels in accordance with KDIGO 2021 guidelines which indicate that eGFR changes need to be confirmed over time to determine progression of CKD (11).
Utilities	A pooled regression analysis for AURORA 1 and AURORA 2 utilities are applied to reflect LN patients in CKD 1-3a. Due to lack of trial data, literature was used beyond CKD 3b.	Beyond CKD 1-3a, data from the AURORA 1/AURORA 2 trials could not be used for other health states. Therefore, health state utility values identified in the literature were used for these health states within the model. The CKD 1-3a to CKD 3b-4 progression-related utility decrement reported in an observational study (153) was applied to the CKD 1-3a utility values to inform CKD 3b-4 utility.

Adverse events	It is assumed that only grade III/IV TEAEs identified in ≥1% of patients in the AURORA 1 are associated with disutility and costs	Grade III/IV TEAE frequencies were collected from AURORA 1 for both VCS + MMF and MMF alone. For all other comparators, Grade III/IV TEAE frequencies were sourced from the literature identified by the clinical SLR.
	It is assumed that in the absence of Grade III/IV TEAE data for comparators, they either have the same grade III/IV incidence as the AURORA 1 MMF (when the treatment regimen includes MMF) or they have no incidence of Grade III/IV TEAEs	Conservative assumption is applied to reflect the likelihood of Grade III/IV TEAEs expected in all MMF-containing comparator treatment regimens, or exclude consideration for Grade III/IV TEAEs entirely for comparator regimens that do not contain MMF.
Morality rates AD CKD 1-3a	Set to 0.3458%	In absence of LN-related CKD-specific data, the average 6-month mortality rate reported in AURORA 1 and AURORA 2 for the MMF arm (6 deaths recorded over 347 periods of 6 months - 6/347 = 1.73%) was presented for the Danish KOLs. However, the Danish KOLs indicated that this rate was too high by a factor ~5, and hence we have scaled this 1.2/347 = 0.3458%.

Abbreviations: AD = Active Disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; EULAR/ERA-EDTA = Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association; KOLs = key opinion leaders; LN = lupus nephritis; MMF = mycophenolate mofetil; SLR = systematic literature review; TAC = tacrolimus; TEAEs = treatment-emergent adverse event; TTD = time to treatment discontinuation; VCS = voclosporin

8.1.8 Model outcomes

The analyses allow benefits to be measured in terms of life-years (LYs) and QALYs. Base case results were generated using QALYs as the measure of benefit and the primary outcome was the incremental cost per QALY (ICER).

8.1.9 Limitations of the model

Data supporting the efficacy and safety of voclosporin is provided by a Phase 3 trial (AURORA 1), a Phase 3 extension trial (AURORA 2), and a Phase 2 trial (AURA-LV). Therefore, there is sufficient quality of evidence to support the use of voclosporin in patients with LN.

However, certain aspects of LN introduce some uncertainties to the economic analysis. Firstly, the rarity of the disease means that there is generally limited published clinical, humanistic, and economic data available for LN and/or SLE. Therefore, there is some uncertainty in terms of long-term transitions to advanced CKD stages. Secondly, the chronic, progressive nature of the disease means that patients typically remain on treatment for a number of years and there is some variation in clinical practice in terms of treatment duration on a treatment-by-treatment basis. Thirdly, there is currently limited knowledge of treatment waning effects in the field of LN.

For the above reasons, substantial KOL expert advice has been sought to inform the cost-effectiveness model presented in this submission, including the population of any key assumptions.

The model may also include some limitations in terms of calculations of QALY, as additional benefits in introducing voclosporin as a treatment option for patients with active LN may not have been captured in the QALY calculation:

- Voclosporin's novel molecular structure and mechanism of action eliminate the need for regular therapeutic drug monitoring required with currently available CNIs (14). Voclosporin, therefore, has the potential to alleviate the monitoring burden on patients and healthcare professionals.
- Voclosporin is administered orally, whereas some other treatment options for LN (e.g., rituximab) are administered intravenously. There may be potential benefits associated with oral therapy vs therapy delivered intravenously, including a reduced need for hospital visits, which may not be fully captured by the current model.

8.1.10 Validation of the model

The cost-effectiveness analysis was subject to an internal quality control check prior to submission. An internal validation comparing the AURORA 1 Phase 3 trial data (136) to the model outcomes in terms of CR and PR rates for voclosporin + MMF and MMF alone was conducted. Model-estimated 12-month CR and PR rates were generally consistent with the raw count data of AURORA 1; which is presented in Table 42.

Table 42: Internal validation of model outputs at 12 months

Treatment	Health state	AURORA 1 data	Model Output
VCS + MMF	CR	40.78%	44.17%
	PR	34.08%	37.05%
MMF	CR	22.47%	25.91%
	PR	29.21%	35.13%

Abbreviations: CR = complete response, MMF = mycophenolate mofetil, PR = partial response, VCS = voclosporin

Additionally, the model and trial were clinically validated in DK via an advisory board and via KOL meetings.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

The direct clinical evidence for the efficacy of voclosporin is based on IPD from the AURORA 1 and 2 trials, which were used to estimate transitions between health states for VCS+MMF and MMF alone arms. There are no specific reasons to expect distinct differences between Danish LN patients and the patients included in the AURORA 1 and 2 trials. Table 43 summarises the inputs included in the model and how they were obtained/estimated. Details on the approach to modelling efficacy are presented in sections 8.2.1 and 8.3, while the transition probabilities are presented in Appendix K Transition probabilities Details on the health state utility values (HSUV) are presented in section 8.4. Safety inputs, grade ≥3 TEAE rates are presented in section 8.2.2.5.

Table 43: Summary of efficacy inputs included in the economic model

Name of estimates	Results from study or indirect treatment comparison (ITC)	Input value used in the model	How is the input value obtained/estimated**
Voclosporin+MMF			
Transition first 36 months	See Section 8.2.1	See Appendix K Transition probabilities	AURORA 1 and 2
Long-term transition	See Section 8.3	See Appendix K Transition probabilities	Literature and KOL feedback. See Section 8.3
Treatment waning	See Section 8.3.4	See Section 8.3.4	Assumption
TTD	See Section 8.3.5	See Section 8.3.5	AURORA 1 and 2
Grade ≥3 TEAE	See Section 8.4.1.4	See Section 8.4.1.4	AURORA 1 and 2
MMF			
Transition first 36 months	See Section 8.2.1	See Appendix K Transition probabilities	AURORA 1 and 2
Long-term transition	See Section 8.3	See Appendix K Transition probabilities	Literature and KOL feedback. See Section 8.3
Treatment waning	See Section 8.3.4	See Section 8.3.4	Assumption
TTD	See Section 8.3.5	See Section 8.3.5	AURORA 1 and 2
Grade ≥3 TEAE	See Section 8.4.1.4	See Section 8.4.1.4	AURORA 1 and 2
BEL + MMF/CYC			
Transition first 36 months	See Section 8.2.1.1.2	See Appendix K Transition probabilities	HR from NMA analysis
Long-term transition	See Section 8.3	See Appendix K Transition probabilities	Literature and KOL feedback. See Section 8.3
Treatment waning	See Section 8.3.4	See Section 8.3.4	Assumption

Name of estimates	Results from study or indirect treatment comparison (ITC)	Input value used in the model	How is the input value obtained/estimated**
TTD	No data on TTD was available for non-AURORA regimens	No discontinuation	Assumption
Grade ≥3 TEAE	See Section 8.4.1.4	See Section 8.4.1.4	TEAE literature research

Abbreviations: HR = Hazard ratio, ITC = indirect treatment comparison; KOL = key opinion leader; MMF = mycophenolate mofetil; NMA = network meta-analysis; TEAEs = treatment-emergent adverse event; TTD = time to treatment discontinuation

8.2.1.1 Methods for Transition probabilities per health state

The health states included within CKD stages 1-3a are informed by the AURORA 1 and AURORA 2 trial data. The response data estimated from the trial for use in the model focused on eGFR levels which corresponded with CKD progression thresholds, defined as:

- CKD 1: >90ml/min/1.73m^2
- CKD 2: 60–89ml/min/1.73m^2
- CKD 3a: 45–59ml/min/1.73m^2
- CKD 3b: 30-44ml/min/1.73m^2
- CKD 4: 15–29ml/min/1.73m^2
- CKD 5: <15ml/min/1.73m^2

The count data in the trial also captured eGFR changes based on a single timepoint measurement of eGFR. Changes to eGFR need to be confirmed over time to determine progression of CKD (12). As eGFR levels are also associated with reversible dips due to either a flare or other factors such as medication or dehydration. Our decision problem focuses on modelling CKD progression to confirmed and irreversible eGFR changes which result in deterioration in kidney function defined by CKD thresholds as opposed to the reversible changes in eGFR levels.

At baseline, two sets of eGFR levels (low and high) were identified. This indicated that after the screening, a proportion of patients had lower eGFR levels, which did not align with the inclusion criteria for the cohort of patients that are being modelled. However, as noted in the AURORA 2 CSR, no subjects experienced CKD as defined by eGFR < 60 ml/min/1.73m^2 for more than 3 months, irrespective of kidney damage (136). Therefore, for the purposes of the model, the low and high eGFR patients at baseline were combined, since at screening these patients were eligible for inclusion in the trial.

Transition probabilities were generated by counting the transitions per period (termed the 'count method'). A second approach was explored by fitting a multinomial logit model per transition per health state. However, the multinomial method provided unrealistic outcomes, specifically the results did not match the trial data. Therefore, the approach was not incorporated into the model.

8.2.1.1.1 The count method

In the AURORA 1 trial, all patients are assumed to begin in the CKD 1-3a AD health state, due to average baseline eGFR being in CKD stage 1 for both treatment groups.

For every six-month period, the transition of each patient to CR, PR or death is recorded. A transition probability can be generated for each transition within the CKD stages 1-3a by dividing the number of transitions from some health state A to health state B by the total number of patients starting in health state A at the beginning of the six-month period. This method resulted in six transition matrices for both VCS+MMF and MMF alone, one for each six-month period in the 36-month period spanning AURORA 1 and AURORA 2. AURORA 1 is used to inform the transitions between baseline to 6 months and 6 months to 12 months, with AURORA 2 being used to inform the transitions from 12 months onwards. As not every patient that completed AURORA 1 went on to AURORA 2, there is censoring occurring between the second and the third transition period. The transition probabilities for voclosporin+MMF and MMF can be found in Appendix K Transition probabilities

8.2.1.1.2 Application of the indirect treatment comparison

For the effectiveness of belimumab, the NMA results were used to calculate the transition probabilities. Since the NMA reports the odds ratio anchored on MMF, this must be adjusted to return the transition probability per treatment. The indirect treatment comparison (ITC) results used in the cost-effectiveness model are presented in Table 44 and Table 45.

Table 44: ITC CR results included in the cost-effectiveness model

Treatment	Median OR	CrI 2.5%	CrI 97.5%
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BEL = belimumab; CR = complete response; CrI = credible interval; CYC = cyclophosphamide; ITC = indirect treatment comparison; MMF = mycophenolate mofetil; OR = odds ratio; VCS = voclosporin

Table 45: ITC PR results included in the cost-effectiveness model

Treatment	Median OR	CrI 2.5%	CrI 97.5%
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BEL = belimumab; CrI = credible interval, CYC = cyclophosphamide; ITC = indirect treatment comparison; MMF = mycophenolate mofetil, OR = odds ratio, PR = partial response VCS = voclosporin

ITC ORs (vs MMF) were adjusted to estimate the transition probability per treatment. To apply the indirect treatment comparison (ITC) OR to the transition probabilities of MMF, the following formula is used, where O_X is the odds of treatment X and $OR_{X,Y}$ is the OR of treatment X vs. treatment Y:

$$\frac{O_{MMF} * OR_{X,MMF}}{O_{MMF} * OR_{X,MMF} + 1}$$

This simplifies to the transition probability of treatment X, since

$$O_{MMF} * OR_{X,MMF} = O_{MMF} * \left(\frac{O_X}{O_{MMF}}\right) = O_X$$

$$\frac{O_{MMF} * OR_{X,MMF}}{O_{MMF} * OR_{X,MMF} + 1} = \frac{O_X}{O_X + 1}$$

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The modelled patient population is presented in Table 46. The patient population is based on the AURORA 1 trial reflecting the start of the model (12).

Table 46: Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice [ITQ] (source)
Age (years)	33.2 (12)	33.2 (12)	42 [31-56] (6)
Female %	87.7% (12)	87.7% (12)	76% (6)
Weight	66.5 kg (12)	66.5 kg (12)	No particular reason to expect this to vary from the Danish population
Height	161.6 cm (12)	161.6 cm (12)	No particular reason to expect this to vary from the Danish population

Abbreviations: ITQ = interquartile range

8.2.2.2 Intervention

Table 47: Intervention

Voclosporin + MMF	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	The recommended starting dosage of voclosporin is 23.7 mg twice daily. Oral MMF at a target dose of 2 g/day (1 g twice a day). (Patients not already receiving MMF were started on MMF 500 mg twice a day with escalation to MMF 1 g twice a day after the first week.) Dose increases up to 3 g/day were allowed (12)	23.7 mg voclosporin twice daily 2.5 g MMF per day (12)	Per Summary of Product Characteristics (SmPC) (when published)
Criteria for discontinuation	Stopping rule assumptions were applied on the basis that patients received up to 36 months of treatment with voclosporin + MMF and MMF alone across the AURORA 1 and AURORA 2 trials. In particular, 87.1% of all patients enrolled in AURORA 2 reached Month 36 of treatment with voclosporin + MMF (15).	A 36-month stopping rule is applied for voclosporin + MMF and all other treatments in line with the length of the AURORA trial (15).	Per SmPC (when published). Danish KOLS confirmed that they would limit the treatment period to 36 months equal to the AURORA trial period.
Treatment effect waning	See section 8.3.4	See section 8.3.4	N/A

Abbreviations: KOLs = key opinion leaders; MMF = mycophenolate mofetil; N/A = not applicable; SmPC = Summary of Product Characteristics

8.2.2.3 Comparators

Table 48: Comparator - MMF

MMF	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	Oral MMF at a target dose of 2 g/day (1 g twice a day). (Patients not already receiving MMF were started on MMF 500 mg twice a day with escalation to MMF 1 g twice a day after the first week.) Dose increases up to 3 g/day were allowed.	2.5 g per day	Start dose of 1 g per day (separated into 2-3 doses). Increasing the dose over 14 days to 3g per day if this is well tolerated.
Criteria for discontinuation	Stopping rule assumptions were applied on the basis that patients received up to 36 months of treatment with voclosporin + MMF and MMF alone across the AURORA 1 and AURORA 2 trials. In particular, 87.1% of all patients enrolled in AURORA 2 reached Month 36 of treatment with voclosporin + MMF (15).	A 36-month stopping rule is applied for all treatments. However, patients can continue on MMF as a 2nd line treatment for further 48 months.	KOLs indicated that MMF can be used for a longer period of time. Thus, it was possible to stay on MMF for a total of 36+48=84 months in the model.
Treatment effect waning	See section 8.3.4	See section 8.3.4	N/A

Abbreviations: KOLs = key opinion leaders; MMF = mycophenolate mofetil; N/A = not applicable

Table 49: Comparator - Belimumab + MMF/CYC

Belimumab + MMF/CYC	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	In patients initiating therapy with SC belimumab for active lupus nephritis, the recommended dosage regimen is a 400 mg dose (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter.	Either SC or IV belimumab: SC is 400 mg dose (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter. IV is 665.2 mg administrated	Per Summary of Product Characteristics (67)

Belimumab + MMF/CYC	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
	IV belimumab is administrated at a dose of 10 mg per kilogram of body weight on days 1 (baseline), 15, and 29 and every 28 days hereafter. Standard induction therapy, chosen by the investigators and initiated within 60 days before day 1, consisted of intravenous cyclophosphamide (500 mg every 2 weeks [±3 days] for 6 infusions) or mycophenolate mofetil (target dose, 3 g per day).	at days 1, 15, and 29 and every 28 days hereafter. Either CYC or MMF: CYC is 500 mg every 2 weeks for 6 infusions. MMF is 3 g per day peroral.	
Criteria for discontinuation	Stopping rule assumptions were applied on the basis that patients received up to 36 months of treatment with voclosporin + MMF and MMF alone across the AURORA 1 and AURORA 2 trials (15), despite the BLISS-LN trial only included 104 weeks (24 months) of intervention. No exact stopping rule is applied in the EPAR (67).	A 36-month stopping rule is applied for all treatments.	Clinicians are expected to decide whether the patient should discontinue treatment (67).
Treatment waning	See section 8.3.4	See section 8.3.4	N/A

Abbreviations: EPAR = European public assessment report; CYC = cyclophosphamide; IV = intravenous; MMF = mycophenolate mofetil; N/A = not applicable; SC = subcutaneous

8.2.2.4 Relative efficacy outcomes

The clinical efficacy of Voclosporin+MMF vs. MMF was assessed in the AURORA 1 and 2 trials. The clinical efficacy of voclosporin+MMF vs. belimumab was incorporated into the model based on the results of an ITC linked to MMF as the reference. The application of the ITC was described in section 8.2.1.1.2. The relative efficacy for complete response derived from the ITC is presented in Table 44, while the relative efficacy for PR derived from the ITC is presented in Table 45.

The relative trial outcomes from AURORA 1 and 2 are presented in Table 50 and Table 51. All transition probabilities are presented in Appendix K Transition probabilities

Table 50: Absolut and relative complete response rate for voclosporin+MMF and MMF

	Patients, n (%)			
	Voclosporin+MMF: n=179	MMF: n=178	OR (95% CI)	p-value
CRR at 6 months	58 (32.4)	35 (19.7)	2.43 (1.56, 3.79)	<0.0001
CRR at 12 months	73 (40.8)	40 (22.5)	2.65 (1.6, 4.3)	<0.0001
CRR at 18 months	[redacted]	[redacted]	[redacted]	[redacted]
CRR at 24 months	[redacted]	[redacted]	[redacted]	[redacted]
CRR at 30 months	[redacted]	[redacted]	[redacted]	[redacted]
CRR at 36 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; CRR = complete renal response; MMF = mycophenolate mofetil; OR = odds ratio
Source: AURORA 1 (14) , AURORA 2 CSR(15)

Table 51: Absolut and relative partial response rate for voclosporin+MMF and MMF

	Patients, n (%)		OR (95% CI)	p-value
	Voclosporin+MMF: n=179	MMF: n=178		
PRR at 6 months	126 (70)	89 (50)	2.43 (1.56, 3.79)	< 0.001
PRR at 12 months	125 (70)	92 (52)	2.26 (1.45, 3.51)	< 0.001
PRR at 18 months	[redacted]	[redacted]	[redacted]	[redacted]
PRR at 24 months	[redacted]	[redacted]	[redacted]	[redacted]
PRR at 30 months	[redacted]	[redacted]	[redacted]	[redacted]
PRR at 36 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; PRR = partial renal response; MMF = mycophenolate mofetil; OR = odds ratio
Source: AURORA 1 (14) , AURORA 2 CSR(15)

8.2.2.5 Adverse reaction outcomes

Only grade III/IV TEAEs with an incidence of ≥ 1% in AURORA 1 are included in the base case of the model. Each type of TEAE has an associated frequency per treatment arm. For Voclosporin + MMF and MMF regimens, the AE occurrence rates were sources directly from the AURORA trial.

For belimumab, two options are available in the model:

- Option 1: belimumab + MMF/CYC AEs equal to MMF, as the regime includes MMF
- Option 2: belimumab + MMF/CYC AEs reported by regimen in the pivotal trial (154)

In the base case analysis, option 1 was selected as the most conservative assumption, to avoid the AE rates to be influenced by trial differences. Option 2 was explored in a scenario analysis found in section 8.7.1.3.

The TEAEs event rates are presented in Table 52. Adverse event rates were similar between MMF and voclosporin, with increased anaemia and gastroenteritis in the voclosporin arm, but with increased septicaemia/sepsis in the MMF arm. Belimumab + MMF/CYC is associated with lower/lack of incidence of pneumonia, gastroenteritis, headache and hypertension/hypertensive crisis, compared with voclosporin, but is also associated with incidence of infections/infestations, respiratory/thoracic/mediastinal disorder, blood and lymphatic system disorders and herpes zoster/ varicella zoster virus.

Table 52: Adverse event occurrence

Adverse event	VCS+MMF (SE)	MMF (SE)	Belimumab + MMF/CYC (SE)
Pneumonia	0.04 (0.008)	0.04 (0.009)	0.01 (0.003)
Gastroenteritis	0.02 (0.003)	0.00 (0)	0.00 (0)
Headache	0.01 (0.002)	0.01 (0.001)	0.00 (0)
Hypertension/hypertensive crisis	0.02 (0.004)	0.02 (0.003)	0.00 (0)
Anaemia	0.02 (0.003)	0.00 (0)	0.00 (0)
Neutropenia	0.00 (0)	0.00 (0)	0.00 (0)
Infections and infestations	0.00 (0)	0.00 (0)	0.07 (0.013)
Respiratory, thoracic, and mediastinal disorder	0.00 (0)	0.00 (0)	0.02 (0.004)
Blood and lymphatic system disorders	0.00 (0)	0.00 (0)	0.01 (0.003)
Herpes Zoster/ Varicella zoster virus	0.00 (0)	0.00 (0)	0.01 (0.003)
Nausea and vomiting	0.00 (0)	0.00 (0)	0.00 (0)
Upper respiratory tract infection	0.00 (0)	0.00 (0)	0.00 (0)
Epilepsy	0.00 (0)	0.00 (0)	0.00 (0)
Septicaemia / Sepsis	0.00 (0)	0.02 (0.003)	0.00 (0)
Source:	AURORA 1 (12)	AURORA 1 (12)	Furie 2020 (154)

Abbreviations: CYC = cyclophosphamide; MMF = mycophenolate mofetil; SE=standard error; VCS = voclosporin

8.3 Extrapolation of relative efficacy

For the count data, the model includes 36-month count data (from AURORA 1 and 2), and thereafter a post-follow-up transition matrix is being used. Currently, for the post-follow-up transition matrix, the user has the option to choose between using the transitions of the last included period (36 months) and the average of the transitions from the last two periods (30 and 36 months). The latter is calculated using a macro in Excel. In a scenario analysis, it is tested to set the long-term transition matrix for each treatment to that of MMF.

Relying on the results of the count data for long-term extrapolation has the potential to have large variations based on the choice of the long-term transition matrix. Therefore, the outcomes of the long-term transitions have been validated using external data sources and clinical opinion.

8.3.1 The transition between AD CKD 1-3a and AD CKD 3b-4

Transitions between AD CKD 1-3a to AD CKD 3b-4 were informed by literature searches, external health economists and external KOL experts to reach a plausible estimate for the entire time horizon of the cost-effectiveness model. No

external data sources were identified to provide estimates of progression from CKD 1-3a to CKD 3b-4. However, according to KOL clinical experts, an estimated 15% of patients transition from CKD 1-3a to CKD 3b-4 over 10 years (0.7472% per 6-month cycle). In addition, the transition probability from AD CKD 1-3a to death could be informed by mortality data collected in the MMF arm in AURORA 1 and AURORA 2 ([redacted]% per 6-month cycle) (155, 156), however, the Danish KOLs indicated that this rate was too high by a factor of 5 (0.346% per 6-month cycle).

Table 53 presents the transition probabilities for AD CKD 1-3a which are not treatment-specific. Explicitly, mortality and the transition to AD CKD 3b-4 are assumed to be equal across all treatments.

Table 53. Transition probabilities in CKD stages 1-3a, all treatments

Transition	Transition probability (SE)	Reference
AD CKD 1-3a → AD CKD 3b-4	0.0081 (0.0016)	Danish KOL expert feedback. A probability of 15% transitioning to CKD 3b-4 over 10 years.
AD CKD 1-3a → Death	0.0035 (0.0007)	In absence of LN-related CKD-specific data, the average 6-month mortality rate reported in AURORA 1 and AURORA 2 for the MMF arm (6 deaths recorded over 347 periods of 6 months - 6/347 = 1.73%) was presented for the Danish KOLs. However, the Danish KOLs indicated that this rate was too high by a factor of 5.

Abbreviations: AD = active disease; CKD = chronic kidney disease; KOL: key opinion leader; LN = lupus nephritis; MMF = mycophenolate mofetil; SE= standard error.

As the AURORA 2 trial did not report any incidence of CKD 3b-4 progression, the model includes a toggle for allowing transitions to CKD 3b-4 in the first three years. In the base case, it is assumed patients do not transition into CKD 3b-4.

8.3.2 LN patients with CKD stages 3b-4

Patients transition to active disease in CKD stages 3b-4 from the active disease state in CKD stages 1-3a. From this point on, patients cannot return to an earlier CKD stage, based on the progressive, irreversible damage to nephrons occurring. Therefore, they can remain in active disease, respond, or deteriorate further, reaching CKD stage 5.

Data to support treatment-specific transitions were not identified for LN patients in CKD stage 3b-4. KOLs consulted also noted that the proportion of patients achieving response in this progressed stage can be as low as 2.5-5%. Therefore, in the base case, no patients can reach response states in CKD stage 3b-4, and all patients, regardless of treatment, have the same probability of transitioning to CKD stage 5.

The probability for an LN patient to transition from AD CKD stage 3b-4 to CKD stage 5, dialysis, is informed using the KOL provided probability of 3.5% over 10 years (0.1748% per 6-month cycle). Transitions to death could be informed by a CKD-specific literature review on transitions reported in CKD, Sugrue et al., 2019 (157) which reported an 8% yearly rate which was presented for KOL experts. The KOLs agreed that the true mortality for LN patients was lower than found in CKD publications by a factor of 5 (0.7842% per 6-month cycle).

Table 54. Transition probabilities in CKD stages 3b-4, all treatments

Transition	Transition probability (SE)	Reference
AD CKD 3b-4 → CR CKD 3b-4	0 (0)	Assumption based on lack of data being identified
AD CKD 3b-4 → PR CKD 3b-4	0 (0)	Assumption based on lack of data being identified
AD CKD 3b-4 → CKD stage 5, dialysis	0.0017 (0.0003)	KOL expert feedback. Probability of 3.5% over 10 years
AD CKD 3b-4 → Death	0.0078 (0.0016)	KOL expert feedback. Estimated the Sugrue et al., 2019 (157) input of an 8% yearly rate was too high by a factor 5
AD CKD 3b-4 → AD CKD 3b-4	0.9904 (0.1981)	Remaining probability

Abbreviations: AD = active disease; CKD = chronic kidney disease; CR = complete response; KOL: key opinion leader; PR = partial response.

8.3.3 LN patients with CKD stage 5

A targeted literature search was undertaken and identified no LN-specific data to inform this state. As such, KOL expert feedback was sought to confirm the relevance of CKD-specific data for LN patients.

KOLs reported that 90% of LN patients who enter CKD stage 5 receive a transplant within 2 years (43.77% per 6-month cycle). This is a higher rate than reported in the literature for CKD patients, as the average LN patient is younger and therefore more suitable for receiving a transplant.

To estimate a mortality transition probability for LN dialysis patients, a CKD-specific transition rate of 15.54% from Palmer et al., 2014 (158) was presented for the KOLs. KOLs disagreed on whether this rate was representative of Danish clinical practice or whether this rate was too high (suggesting the rate was too high by a factor of 2). An approach was taken to average this out (6.42% per 6-month cycle). The transition probabilities for dialysis patients are presented in Table 55.

The clinicians also stated that LN patients have an additional risk of mortality due to LN-related cardiovascular events. However, no LN-specific sources were identified for mortality risks in CKD stage 5, and as such, it was considered an assumption that no LN-related cardiovascular events are included in the model. This assumption is conservative as VCS+MMF results in patients remaining longer in CKD 1-3a stages, and as such, it would primarily be comparators who would have been incurring LN-related cardiovascular event costs.

For the transition for the transplanted patients back to dialysis, the yearly transition probability of 6% from Palmer et al., 2004 (158) was used and confirmed with KOLs (3.05% per 6-month cycle). For the mortality transition probability for transplanted patients, the yearly rate of 5.3% from Surgrue et al., 2019 (157) was used and confirmed with KOLs (2.62% per 6-month cycle). The transition probabilities for transplanted patients are presented in Table 56.

Table 55. Transition probabilities in CKD stage 5 dialysis, all treatments

Transition	Transition probability (SE)	Reference
CKD Stage 5 dialysis → CKD Stage 5 transplant	0.4377 (0.0875)	KOL expert feedback. Probability of 90% transplant over 2 years
CKD Stage 5 dialysis → Death	0.0642 (0.0128)	KOL expert feedback and Palmer et al., 2004 (158)
CKD Stage 5 dialysis → CKD stage 5 dialysis	0.4982 (0.0996)	Remaining probability

Abbreviations: CKD = chronic kidney disease; KOL = key opinion leader; SE= Standard error.

Table 56: Transition probabilities in CKD stage 5 transplant, all treatments

Transition	Transition probability (SE)	Reference
CKD Stage 5 transplant → CKD Stage 5 dialysis	0.0305 (0.0061)	KOL expert feedback and Palmer et al., 2004 (158)
CKD Stage 5 transplant → Death	0.0262 (0.0052)	KOL expert feedback and Sugrue et al., 2019 (157)
CKD Stage 5 transplant → CKD Stage 5 transplant	0.9434 (0.1887)	Remaining probability

Abbreviations: CKD = chronic kidney disease; KOL = key opinion leader; SE= Standard error.

8.3.4 Treatment effect waning

The model includes a function to apply treatment waning after 36 months (i.e., after the AURORA trial period). The stopping rule stops treatment (and treatment costs) after a certain period of time, and therefore waning of the treatment effect at this time should be considered. AURORA 1 and AURORA 2 trials have collected data for up to 36 months of patient follow-up for patients treated with either VCS+MMF or MMF (each in combination with corticosteroids). Therefore, there is some uncertainty in terms of any sustained efficacy benefit beyond the duration of the trial, although any loss of treatment effect is unlikely to occur instantaneously.

The functionality in the model allows for two scenarios. In the base case, the VCS+MMF transition probabilities to an average (i.e., midpoint) of those recorded within the AURORA 2 trial at months 30 and 36 for the VCS+MMF arm, and those recorded at months 30 and 36 months for the MMF alone arm. Similarly, for all other treatments, long-term health state transition probabilities wane to an average of those derived from ITC data and those recorded at months 30 and 36 months for the MMF alone arm in AURORA 2. A more extreme scenario is explored in which the long-term transition probabilities for VCS+MMF and other interventions are set to match MMF (as opposed to the mid-point) after the trial period, i.e., from 36 months. In both scenarios, the treatment waning effect is applied to all treatments

following treatment discontinuation and maintained for the outstanding duration of the lifetime horizon. This is presented in section 8.7.1.3.

8.3.5 Time to event data - summarized:

Patient-level data from the AURORA 1 and 2 trials was used to generate the time to treatment discontinuation (TTD) outcomes for both voclosporin + MMF and MMF. In the base case analysis, parametric models were fitted to the Kaplan-Meier TTD data from AURORA 1 and AURORA 2 trials (Figure 13) to estimate treatment discontinuation for patients over the 36-month treatment period. The model duration of treatment is determined by the TTD curves of the voclosporin + MMF and MMF-only treatment arms. [redacted]

[redacted]

Figure 13: Time to study drug discontinuation (AURORA 1 and AURORA 2)

[redacted]

Abbreviations: BID = twice daily
Source: Otsuka 2022(159)

Parametric model fitting for TTD was conducted according to the following steps recommended in the NICE DSU TSD 14 (160). Proportional hazards (PH) assumption was tested between treatment arms (Section 8.3.5.1), which inferred the choice of fitting independent or dependent models. If the PH assumption could not be rejected, a single dependent model for each survival curve was estimated, with treatment modelled as a single covariate. Otherwise, an independent model was fitted.

Following the PH test, parametric survival models were fitted to the survival data of the pivotal trial (Section 8.3.5.2). An initial selection of extrapolation models was based on visual inspection and statistical fit of the models to the trial data, based on Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC), as well as visual inspection of the survival and hazard curves. [redacted]

[redacted]

8.3.5.1 Proportional hazards assumption

The PH assumption was tested to indicate whether it may be preferable to separately fit parametric models to each treatment arm (voclosporin + MMF and MMF alone). The PH assumption was investigated by constructing log-cumulative hazard plots, and performing both a Schoenfeld residuals test, and a Supremum test. [redacted]

Figure 14: TTD log-cumulative hazard plot (AURORA 1 and AURORA 2)

Abbreviations: BID = twice daily; TTD = time to treatment discontinuation
Source: Otsuka 2022 (159)

Figure 15: TTD Schoenfeld residual plot (AURORA 1 and AURORA 2)

Abbreviations: TTD = time to treatment discontinuation
Source: Otsuka 2022 (159)

8.3.5.2 Survival model selection

Exponential, Weibull, log-normal, log-logistic and gamma parametric distributions were fitted to the trial TTD data and final model selection was based on statistical fit (AIC and BIC) and visual inspection of the extrapolated curves and hazard plots. The five parametric distributions were fit using a dependent model to the TTD Kaplan-Meier data, whereby treatment and MMF use at screening were additional covariates. Based on the AIC and BIC results (Table 57) and the visual fits, the log-logistic distribution was the best fitting distribution and therefore selected for use in the cost-effectiveness model to extrapolate TTD over time for the voclosporin + MMF and the MMF arms. The selected curves are illustrated in Figure 16. Full details of extrapolation are provided in Appendix G Extrapolation. No adjustment was required for treatment switching/cross-over as this did not occur in the trial.

Table 57: AIC and BIC values for TTD extrapolations

Distributions	AIC	BIC
Exponential		
Weibull		
Log-logistic		
Gamma		
Log-normal		

Abbreviations: AIC = Akaike's Information Criterion, BIC = Bayesian Information Criterion; TTD = time to treatment discontinuation

Figure 16: Selected TTD curves for MMF and voclosporin+MMF

KM = Kaplan–Meier; MMF = Mycophenolate mofetil; TTD = time to discontinuation; VCS = voclosporin
The estimates are based on the log-logistic curves

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

8.4.1.1 HRQoL from the clinical trials

HRQoL data were collected in the AURORA 1 trial using the LupusPRO and SF-36 PRO questionnaires at baseline, Week 12, Week 24, and Week 52 of the study. Additional HRQoL data was then collected in the AURORA 2 trial using the SF-36 PRO questionnaire every six months until 36 months from AURORA 1 baseline. Two sets of analyses were performed, to include only patients in AURORA 1 assessed over a 12-month period, or those who entered AURORA 2 for assessment of up to 36 months. Both analyses were conducted as the AURORA 1 population starts with a larger sample size, while the combined AURORA 1 and AURORA 2 population has data until 36 months. Due to the longer data period, the combined AURORA 1 and AURORA 2 population data was used to inform the base case. The cost-effectiveness model also includes an option to choose from either AURORA 1 or the AURORA 2 utility estimates. However, health state-specific utility values were required to calculate the cost-effectiveness of treatments in terms of incremental cost per QALY in accordance with DMC guidelines (140). A summary of the SF-36 PRO over time from the AURORA and AURORA 2 trials and a summary of the LupusPro v1.7 from the AURORA trial are provided in Appendix L Summary of patient-reported outcomes

8.4.1.2 Mapping

SF-36 data can be used to generate utility values by conversion to EuroQol Five Dimension (EQ-5D) scores. Although SF-36 data may be mapped to EQ-5D data. Currently, there are no available conversion methods to generate utility values from LupusPRO, and therefore it was not possible to use the disease-specific instrument in a scenario analysis for the economic model.

Using SF-36-derived EQ-5D utility values, linear mixed-effects models (LMMs) were then used to generate health state-specific values (Appendix I Mapping of HRQoL data). As HRQoL data is typically collected by repeat measurements over time, observations tend to be correlated between time points (i.e., time-dependent). LMMs were chosen to account for the longitudinal nature of the HRQoL data and explore the influence of patient demographics and time from treatment on health state-specific EQ-5D values. LMMs represent a robust method to produce unbiased estimates of the impact of risk factors under the 'missing-at random' assumption and are often used to analyse PRO data which is typically both longitudinal and hierarchical in nature (i.e., level 1 = repeated measures; level 2 = patient factors) (161, 162).

As the AURORA 1 and 2 studies did not collect EQ-5D data, the SF-36 data were mapped into EQ-5D three-level data (EQ-5D-3L). However, this excluded the possibility of applying Danish-specific preference weights as an algorithm using Danish weights is not available, and instead UK weights are used. As patient-level SF-36 data were available from the AURORA 1 and AURORA 2 studies, the Rowen et al., 2009 method (163) was used to convert SF-36 to EQ-5D-3L. The Rowen algorithm has been both validated and published, as required by Danish submission guidance. A summary of AURORA 1 and AURORA 2 SF-36 scores is provided in Appendix I Mapping of HRQoL data and the mapped EQ-5D scores are presented below in Table 58.

Table 58: Summary of mapped EQ-5D scores based on SF-36 data (AURORA 1 and AURORA 2)

Study visit	n	Mean (SD)	Median	Q1/Q3	Min/Max
Baseline	215	0.70 (0.19)	0.73	0.58/0.86	-0.02/0.97
Month 6	215	0.77 (0.17)	0.80	0.66/0.90	-0.00/0.99
Month 12	215	0.80 (0.16)	0.85	0.71/0.92	0.18/0.99
[redacted]					

Abbreviations: EQ-5D = EuroQol 5 Dimension; Max = maximum; Min = minimum; SD = standard deviation; SF-36 = 36-Item Short Form Survey; Q1 = first quartile; Q3 = third quartile

LMMs were then utilised to generate health state-specific utility values, using the mapped EQ-5D utility values as a dependent variable. Various regression models were then implemented using forward and backward selection model-building methods to identify relevant covariates. The covariates investigated in the models were EQ-5D (baseline), Biopsy Class, MMF Use at Screening, Sex, Treatment Group, Response Category, Response Category at Previous Visit and Age (years), as these variables encompassed standard demographic and disease-specific covariates potentially relevant for utility scores. Biopsy class and MMF use at screening were stratification variables at randomisation. Sex, Age and Treatment Group were included due to the potential clinical relevance. Response Category was the main explanatory variable of interest, so a lag of the same term was also included.

A 'Visit' covariate was included in every model, and each covariate had an interaction term with Visit. Results showed that Sex, MMF Use at Screening, Biopsy class and Response Category at Previous Visit were not significant covariates and therefore were not included in the final best-fitting model. The variables used encompass standard demographic and disease-specific covariates potentially relevant for utility scores. Biopsy class and MMF use at screening were stratification variables at randomisation. Sex, Age and Treatment Group were included due to the potential clinical relevance. Response Category was the main explanatory variable of interest, so a lag of the same term was also included.

The results demonstrated that AD is associated with the lowest utility value followed by PR and CR; and a trend in utility was observed values over the first 18 months. A summary of mapped EQ-5D scores by Visit and patient response status is presented in Table 59.

Table 59: Summary of mapped EQ-5D by Visit and response status

Study visit	Response category	n	Mean (SD)
Baseline	AD: Non-Response	215	0.70 (0.19)
Month 6	CR	73	0.77 (0.15)
	PR	86	0.79 (0.17)
	AD: Non-Response	56	0.72 (0.18)
Month 12	CR	95	0.81 (0.15)
	PR	77	0.81 (0.15)
	AD: Non-Response	43	0.74 (0.20)
[redacted]			

Abbreviations: AD = active disease; CR = complete response; EQ-5D = EuroQol 5 Dimension; PR = partial response; SD = standard deviation

8.4.1.3 Health-related quality-of-life studies

An SLR was also conducted to identify relevant HRQoL studies for LN and humanistic outcomes associated with voclosporin and the relevant comparators. The SLR identified 15 HRQoL studies, although no articles assessing utility values in LN were identified. Economic models identified by the SLR and an accompanying targeted literature review included health state-specific utilities. Additional targeted literature reviews were also performed to identify recent and relevant CKD-specific utility estimates outside of the scope of the SLR.

Further three studies were identified in a desktop search during the validation of the application. These are also included below. An overview of all health state-specific estimates identified is presented in Table 60, while the literature review for HRQoL is presented in Appendix H – Literature search for HRQoL data.

Table 60: Overview of all identified utility estimates by health state

Health state	Options for utilities	Source
CKD 1–3a		
CR	Option 1: 0.800 (SE: 0.160) EQ-5D, Sweden	Bexelius et al., 2013 (164) / Institute for Clinical and Economic Review 2021 (147)
	Option 2: 0.820 (SE: 0.180) Time trade-off UK SLE population reporting on mild, moderate, severe SLR flares, and severe renal flares	Pollard et al., 2015 (165)
	Option 3: 0.750 (SE: 0.180) EQ-5D, US Corresponds to a SLEDAI score < 5	Aggarwal et al., 2009 (166)
PR	Decrement: -0.090 (SE: -0.018)	Mohara et al., 2014 (145) / Institute for Clinical and Economic Review 2021 (147)
AD	Option 1: -0.176 (SE: -0.035)	Mohara et al., 2014 (145)
	Option 2: 0.450 (SE: NR)	Pollard et al., 2015 (165)
CKD 3b–4*		
	Option 1: -0.055 (SE: NR) EQ-5D, UK Decrement is currently between a population of equal parts CKD 1/2 and CKD3a, and a population of equal parts CKD 3b and CKD 4.	Jesky et al., 2016 (153)
	Option 2: -0.052666667 (SE: NR) EQ-5D, Japan Decrement is currently between a population of equal parts CKD 1, 2 and 3, and a population of equal parts CKD 3 and 4.	Tajima et al., 2010 (167)
CKD 5, pre-transplant/dialysis		
	Option 1: Peritoneal dialysis: 0.65 (SE: NR) Haemodialysis: 0.46 (SE: NR EQ 5D, Sweden	Sennfalt et al., 2002 (168)
	Option 2: Peritoneal dialysis: 0.53 (SE: 0.34) Haemodialysis: 0.44 (SE: 0.36) EQ-5D, Wales	Lee et al., 2005 (169)
	Option 3: 0.549 (SE: NR) Decrement as in Mohara, used in the ICER report	Mohara et al., 2014 (145)
	Option 4: 0.690 (SE: 0.14)	Cooper et al., 2020 (170)
	Option 5: 0.774 (SE: 0.004)	Fletcher et al., 2022 (171)
CKD 5, post-transplant		
	Option 1: 0.86 EQ-5D, Sweden	Sennfalt et al., 2002 (168)
	Option 2: 0.71 (SE: 0.27) EQ-5D, Wales	Lee et al., 2005 (169)
	Option 3: 0.73 (IQR:0.62–1) EQ-5D, UK CKD stage 5 utility, not specifically post-transplant	Jesky et al., 2016 (153)
	Option 4: 0.820 (SE: 0.05)	Li et al., 2017 (172)
	Option 5: 0.840 (SE: 0.01)	Fletcher et al., 2022 (171)

*Utility values stratified by response status (i.e., CR, PR, AD) were not identified in the CKD 3b–4 population)
Abbreviations: AD = active disease; CKD = chronic kidney disease; CR = complete response; EQ-5D = EuroQol 5 Dimension; ICER = incremental cost-effectiveness ratio; IQR = interquartile range; NR = not reported; PR = partial response; SE = standard error; SLE = systemic lupus erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SLR = systematic literature review; UK = United Kingdom

8.4.1.4 Adverse event disutilities

Grade 3/4 TEAEs with an incidence of ≥1% in AURORA 1 are incorporated into the base case of the model to reflect the most common AEs which are also expected to have an impact on HRQoL. A summary of AE frequencies is detailed in Section B.3.5.3, alongside costs incurred for the management of each respective AE.

AE disutility values and duration estimates were included to assess the impact of AEs on QALYs, by multiplying an AE disutility value with the AE duration to estimate a QALY decrement which is applied during the first model cycle. AE disutility values and duration of AEs were informed by the SLR presented in Appendix H – Literature search for HRQoL data and additional targeted searches. AE disutility values for pneumonia and gastroenteritis were collected from Kim et al., 2019 (143), a study identified within the economic SLR, given the lack of Danish-specific data. All other studies that reported relevant AE disutility values and duration of AEs were identified from sources within previous NICE Technology Appraisals. Additional PubMed searches did not uncover any additional AE-related information. Therefore, assumptions were used to fill any remaining data gaps where necessary. Blood and lymphatic system disorders were assumed to correspond to anaemia, as anaemia is included within this general category. For Herpes Zoster/Varicella zoster virus, no information could be found, so it was assumed to be equal to gastroenteritis since this AE had a low utility decrement and decrement length, leading to the assumption to not have much effect on the outcome. For the remaining duration, half a week was assumed. AE disutilities and assumed AE durations applied within the model are summarised in Table 61.

Table 61: Disutility and mean duration of AEs

Parameter	Disutility (SE)	Source	Mean duration (days)	Source
Pneumonia	0.310 (0.062)	Kim et al., 2019 (143)	3.50	Assumption, 0.5 weeks
Gastroenteritis	0.006 (0.001)	Kim et al., 2019 (143)	8.00	Hudgens et al., 2016 (173), assumption, equal to diarrhoea
Urinary tract decrements	0.124 (0.025)	Hudgens et al., 2016 (173)	13.00	Hudgens et al., 2016 (173)
Hypertension/ hypertensive crisis	0.153 (0.031)	Swinburn et al., 2010 (174)	8.00	Swinburn et al., 2010 (174)
Anaemia	0.119 (0.024)	Swinburn et al., 2010 (174)	16.07	Swinburn et al., 2010 (174)
Neutropenia	0.090 (0.018)	Kim et al., 2019 (143)	15.09	Nafees et al., 2008 (175)
Infections and infestations	0.200 (0.040)	Beusterien et al., 2010, (176) assumption, same as pneumonia and infections	3.50	Assumption, 0.5 weeks
Respiratory, thoracic, and mediastinal disorder	0.200 (0.040)	Beusterien et al., 2010, (176) assumption, same as pneumonia and infections	3.50	Assumption, 0.5 weeks
Blood and lymphatic system disorders	0.119 (0.024)	Assumption, same as anaemia	16.07	Assumption, same as anaemia
Herpes Zoster/ Varicella zoster virus	0.006 (0.001)	Assumption, same as gastroenteritis	8.00	Assumption, same as gastroenteritis
Nausea and vomiting	0.048 (0.010)	Nafees et al., 2008 (175)	8.00	Assumption, same as gastroenteritis
Upper respiratory tract infection	0.200 (0.040)	Beusterien et al., 2010, (176) assumption, same as pneumonia and infections	3.50	Assumption, 0.5 weeks
Epilepsy	0.140 (0.028)	Stavem et al., 2010 (177)	10.50	NICE TA316 (178)
Septicaemia / Sepsis	0.200 (0.040)	Tolley et al., 2013 (179)	17.85	Assumed average from NICE TA359 (180) and TA370 (181)
Bronchitis	0.069 (0.014)	NICE TA306 (182)	24.00	NICE TA306 (182)

Abbreviations: AE = adverse event; NICE = National Institute of Health and Care Excellence; SE = standard error; TA = technology appraisal

8.4.1.5 Health state utility values used in the health economic model

Utility analyses conducted using data from the AURORA 1 and 2 trials led to clinically implausible results and were not reflective of utility data identified in published literature. AURORA 1 and AURORA 2-derived utility estimates were prioritised over literature-based utility estimates as they were collected within pivotal voclosporin clinical trials and represent utilities for LN-related CKD stages 1-3a. LN-specific utilities could not otherwise be sourced from the literature for CKD stages 1-3a; however, literature sources were used to inform health state-specific utilities for LN-related CKD

stages ≥3b, due to a lack of Danish-specific data, UK data were used. The final approach taken for the response-based health states included in the cost-effectiveness model is based on data collected in AURORA 2, with patients matched to their AURORA 1 data to inform the CKD 1-3a health state, and thus the Month 36 utilities from AURORA 2 are used in the base case, which corresponds to a CR, PR and AD utility of 0.83, 0.80 and 0.71, respectively. Literature-derived utilities (164-166) were used for scenario analysis; however, for the scenario analysis, it was necessary to apply utility decrements to the PR and AD health states from Mohara et al., 2014 (145) (data from Thailand), which may not be relevant to the Danish population.

It is then assumed that the decrement observed in Jesky et al., 2016 (153) between CKD 1-3a and CKD 3b-4 can be applied to the CKD 1-3a CR, PR, and AD utilities. The only other option for these health states was the Japanese study by Tajima et al., 2010 (167). The decrements from Jesky et al., 2016 (153) and Tajima et al., 2010 (167) are very similar, and due to the population differences between Denmark and Japan, the Tajima et al., 2010 (167) data was not used for scenario analysis. The literature was used to inform the utility of the two CKD 5 health states due to an absence of LN-specific values. For the two CKD 5 health states (dialysis and transplanted), Lee et al., 2005 (169) was chosen over Sennfalt et al., 2002 (168) and Jesky et al., 2016 (153), as the Welsh population of Lee et al., 2005 (169) would match the UK data used for CKD 3b-4 health states better than the Swedish data from Sennfalt et al., 2002 (168), however, it was not possible to apply the data from Jesky et al., 2016 (153) to the CKD 5 health states, as this study did not include specific utilities for dialysis and transplanted patients, respectively. Death has been assumed to have a utility of zero.

All utility options were presented in Table 60. Only relevant utility estimates were included in the scenario analyses. A summary of the utility values used in the cost-effectiveness model and the relevant scenarios are presented in Table 62.

Utility values of the model health states are adjusted to account for the natural decrease in QoL associated with age. Adjusting utilities for age can prevent the overestimation of benefits associated with treatment that can occur if otherwise a baseline of perfect health is assumed. The data published by Wittrup-Jensen et al., 2009 (183, 184), is used in the model to provide general Danish population utility estimates, as presented in Table 63. The model also allows the use of the age-specific utility values collected in a pooled analysis of four consecutive health surveys conducted in the English general population by Ara and Brazier, 2011 (185).

In the absence of available data for the individual health states, the reference age for each health state is assumed the same as the age of participants from the AURORA trials with a starting age of 33.2 years.

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Table 62: Summary of utility values for cost-effectiveness analysis

Health state		Utility: mean (SE)	Ref. number	95% CI*	Ref. in submission	Justification	Strengths/ weaknesses	Scenario(s) (SE)
CKD 1–3a	[redacted]	[redacted]	[redacted]	[redacted]	Section 8.4.1	Utility values derived via regression pooled from the pivotal AURORA 1 and AURORA 2 SF-36 trial data	Collected within the pivotal trials. Did not always present expected relationships with health states over time. E.g., the CR health state was estimated to have lower utility values than the PR health state at certain time points (not overall).	0.800 (0.160) Swedish EQ-5D from Bexelius et al., 2013 (164). Decrement: -0.090 (-0.018) Thai from Mohara et al., 2014 (145). Decrement: -0.176 (-0.035) Thai from Mohara et al., 2014 (145).
CKD 3b–4	CR	0.775 ¤ (0.010**)	(153)	0.755, 0.795		In absence of LN-related CKD 3b-4 utility data, a progression-related utility decrement (0.055) was applied to the CKD 1-3a utility values based on a Jesky et al., 2016 (153)	Decrement identified in an observational study from UK, as no Danish study was identified. No CKD 3b-4 utility data in the AURORA trial.	No relevant study identified for scenario analysis
	PR	0.745 ¤ (0.010**)	(153)	0.725, 0.765				
	AD	0.655 ¤ (0.012**)	(153)	0.631, 0.679				
CKD 5	Dialysis	0.690 (0.140)	(170)	0.416, 0.964		Utility values are based on EQ-5D data identified in the publications by Cooper et al., 2020 (170) and Li et al., 2017	No Danish study was identified. No CKD 5 utility data in the AURORA trial.	Utilities identified in Fletcher et al., 2022 (171) were investigated in the scenario analysis. The values were 0.774 for dialysis and 0.840 for transplant
	Trans-plant	0.820*** (0.050)	(172)	0.722, 0.918				

*Assuming a beta distribution.
** SE from the matching health state of CKD 1-3a was used here, as the reference used did not provide.
*** This value will be set to 0.810 in the model equal to CR CKD 1-3a, as it was found clinically implausible that transplanted patients would experience higher utility than patients with a complete response in CKD 1-3a.
¤ Based on a decrement from another health state
Abbreviations: AD = active disease; CI = confidence interval; CKD = chronic kidney disease; CR = complete response; EQ-5D = EuroQol-5 Dimension; HD = heamodialysis; PD = peritoneal dialysis; PR = partial response; ref=reference; SE = standard error; SF-36 = 36-item Short Form Survey

Table 63: EQ-5D Population Norms in Denmark

Age Group	QoL	Source
18 –29	**0,871**	**Wittrup-Jensen et al., 2009 (183)**
30 –39	**0,848**	
40 –49	**0,834**	
50 –69	**0,818**	
70 –79	**0,813**	
80+	**0,721**	

Abbreviations: EQ-5D = EuroQol-5 Domain; QoL = Quality of Life

8.5 Resource use and costs

All costs were valued in 2022 DKK. Where necessary, costs were projected into current value using the index available on the Statistics Denmark website (Table PRIS114).

8.5.1 Resource use

The resource use in the model was informed by the EULAR/ERA-EDTA clinical guidelines (9) and confirmed with KOLs. The average estimated resource use between the KOLs was inputted in the model. The resource use was applied per health state and can largely be considered in three categories: LN-related costs, CKD-related costs, and costs specific to CKD stage 5. The only treatment-specific resources applied were the administration cost. The resource use is presented in Table 65.

The costs related to minor clinical tests and measurements were informed by labportal.dk (186). For the Anti-dsDNA and C3 and C4 level monitoring the prices were not available at labportal.dk, however, the prices for these tests were revealed by staff at Rigshospitalet via the KOLs. A health economic report by 7LIV and DAMVAD Analytics (187) informed the per-cycle cost of dialysis, and costs related to post-kidney transplantation.

As resource use of supplementary medicines for LN patients was not identified in the literature, the resource use of supplementary medicine was informed by a retrospective study from April–December 2014 in Denmark, Finland, Norway, and Sweden by Eriksson et al., 2017 (188), which reported the annual cost of these medicines per CKD stage in autosomal dominant polycystic kidney disease patients. Only the Danish data was used to inform the current health economic analysis. The Eriksson study used the groups, CKD 1-3, CKD 4-5, dialysis, and transplant, which were assumed to be similar to the health states CKD 1-3a, CKD 3b-4, dialysis, and transplant used in this analysis, respectively. Due to the construction of the model, it was not possible to assign a specific cost directly to each health state. This was solved by inputting the CKD 4-5 cost and adjusting for the cost difference between health states in the resource use per cycle (Table 69). The annual cost was reported to Eriksson et al., 2017. The costs the model calculates are presented in Table 64. The remaining costs were informed by the Danish diagnosis-related group (DRG) 2022 tariff system (189). The healthcare resource use categories are presented in Table 66.

Table 64: The annual cost reported to Eriksson et al., 2017, and the costs the model calculates

Costs	Annual cost reported in Eriksson et al., 2017 – DKK (CI 95%)				Cost per patient per cycle (6 months) calculated by the model* – DKK (CI 95%)			
	CKD 1-3	CKD 4-5	Dialysis	Transplant	CKD 1-3a	CKD 3b-4	Dialysis	Transplant
Vitamin D supplements	2,004 (937–3379)	6,955 (5201–8861)	13,309 (12,162–14,207)	4,593 (3,129–6,257)	1,046.01 (489.08-1763.7)	3,630.23 (2,714.71-4,625.09)	6,946.77 (6,348.08-7,415.49)	2,397.36 (1,633.21-3,265.9)
ESAs or EPO	60 (0–245)	3,366 (1,286–5,953)	23,281 (19,497–26,558)	3,449 (1,459–6,102)	31.32 (0-127.88)	1,756.92 (671.24-3,107.23)	12,151.75 (10,176.65-13,862.21)	1,800.24 (761.54-3,185)
Phosphate binders	0	1,351 (656–2,160)	10,551 (8,212–13,158)	521 (123–1,242)	0.00	705.17 (342.41-1,127.43)	5,507.2 (4,286.34-6,867.95)	271.94 (64.2-648.27)
ACE inhibitor or ARB	NR	NR	NR	NR	204.09 (153.98-264.63) **	248.45 (205.65-291.78) **	179.03 (141.97-219.22)**	209.31 (158.15-278.73) **
Anti-hypertensive medication	391 (295–507)	476 (394–559)	343 (272–420)	401 (303–534)	204.09 (153.98-264.63)	248.45 (205.65-291.78)	179.03 (141.97-219.22)	209.31 (158.15-278.73)

*Projected to current value and divided by two to calculate the current half-yearly cost. CIs have also been projected. To represent a half-year cost, this assumes that the CIs are proportionate to the mean

** Assumed same as Anti-hypertensive medication

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CI = confidence interval; CKD = chronic kidney disease; DKK = Danish Kroner; ESAs = erythropoiesis-stimulating agents: EPO = erythropoietin; NR = not reported.

Table 65: Resource use per health state

Resource	CR CKD 1-3a		PR CKD 1-3a		AD CKD 1-3a		CR CKD 3b-4		PR CKD 3b-4		AD CKD 3b-4		CKD 5 dialysis		CKD 5 transplant		
	Cycle 1	Cycle 2+	Cycle 1	Cycle 2+	Cycle 1	Cycle 2+	Cycle 1	Cycle 2+	Cycle 1	Cycle 2+	Cycle 1	Cycle 2+	Cycle 1	Cycle 2+	Cycle 1	Cycle 2	Cycle 3+
Specialist visit	2.50	2.50	5.50	5.50	7.50	7.00	2.50	2.50	5.50	5.50	7.50	7.00	2.50	2.50	22.00	5.00	2.00
Kidney biopsy	-	-	-	1.00	1.00	1.00	-	-	-	1.00	0.50	1.00	-	-	-	-	-
Urinalysis*	2.50	2.50	8.00	5.00	10.00	7.00	2.50	2.50	8.00	5.00	10.00	7.00	-	-	22.00	5.00	2.00
Complete blood count	2.50	2.50	8.00	5.00	10.00	7.00	2.50	2.50	8.00	5.00	10.00	7.00	4.50	4.50	22.00	5.00	2.00
S-immunoglobulin measurement	0.75	0.75	2.00	1.50	2.00	3.00	0.75	0.75	2.00	1.50	2.00	3.00	-	-	2.00	1.00	-
Chronic infection screening	1.75	1.75	8.00	5.00	10.00	7.00	1.75	1.75	8.00	5.00	10.00	7.00	4.50	4.50	22.00	5.00	2.00
Cholesterol and lipid monitoring	1.25	1.25	1.25	1.25	1.75	1.75	1.25	1.25	1.25	1.25	1.75	1.75	1.50	1.50	2.00	1.00	0.75
Anti-dsDNA and C3 and C4 monitoring	1.50	1.50	4.00	3.00	4.00	4.00	1.50	1.50	4.00	3.00	4.00	4.00	1.00	1.00	1.50	1.50	0.50
Dialysis	-	-	-	-	-	-	-	-	-	-	-	-	1.00	1.00	-	-	-
Initial assessment for kidney transplant	-	-	-	-	-	-	-	-	-	-	-	-	1.00	-	-	-	-
Transplant waiting list clinic attendance	-	-	-	-	-	-	-	-	-	-	-	-	0.50	0.50	-	-	-
Kidney transplantation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.00	-	-
Post-kidney transplantation Y1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.50	0.50	-
Post-kidney transplantation Y2+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.50
Vitamin D supplements	0.29	0.29	0.29	0.29	0.29	0.29	1.00	1.00	1.00	1.00	1.00	1.00	1.91	1.91	0.66	0.66	0.66
ESAs or EPO	0.02	0.02	0.02	0.02	0.02	0.02	1.00	1.00	1.00	1.00	1.00	1.00	6.92	6.92	1.02	1.02	1.02
Phosphate binders	-	-	-	-	-	-	1.00	1.00	1.00	1.00	1.00	1.00	7.81	7.81	0.39	0.39	0.39
ACEi or ARB	0.82	0.82	0.82	0.82	0.82	0.82	1.00	1.00	1.00	1.00	1.00	1.00	0.72	0.72	0.84	0.84	0.84
Anti-hypertensive medication	0.82	0.82	0.82	0.82	0.82	0.82	1.00	1.00	1.00	1.00	1.00	1.00	0.72	0.72	0.84	0.84	0.84
Ultrasound	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5.50	1.00	0.25
Echocardiogram	-	-	-	-	0.75	1.00	-	-	-	-	0.75	1.00	-	-	-	-	-

*Includes GFR, serum albumin, proteinuria and urinary sediment

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; AD = active disease; ARB = angiotensin receptor blocker; anti-dsDNA = anti-double-stranded deoxyribonucleic acid; CKD = chronic kidney disease; CR = complete response; ESA = erythropoiesis-stimulating agents; EPO = erythropoietin; GFR = glomerular filtration rate; PR = partial response

Table 66: Cost per healthcare resource use categories

Costs	Unit cost (DKK)	Reference
Specialist visit	2,041	DRG 2022: 09MA98: MCD09 1-dagsgruppe, pat. Mindst 7 år. Diagnosis: Lupus Erythematosus DL930A (189)
Kidney biopsy	5,999	DRG 2022: 11PR01 - Cystoskopi, kompliceret, el. urinrørsoperationer el. punktur af prostata (189)
Urinalysis*	122	Labportal: NPU09102 (creatinin [GFR]), NPU19677(Albumin), NPU03958 (protein;U), Internal prices (186)
Complete blood count	46	Labportal: NPU17580 (Leukocytetypes), NPU02902 (neutrofilocytes), and NPU02319 (Haemaglobin + thrombocytes). Internal prices (186)
Serum immunoglobulin measurement	87	Labportal: NPU19795 (IgA), NPU19814 (IgG), NPU19825 (IgM). Internal prices (186)
Chronic infection screening	31	Labportal: NPU19748 (C-reaktivt protein [CRP];P), and NPU04100 (B—Leukocyttype; antalk.) internal prices (186)
Cholesterol and lipid monitoring	91	Labportal: NPU01568 (LDL cholesterol), NPU01569 (VLDL), and NPU01567 (HDL). Internal prices (186)
Anti-dsDNA and C3 and C4 level monitoring	619	Labportal: NPU16393 DNA(dobbeltstrenget)-antistof(IgG);P, NPU19740 Complement C3;P, NPU19742 Complement C4;P (prices revealed by staff from Rigshospitalet
Dialysis	198,206	Samfundsøkonomisk gevinst ved nyretransplantation - DAMVAD Analytics for 7LIV, 2017 and weighting from DNSL Annual report 2020 (187)
Initial assessment for kidney transplant	2,038	DRG 2022: 11MA98 - MDC11 1-dagsgruppe, pat. mindst 7 år (189)
Waiting list clinic attendance (pre-transplant)	2,038	DRG 2022: 11MA98 - MDC11 1-dagsgruppe, pat. mindst 7 år (180)
Kidney transplantation	262,079	DRG 2022: 11MP02 – Nyretransplantation (189)
Post-kidney transplantation, year 1	78,412	Samfundsøkonomisk gevinst ved nyretransplantation - DAMVAD Analytics and 7LIV, 2017 (187)
Post-kidney transplantation, year 2+	37,471	Samfundsøkonomisk gevinst ved nyretransplantation - DAMVAD Analytics and 7LIV, 2017 (187)
Vitamin D supplements	3,630	Eriksson et al., 2017 (188)
ESAs or EPO	1,757	Eriksson et al., 2017 (188)
Phosphate binders	705	Eriksson et al., 2017 (188)
ACE inhibitor or ARB	248	Assumed same as Anti-hypertensive medication
Anti-hypertensive medication	248	Eriksson et al., 2017 (188)
Ultrasound	1,462	DRG 2022: 30PR11 - UL-scanning, ukompliceret (189)
Echocardiogram	1,910	DRG 2022: 05PR04 - Kardiologisk undersøgelse, udvidet (189)

*includes GFR, serum albumin, proteinuria and urinary sediment

Abbreviations: ACE = Angiotensin-converting enzyme; anti-dsDNA = anti-double-stranded deoxyribonucleic acid; ARB = angiotensin receptor blocker; DKK = Danish Kroner; ESAs = erythropoiesis-stimulating agents, EPO = erythropoietin; GFR = glomerular filtration rate

8.5.2 Intervention costs

Voclosporin is an oral treatment provided as capsules containing 7.9 mg. The list price is DKK 6,750 for a package containing 180 capsules. The recommended dosing of voclosporin is 23.7 mg twice daily. Voclosporin is recommended in combination with MMF. Four different formulations of MMF were identified, and the recommended dose of MMF is between 2000 and 3000 mg per day. Table 67 summarises the drug costs for the Voclosporin + MMF regime. As both voclosporin and MMF are administrated orally, no administration costs were assumed for the voclosporin + MMF regime. Patients are assumed to receive voclosporin for a maximum of 3 years before preceding to second-line treatment corresponding to the total time horizon of AURORA 1 and AURORA 2.

Table 67: Drug costs for the voclosporin + MMF regime

Drug (administration)	Strength (mg)	Cost per pack (DKK)	Units per pack	Cost per mg (DKK)
Voclosporin (oral)	7.9	6,750	180	5.63
MMF (oral)	180	925.65	120	0.04

	250	537.00	300	0.01
	360	1,851.30	120	0.04
	500	770.00	150	0.01

Abbreviations: DKK = Danish Kroner; MMF = mycophenolate mofetil

8.5.3 MMF regime

Four different formulations of MMF were identified. For MMF alone, the recommended dose of MMF is also between 2000 and 3000 mg per day. The MMF regime was modelled in line with the AURORA trials with an average daily dose of 2500 mg (12). Table 68 summarises the drug costs for the MMF regime. As MMF is administrated orally, no administration costs were assumed for the MMF regime. In line with the Voclosporin + MMF regime, patients are assumed to receive MMF for a maximum of 3 years before preceding to second-line treatment.

Table 68: Drug costs for the MMF regime

Drug (administration)	Strength (mg)	Cost per pack (DKK)	Units per pack	Cost per mg (DKK)
MMF (oral)	180	925.65	120	0.04
	250	537.00	300	0.01
	360	1,851.30	120	0.04
	500	770.00	150	0.01

Abbreviations: DKK = Danish Kroner; MMF = mycophenolate mofetil

8.5.4 Belimumab + MMF/CYC regime

Three different formulations of belimumab were identified, two IV formulations of 120 mg and 400 mg and one SC formulation of 200 mg. The AIP per pack for the 120 mg IV is DKK 1,179.84 and DKK 3,932.80 for the 400 mg each containing one unit. The AIP per pack for the 200 mg SC formulation is DKK 6,545.57 containing four units. Belimumab can be administrated either IV or SC. Belimumab IV is administrated at 10 mg/kg every two weeks for three doses, and 10 mg/kg every four weeks thereafter. Belimumab SC is administrated at 200 mg once weekly (67). Belimumab is recommended in combination with either MMF or cyclophosphamide. In the model, 74% of patients were assigned to MMF 3000 mg/day and 26% of patients were assigned to 500 mg IV cyclophosphamide every two weeks for six cycles in line with the belimumab pivotal trial (84). Four different formulations of MMF and three different formulations of cyclophosphamide were identified. Table 69 summarises the drug costs for the belimumab + MMF regime. Costs related to IV and SC administration are described in section 8.5.7. In line with the Voclosporin + MMF regime, patients are assumed to receive belimumab + MMF/CYC for a maximum of 3 years before preceding to second-line treatment.

Table 69: Drug for the belimumab + MMF/CYC regime

Drug (administration)	Strength (mg)	Cost per pack (DKK)	Units per pack	Cost per mg (DKK)
Belimumab (IV)	120	1,179.84	1	9.83
	400	3,932.80	1	9.83
Belimumab (SC)	200	6,545.57	4	8.18
MMF (oral)	180	925.65	120	0.04
	250	537.00	300	0.01
	360	1,851.30	120	0.04
	500	770.00	150	0.01
Cyclophosphamide (IV)	200	61.04	1	0.31
	500	180.00	1	0.36
	1000	330.00	1	0.33

Abbreviations: DKK = Danish Kroner, IV = intravenous, MMF = mycophenolate mofetil, SC = subcutaneous

8.5.5 Second-line treatment

Following the initial 36 months of treatment, patients in the model proceed to second-line treatment. The drug cost of the second-line treatments is presented in Table 70, the dosing scheme of the second-line treatment regimens is presented in Table 71, and the percentage of patients receiving the regimens is presented in Table 72.

Table 70: Drug cost - second-line treatment

Drug (administration)	Strength (mg)	Cost per pack (DKK)	Units per pack	Cost per mg (DKK)
MMF (Oral)	180	925.65	120	0.04
	250	537.00	300	0.01
	360	1,851.30	120	0.04
	500	770.00	150	0.01
Azathioprine (oral)	25	67.34	50	0.05
	50	34.30	100	0.01
Rituximab (IV)	100	2,675.80	2	13.38
	500	6,687.00	1	13.37
	1400	12,377.73	1	8.84
Tacrolimus (Oral)	.50	385.76	50	15.43
	.75	577.75	50	15.41
	1	595.48	50	11.91
	2	856.04	50	8.56
	3	1,900.52	50	12.67
	4	2,894.25	50	14.47
	5	1,894.25	50	7.58

Abbreviations: DKK = Danish Kroner; IV: intravenous, MMF = mycophenolate mofetil

Table 71: Second-line treatment regimens

Regimen	Drug name	Dosing schedule	Stopping rule	Reference
MMF	MMF	1000-2000 mg/day, oral	48 months	EULAR/ERA-EDTA (9)
Azathioprine	Azathioprine	2 mg/kg/day, oral	48 months	EULAR/ERA-EDTA (9)
	Prednisone	2.5–5 mg/day, oral, when needed to control disease activity		
Rituximab + MMF	Rituximab	1000 mg IV on days 1, 15, 168, and 182	36 months	Rovin et al., 2012 (86) and assumption
	MMF	3000 mg per day, oral		
	Methylprednisolone	1,000 mg IV, on day 1 and again within 3 days, and 100 mg IV on days 15, 168 and 182		
	Prednisone	Dosage of 0.75 mg/kg/day (max 60 mg) was administered until day 16 and tapered to ≤10 mg/day by week 16		
Tacrolimus + MMF	Tacrolimus	4 mg/day, oral	12 months	(190)
	MMF	1000 mg/day, oral		

Abbreviations: EULAR/ERA-EDTA = Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association; MMF = mycophenolate mofetil

Table 72: The distribution of second-line treatment regimens

Regime	MMF	Azathioprine	Rituximab + MMF	Tacrolimus + MMF	Reference
Voclosporin + MMF	33%	33%	33%	0%*	Danish KOL expert validation
MMF	33%	22%	22%	22%	
Belimumab + MMF/CYC	33%	22%	22%	22%	

*No patients were expected to receive another CNI agent following treatment with voclosporin.
Abbreviations: CYC = cyclophosphamide; KOL = key opinion leader; MMF= Mycophenolate mofetil

8.5.6 Background treatment

Corticosteroids and hydroxychloroquine are considered standard background therapies and are included with the intervention and comparator regimens when appropriate (149). The background treatment was also included in the AURORA trials. The background treatment (Table 73) is initiated at the same time as the initial treatment regimen and is assumed to continue for a maximum of 84 months covering both the initial (36 months based on the AURORA trials) and second-line treatment (maximum of 48 months based on guidelines (9, 191)), however, hydroxychloroquine is assumed to continue for the lifetime horizon (based on guidelines (9, 191)). The tapered glucocorticoids regime used in AURORA was applied for both the Voclosporin + MMF and MMF arm, while the tapered glucocorticoids regime was applied per EULAR/ERA-EDTA guidelines for the belimumab + MMF arm. The drug cost of the background treatment regimens is presented in Table 73, the background treatment regimens are presented in Table 74, and the percentages of patients receiving the regimens are presented in Table 75.

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Table 73: Background treatment - drug cost

Drug (administration)	Strength (mg)	Cost per pack (DKK)	Units per pack	Cost per mg (DKK)
Methylprednisolone (IV)	40	21.68	1	0.54
	125	64.00	1	0.51
	500	284.05	1	0.57
	1000	568.09	1	0.57
Prednisone (oral)	5	56.38	100	0.11
	25	207.67	56	0.15
Hydroxychloroquine (oral)	180	142.60	120	0.01

Abbreviations: DKK = Danish kroner; IV=Intravenous.

Table 74: Background treatment regimens

Regimen	Drug(s)	Dosing*	Stopping rule	Reference
Tapered corticosteroids (AURORA)	Methylprednisolone	500 mg IV, per day for 2 days	84 months – assumed to cover initial (36 months) and second-line (48 months) treatment duration	Rovin et al., 2021(14)
	Prednisone	20-25 mg/day on day 3, decreased to 2.5 mg/day at week 16 according to protocol-defined schedule		
Tapered corticosteroids	Methylprednisolone	500-2500 mg, IV, total dose	84 months – assumed to match other the glucocorticoid regimen	EULAR 2020(9)
	Prednisone	Starting oral dose of 0.3-0.5 mg/kg/day, tapered to <7.5mg/day after 3-6 months		
Hydroxychloroquine	Hydroxychloroquine	5 mg/kg/day, oral	Assumed to match lifetime horizon	EULAR 2020(9)

Abbreviations: IV = Intravenous; EULAR/ERA-EDTA = Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association

Table 75: Percentage of patients receiving background therapy per regimen

Regimen	Tapered glucocorticoids (AURORA)	Tapered glucocorticoids	Hydroxychloroquine	Reference
Voclosporin + MMF	99.2%	0%	76.9%	AURORA 1 CSR (136)
MMF	99.2%	0%	76.9%	AURORA 1 CSR (136)
Belimumab + MMF/CYC	0%	99.2%	76.9%	Assumption – same as MMF arm

Abbreviations: CYC = cyclophosphamide; CSR = Clinical study report; MMF = Mycophenolate mofetil

Four different formulations were identified for IV methylprednisolone; 40 mg, 125 mg, 500 mg, and 1000 mg. Two different formulations were identified for oral prednisone; 5 mg and 25 mg. One formulation was found for oral hydroxychloroquine, 200 mg. Table 76 summarises the drug costs for the background treatment.

Table 76: Drug cost for the background treatment

Drug (administration)	Strength (mg)	Cost per pack (DKK)	Units per pack	Cost per mg (DKK)
Methylprednisolone (IV)	40 mg	21.68	1	0.54
	125 mg	64.00	1	0.51
	500 mg	284.05	1	0.57
	1000 mg	568.09	1	0.57
Prednisone (oral)	5 mg	56.38	100	0.11
	25 mg	207.67	56	0.15
Hydroxychloroquine (oral)	200 mg	142.60	120	0.01

Abbreviations: DKK = Danish Kroner; IV = Intravenous
Source: Medicinpriser.dk

8.5.7 Administration cost

The unit costs of administration were obtained using the Danish DRG grouper, interactive DRG, and are applied to the administrations in the model. The unit cost of administration is presented in Table 77.

Table 77: Unit costs of modes of administration

Mode of administration	Unit cost (DKK)	Source
Exclusively oral treatment	-	Assumption

Intravenous administration	1,645.00	DRG 2022: 08MA98 MDC08 1-dagsgruppe, pat. mindst 7 år - (BWAA60) Medicingivning ved intravenøs injektion (189)
Subcutaneous administration – first visit	1,645.00	DRG 2022: 08MA98 MDC08 1-dagsgruppe, pat. mindst 7 år - (BWAA31) Medicingivning ved subkutan injektion (189)
Subcutaneous administration – second visit	0.00	Assumption that the patient will self-administrate following first visit. This is based on the belimumab subcutaneous EMA label (67)

Abbreviations: DKK = Danish Kroner; DRG = diagnosed-related groups

8.5.8 Adverse events cost

The AE costs are applied as a one-off cost when a treatment regime is started. The AEs were included based on the criteria stated in section 8.2.2.5. The rates of AEs were presented in Table 52. The costs per AE were derived from the DRG 2022 tariff system (189). The cost related to each event is presented in Table 78.

Table 78: Summary of cost of the treatment-emergent adverse events

Adverse event	Value (DKK)	SE (DKK)	Reference
Pneumonia	30,912	6,182	DRG 2022: 04MA14: Lungebetændelse og pleurit, pat. 18-59 år, Diagnose: DJ189: Pneumoni UNS (189)
Gastroenteritis	6,756	1,351	DRG 2022: 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS (189)
Urinary tract infection	2,038	408	DRG 2022: 11MA98: MDC11 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DN390: Urinvejsinfektion uden angivelse af lokalisation"(189)
Hypertension/ hypertensive crisis	1,318	264	DRG 2022: 05MA98: MDC05 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DI109: Essentiel hypertension (189)
Anaemia	3,176	635	DRG 2022: 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD592: Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel (189)
Neutropenia	3,176	635	DRG 2022: 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel (189)
Infections and infestations	3,176	635	DRG 2022: 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DA499: Bakteriel infektion UNS (189)
Respiratory, thoracic, and mediastinal disorder	52,162	10,432	DRG 2022: 04MA06: Infektioner og betændelse i luftveje, pat. 0-64 år, Diagnosis: DJ229: Akut nedre luftsvejsinfektion UNS (189)
Blood and lymphatic system disorders	30,290	6,058	DRG 2022: Weighted average for neutropeni and leukopeni (CSR p. 107): 16MA03: Granulo- og trombocytopeni + DRG 2020: DRG 2022, 16MA10: Øvrige sygdomme i blod og bloddannende organer, Diagnosis: DD728H: Leukopeni (189)
Herpes Zoster/ Varicella zoster virus	8,868	1,774	DRG 2022: 09MA03 - Lettere eller moderat hudsygdom, u. kompl. bidiag., Diagnose: DB029: Herpes zoster-infektion uden komplikation (189)
Nausea and vomiting	6,756	1,351	DRG 2022: 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DR119C: Opkastning (189)
Upper respiratory tract infection	52,162	10,432	DRG 2022: 03MA05 Mellemørebetændelse og øvre luftvejsinfektion, pat. mindst 18 år, u. kompl. Bidiag, Diagnose: DJ069: Akut øvre luftsvejsinfektion UNS(189)
Epilepsy	21,821	4,364	DRG 2022: 01MA10 Anfaldssygdomme og hovedpine, pat. mindst 18 år, Diagnose: DG409: Epilepsi UNS-2 (189)
Septicaemia / Sepsis	42,770	8,554	DRG 2022: 18MA01: Sepsis, Diagnosis: DA419: Sepsis UNS (189)
Bronchitis	2,180	436	DRG 2022: 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DJ209: Akut bronkitis UNS (189)

Abbreviations: DKK = Danish Kroner; DRG = diagnosed-related groups; SE = standard error

8.5.9 Patients and transportation costs

Productivity costs (defined as patient costs in DMC guidelines) and transportation costs are included in the model in line with the DMC method guidelines. The unit cost per patient hour is assumed to be DKK 181. The transportation cost was assumed to be DKK 3.51 per kilometre and a 20-kilometre distance to the hospital in line with the DMC guidelines, which was sourced from DMC's unit cost catalogue. The resource use for patient cost and transportation is presented in Table 79. The patient time used and the number of visits per cycle for each health state and the mean distance to the hospital is presented in Table 80.

Table 79: The unit cost of patient cost and transportation cost

Resource	Unit cost (DKK)	Source
Average hourly wage	181	Medicinrådet - (140)
Transportation cost per KM	3.51	Medicinrådet - (140)

Abbreviations: DKK = Danish Kroner; KM=kilometer

Table 80: Patient time and travel distance

Resource use	Amount	Source
Patient time used per cycle (hours)		
- CR CKD 1-3a	3.75	KOL expert estimate
- PR CKD 1-3a	8.25	KOL expert estimate
- AD CKD 1-3a	12.00	KOL expert estimate
- CR CKD 3b-4	3.75	KOL expert estimate
- PR CKD 3b-4	8.25	KOL expert estimate
- AD CKD 3b-4	12.00	KOL expert estimate
- CKD 5 dialysis	315.00	KOL expert estimate
- CKD 5 transplant	15.00	KOL expert estimate
Distance to and from the hospital (KMs)	40	Medicinrådet - (140)
Number of visits per cycle		
- CR CKD 1-3a	2.50	KOL expert estimate
- PR CKD 1-3a	5.50	KOL expert estimate
- AD CKD 1-3a	8.00	KOL expert estimate
- CR CKD 3b-4	2.50	KOL expert estimate
- PR CKD 3b-4	5.50	KOL expert estimate
- AD CKD 3b-4	8.00	KOL expert estimate
- CKD 5 dialysis	63.00	KOL expert estimate
- CKD 5 transplant	10.00	KOL expert estimate

Abbreviations: AD = active disease; CR = complete response; CKD = chronic kidney disease; KMs = kilometres; KOL = key opinion leader; PR = partial response

8.6 Results

8.6.1 Base case overview

Table 81: Modelling overview for the base case

Overview	
Intervention	Voclosporin+MMF
Comparator	MMF Belimumab+MMF/CYC
Type of model	Markov model, cost-utility analysis
Time horizon	Lifetime (until less than 0.1% of the population is alive)
Treatment line	1st line
Discount rate	3.5% until year 35, 2.5% beyond year 35, 1.5% beyond year 70.
Perspective	Restrictive societal perspective
Measurement and valuation of health effects	Patient-level SF-36 data from the AURORA 1 and AURORA 2 studies converted to EQ-5D-3L (UK weights) using the Rowen et al., 2009 method (163)
Included costs	• Resource use • Drug acquisition • Drug administration • AE management • Disease management • Patient costs • Subsequent treatment costs

Time to discontinuation	TTD was based on log-logistic distributions extrapolated from patient-level data from the AURORA 1 and 2 trials.
Stopping rule	Maximum treatment time was assumed to be 36 months per AURORA 1 and 2.
Initial transition	Count method based on AURORA 1 and 2 trials for voclosporin+MMF NMA results applied for belimumab+MMF/CYC
Long-term transition	Equal to the weighted transition matrix per 6-months per person for the last two time periods included
Subsequent treatment	• MMF • Azathioprine • Rituximab+MMF • Tacrolimus+MMF
Background treatments	• Tapered glucocorticoids (AURORA regime) • Tapered glucocorticoids • Hydroxychloroquine

Abbreviations: CYC = cyclophosphamide; EQ-5D-3L = EuroQol Five Dimension Three Level; MMF = mycophenolate mofetil; SF-36 = 36-Item Short Form Survey; TTD = time to treatment discontinuation

8.6.2 Base case results

The undiscounted and discounted base case results are presented in Table 82 and Table 83. The incremental results are presented in Table 84.

Table 82: Base case results from the economic model in the comparison between voclosporin + MMF and MMF (with placebo)

	Voclosporin + MMF		MMF		Difference	
	Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
Life years	**47.36**	**22.67**	**46.19**	**22.20**	**1.18**	**0.46**
Total Costs (DKK)						
Drug acquisition, initial treatment (DKK)						
Drug administration, initial treatment (DKK)						
Drug acquisition second-line (DKK)						
Drug administration second-line (DKK)						
Background therapy (DKK)						
Total Resource use (DKK)						
- CR CKD 1-3a (DKK)						
- PR CKD 1-3a (DKK)						
- AD CKD 1-3a (DKK)						
- CR CKD 3b-4 (DKK)						
- PR CKD 3b-4 (DKK)						
- AD CKD 3b-4 (DKK)						
- CKD 5 dialysis (DKK)						
- CKD 5 transplant (DKK)						
- Death (DKK)						
Patient time costs (DKK)						
Transportation costs (DKK)						
Adverse events (DKK)						
Total QALYs	**36.345**	**18.022**	**35.249**	**17.550**	**1.10**	**0.47**
QALYs in CR CKD 1-3a						
QALYs in PR CKD 1-3a						
QALYs in AD CKD 1-3a						
QALYs in CR CKD 3b-4						
QALYs in PR CKD 3b-4						
QALYs in AD CKD 3b-4						

QALYs in CKD 5 dialysis	[redacted]
QALYs in CKD 5 transplant	
QALY decrement for AEs	

Abbreviations: DKK= Danish kroner; MMF = mycophenolate mofetil; QALY = Quality-Adjusted Life-Year

Table 83: Base case results from the economic model in the comparison between voclosporin + MMF and belimumab + MMF/CYC

	Voclosporin + MMF		Belimumab + MMF/CYC		Difference	
	Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
Life years	**47.36**	**22.67**	**46.49**	**22.31**	**0.87**	**0.36**
Total Costs (DKK)	[redacted]					
Drug acquisition, initial treatment (DKK)						
Drug administration, initial treatment (DKK)						
Drug acquisition second-line (DKK)						
Drug administration second-line (DKK)						
Background therapy (DKK)						
Total Resource use (DKK)						
- CR CKD 1-3a (DKK)						
- PR CKD 1-3a (DKK)						
- AD CKD 1-3a (DKK)						
- CR CKD 3b-4 (DKK)						
- PR CKD 3b-4 (DKK)						
- AD CKD 3b-4 (DKK)						
- CKD 5 dialysis (DKK)						
- CKD 5 transplant (DKK)						
- Death (DKK)						
Patient time costs (DKK)						
Transportation costs (DKK)						
Adverse events (DKK)						
Total QALYs	**36.345**	**18.022**	35.553	17.674	0.79	0.35
QALYs in CR CKD 1-3a	[redacted]					
QALYs in PR CKD 1-3a						
QALYs in AD CKD 1-3a						
QALYs in CR CKD 3b-4						
QALYs in PR CKD 3b-4						
QALYs in AD CKD 3b-4						
QALYs in CKD 5 dialysis						
QALYs in CKD 5 transplant						
QALY decrement for AEs						

Abbreviations: AEs = Adverse events; CYC = cyclophosphamide; DKK= Danish kroner; MMF = mycophenolate mofetil; QALY = Quality-Adjusted Life-Year.

Table 84: Incremental results for the economic model

	VCS + MMF vs MMF		VCS + MMF vs BEL + MMF/CYC	
	Undiscounted	Discounted	Undiscounted	Discounted
Incremental costs (DKK)	[redacted]			
Incremental QALYs				
ICER (incremental cost (DKK) per QALY)	29,398	211,530	Dominant	Dominant

Abbreviations: CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; BEL = belimumab; MMF = mycophenolate mofetil; QALY = Quality-Adjusted Life-Year.

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8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

Deterministic one-way sensitivity analysis was conducted to account for input parameter uncertainty in the deterministic base-case model results. All parameters were systematically and independently varied over a plausible range determined by either the 95% confidence interval, or ±15% where no estimates of precision were available.

8.7.1.1 Deterministic sensitivity analyses - voclosporin+MMF vs. MMF

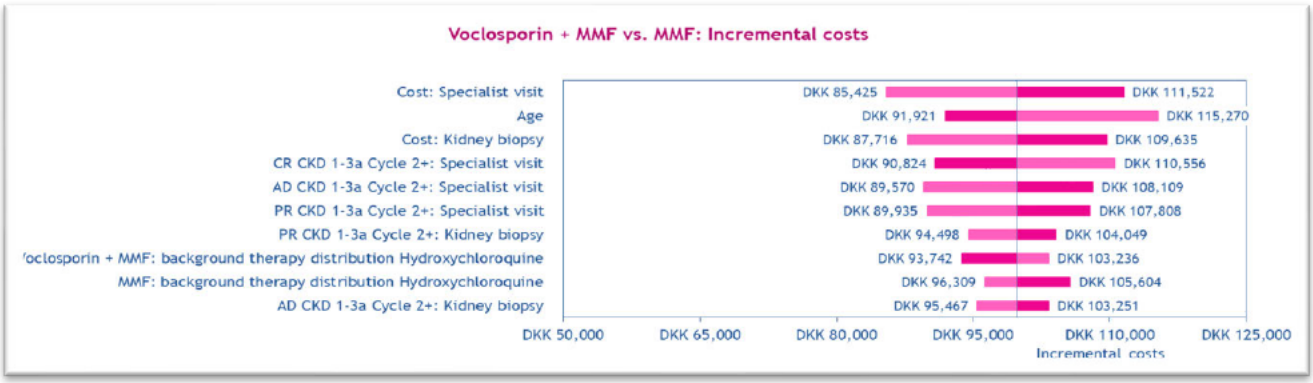
The ten most influential parameters whose uncertainty has the largest impact on the ICER estimates for voclosporin + MMF vs MMF are presented in Table 85. The key drivers of the model-estimated ICERs included utility in patients in the CKD 1-3a health states and patient age. The results are presented as tornado diagrams in Figure **17**, Figure **18**, and Figure **19**.

Table 85: One-way sensitivity analysis results vs. MMF. 10 most influential parameters.

Parameter	Parameter lower and upper value	ICER lower bound	ICER upper bound	Difference in incremental ICER
[redacted]				

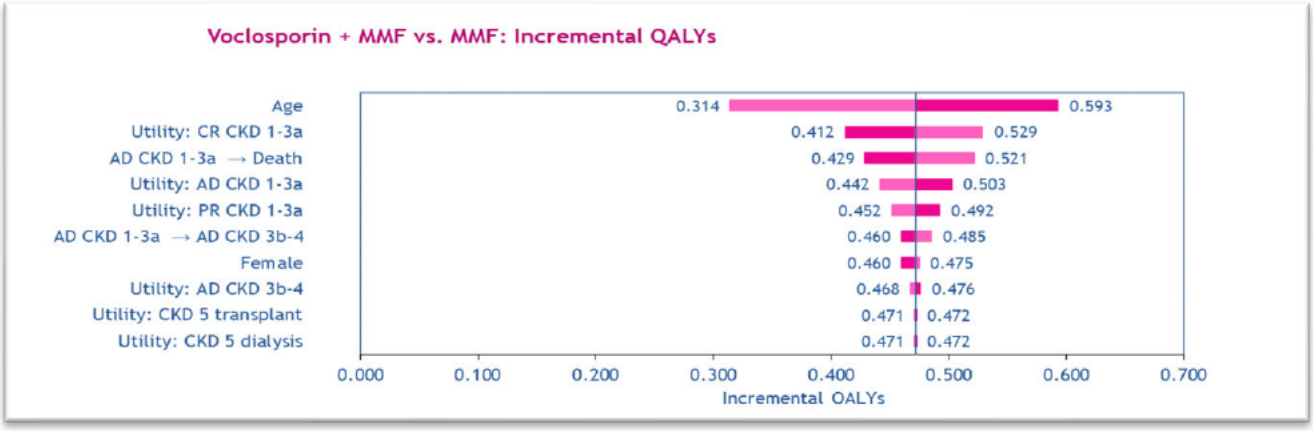
Abbreviations: AD = active disease; CDK = Chronic kidney disease; CR = complete response; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; PR = partial response; QALY = Quality-Adjusted Life-Year.

Figure 17: Incremental cost tornado diagram vs. MMF



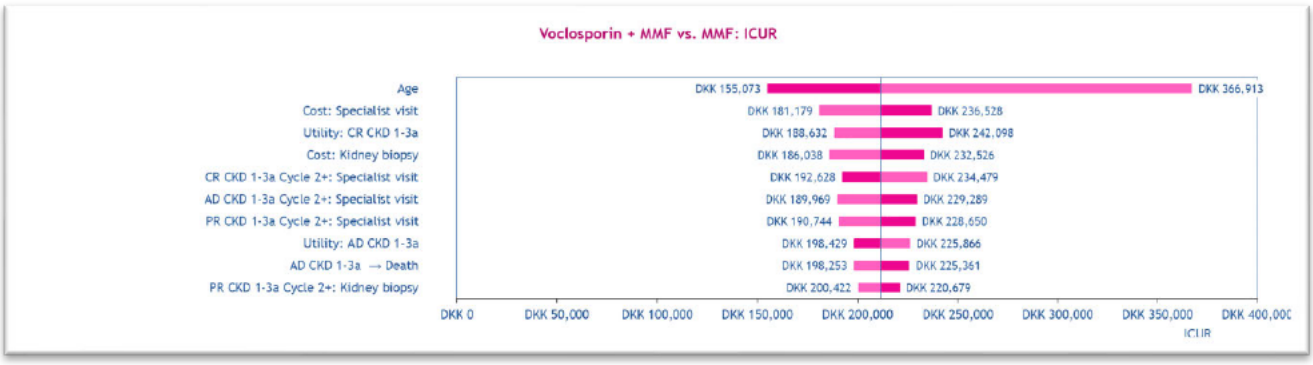
Abbreviations: AD = active disease; CDK = Chronic kidney disease; CR = complete response; MMF = mycophenolate mofetil; PR = partial response

Figure 18: Incremental QALY tornado diagram vs. MMF



Abbreviations: AD = active disease; CDK = Chronic kidney disease; CR = complete response; MMF = mycophenolate mofetil; PR = partial response; QALYs = quality-adjusted life-years

Figure 19: ICER tornado diagram vs. MMF



Abbreviations: AD = active disease; CDK = Chronic kidney disease; CR = complete response; ICUR = incremental cost-utility ratio; MMF = mycophenolate mofetil; PR = partial response

Figure 20 presents the relationship between the cost of voclosporin and the ICER as required by DMC submission guidance. It should be noted that this analysis was only undertaken vs. MMF as the base case ICER vs. belimumab+MMF/CYC was already dominant (so any reduction in cost for voclosporin would only increase it's dominance). As seen in Figure 20 the ICER vs. MMF is [redacted] proportional to the pack cost of voclosporin with the approximate relationship of ICER = [redacted]

Figure 20: Relationship between pack cost of voclosporin and ICER vs. MMF

[redacted]

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8.7.1.2 Deterministic sensitivity analyses - voclosporin+MMF vs. belimumab+MMF/CYC

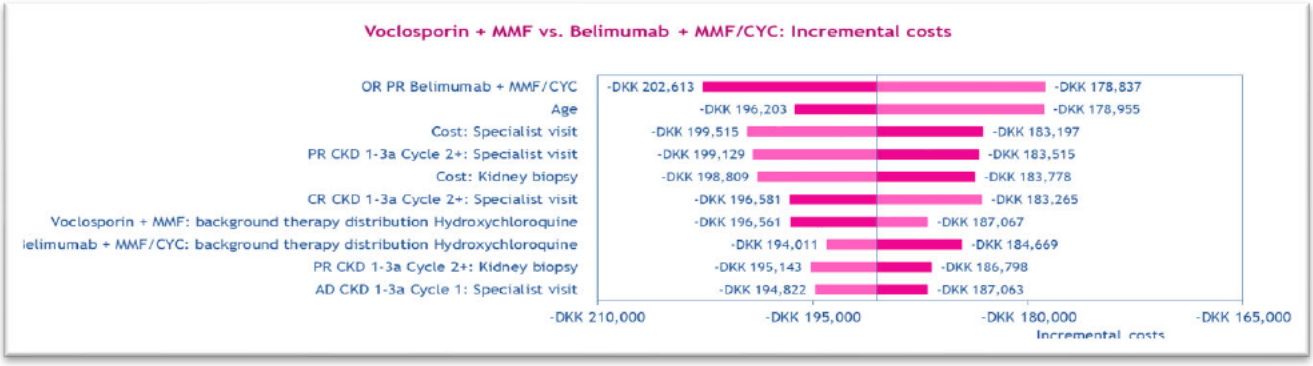
The ten most influential parameters whose uncertainty has the largest impact on the ICER estimates for voclosporin + MMF vs MMF are presented in Table 86. The key drivers of the model-estimated ICERs included utility in patients in the CKD 1-3a health states and patient age. The results are presented as tornado diagrams in Figure 21, Figure 22, and Figure 23.

Table 86: One-way sensitivity analysis results vs. belimumab+MMF/CYC. 10 most influential parameters.

Parameter	Parameter lower and upper value	ICER lower bound	ICER upper bound	Difference in incremental ICER
[redacted]				

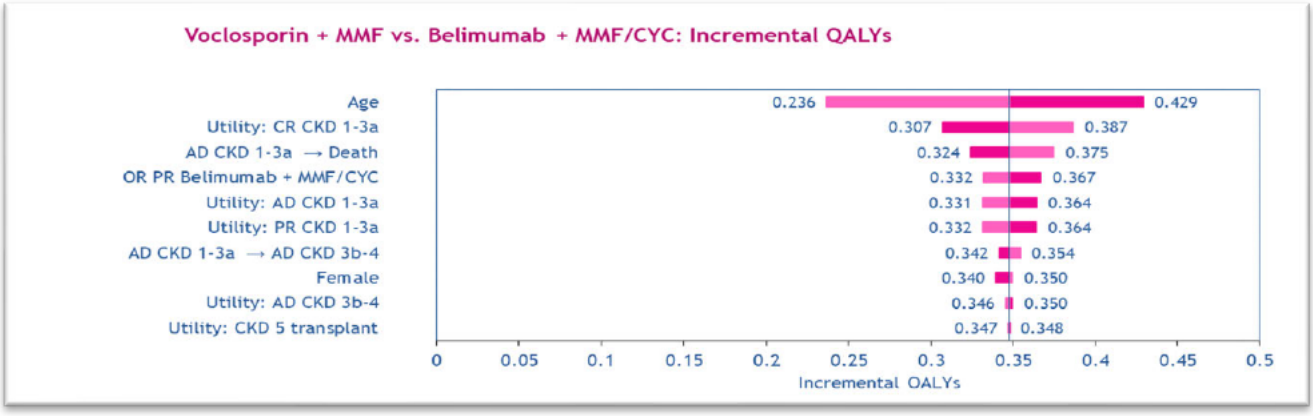
Abbreviations: AD = active disease; CDK = Chronic kidney disease; CR = complete response;. CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; PR = partial response; QALY = Quality-Adjusted Life-Year.

Figure 21: Incremental cost tornado diagram vs. belimumab+MMF/CYC



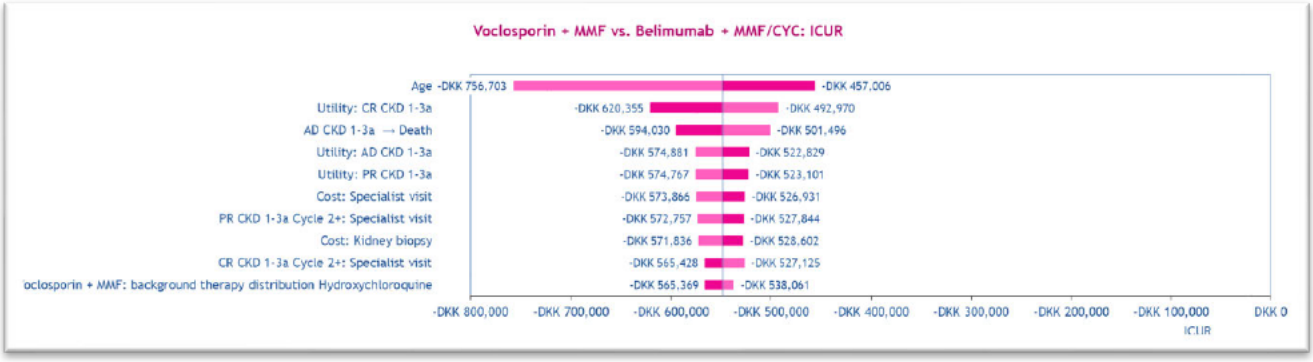
Abbreviations: AD = active disease; CDK = Chronic kidney disease; CR = complete response;. CYC = cyclophosphamide; MMF = mycophenolate mofetil; PR = partial response.

Figure 22: Incremental QALYs tornado diagram vs. belimumab+MMF/CYC



Abbreviations: AD = active disease; CDK = Chronic kidney disease; CR = complete response;. CYC = cyclophosphamide; MMF = mycophenolate mofetil; PR = partial response; QALYs = Quality-adjusted Life-years

Figure 23: ICER tornado diagram vs. belimumab+MMF/CYC



Abbreviations: AD = active disease; CDK = Chronic kidney disease; CR = complete response; CYC = cyclophosphamide; ICUR = incremental cost-utility ratio; MMF = mycophenolate mofetil; PR = partial response

8.7.1.3 Scenario analyses

Table 87: Scenario results (discounted)

Scenario	ICER vs. MMF	ICER vs. belimumab+MMF/CYC
Base case	DKK 211,530	Dominant
Discount rate 0%	DKK 29,398	Dominant
Belimumab + MMF/CYC AEs from the pivotal trial (151)	DKK 211,530	Dominant
No treatment effect waning	DKK 74,308	Dominant
Treatment effect wane to MMF level	DKK 569,651	Dominant
Long-term transitions are equal to the transition of the last time period included	DKK 447,093	Dominant
Apply literature-based utilities for all health states (145, 153, 164)	DKK 143,575	Dominant
Applying AURORA 1 utility data only	DKK 202,906	Dominant
Applying AURORA 2 utility data only	DKK 170,117	Dominant
Utility adjustment by Ara and Brazier, 2011 (185) instead of Wittrup-Jensen (183)	DKK 227,896	Dominant
100% of patients receive MMF as second-line treatment	DKK 202,050	Dominant
Set "consider vial wastage" to "no"	DKK 211,530	Dominant
Use NMA result for voclosporin+MFF and MMF	DKK 194,536	Dominant
Base TTD on AURORA 1 only	DKK 180,481	Dominant
Base TTD on AURORA 1 KM followed by AURORA 2 hazards	DKK 195,291	Dominant
Base TTD on AURORA 1 extrapolation followed by AURORA 2 hazards	DKK 223,516	Dominant
Base TTD on the 36 months stopping rule only	DKK 330,249	Dominant
Time horizon of 40 years	DKK 265,254	Dominant
Time horizon of 30 years	DKK 343,706	Dominant
Time horizon of 20 years	DKK 524,158	Dominant
Time horizon of 10 years	DKK 1,135,483	Dominant

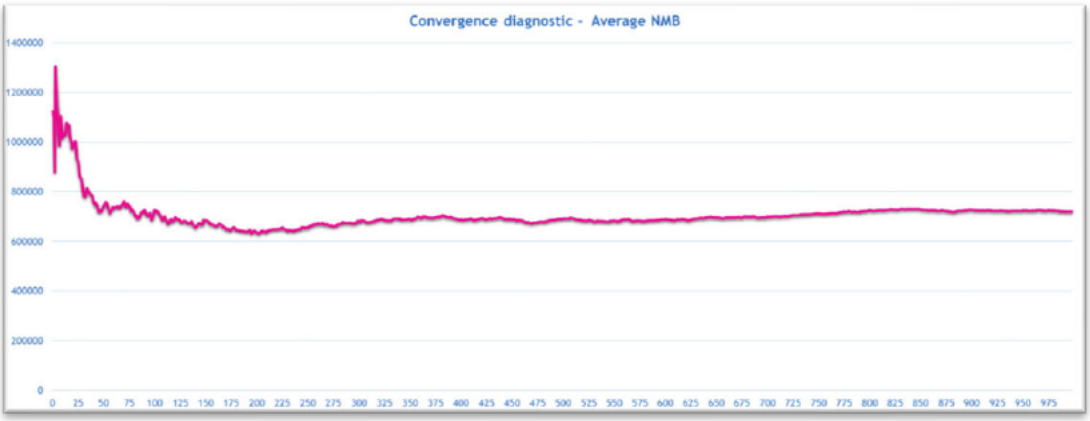
Time horizon of 5 years	DKK 2,532,925	Dominant
Starting age of 42 equal to Hermansen et al. (6)	DKK 256,465	Dominant
Applying UK KOL input for AD CKD 1-3a to AD CKD 3b-4 transition probability (3.05%) (141)	DKK 186,143	Dominant
Applying count data from AURORA trials for AD CKD 1-3a to death transition probability (1.73%) (15, 136)	DKK 148,579	Dominant
Applying UK KOL input for AD CKD 3b-4 to dialysis transition probability (13.91%) (141)	DKK 185,962	Dominant
Applying Sugrue et al. (157) input for AD CKD 3b-4 to death transition probability (3.92%)	DKK 200,980	Dominant
Applying Palmer et al. (158) input for dialysis to death transition probability (8.10%)	DKK 211,550	Dominant

Abbreviation: AEs = adverse events; AD = active disease; CKD = chronic kidney disease; CYC = cyclophosphamide; DKK = Danish Kroner; ICER = Incremental cost-effectiveness ratio; KM = Kaplain Mrier; MMF = mycophenolate mofetil; NMA = Network meta-analysis; TTD = Time-to-discountinueation.

8.7.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was conducted to further explore uncertainty around model inputs by varying all model parameters simultaneously within their respective bounds of uncertainty across 1,000 simulations. As the NMA included a total of 1,000 draws, 1,000 simulations were the maximum possible iterations for the PSA as well. To confirm that 1,000 PSA iterations were sufficient, the test of convergence was used, which is illustrated in Figure 24.

Figure 24: Test of convergence for the PSA



Abbreviations: NMB = net monetary benefit; PSA = probabilistic sensitivity analysis

8.7.2.1 Probabilistic sensitivity analyses results

The mean PSA results for voclosporin + MMF vs. all the two comparators are presented in Table 88. The scatter plot of PSA results for incremental discounted costs and QALYs in the comparison of voclosporin+MMF vs. MMF and voclosporin+MMF vs. belimumab+MMF/CYC is presented in

Figure 25. A multi-way cost-effectiveness acceptability curve is also presented in Figure 26.

Table 88: PSA mean outcomes

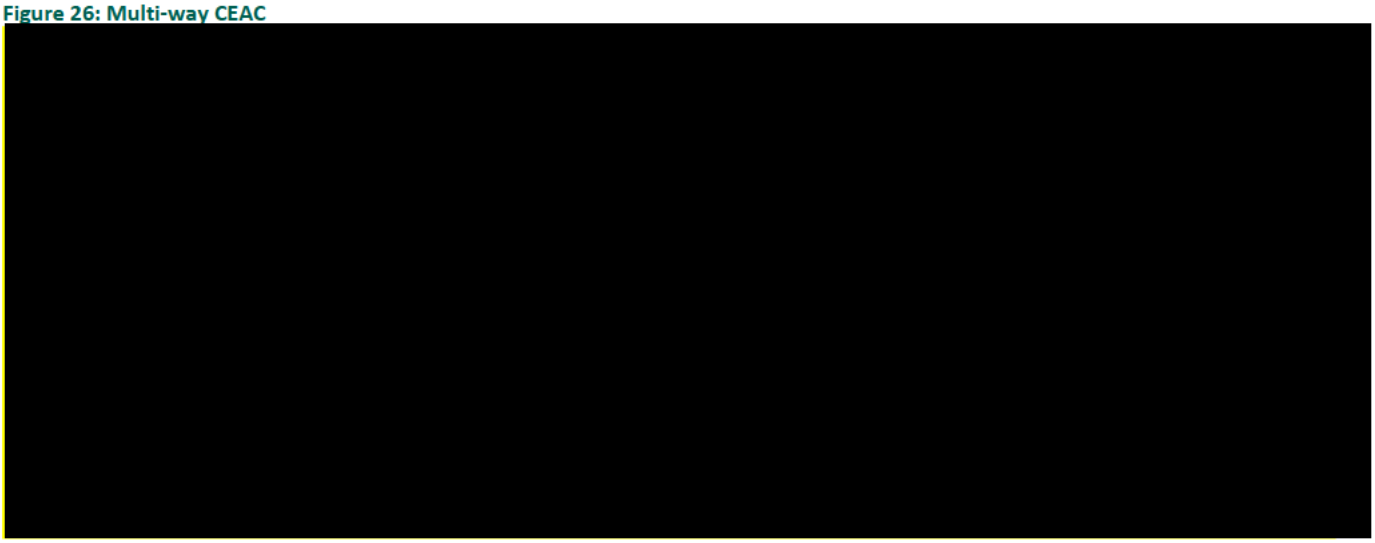
PSA outcomes			
	Voclosporin + MMF	**MMF**	**Belimumab + MMF/CYC**
Mean costs	[redacted]	[redacted]	[redacted]
Mean QALYs	[redacted]	[redacted]	[redacted]
Incremental costs vs voclosporin + MMF		[redacted]	[redacted]
Incremental QALYs vs voclosporin + MMF		[redacted]	[redacted]
ICER relative to voclosporin + MMF		DKK 212,367.56	Dominant

Abbreviation: CYC = cyclophosphamide; DKK = Danish kroner; ICER = Incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; QALY = Quality-adjusted life-years.

Figure 25: Incremental scatterplot for voclosporin+MMF vs. the two comparators

Abbreviation: CYC = cyclophosphamide; DKK = Danish kroner; MMF = mycophenolate mofetil; QALY = Quality-adjusted life-years.

Figure 26: Multi-way CEAC



Abbreviation: CEAC = Cost-effectiveness acceptability curve; CYC = cyclophosphamide; DKK = Danish kroner; MMF = mycophenolate mofetil; QALY = Quality-adjusted life-years.

9. Budget impact analysis

The budget impact model was developed to estimate the expected budget impact of recommending voclosporin+MMF as the standard treatment for patients with LN in Denmark. The budget impact was estimated per year for the first 5 years after the introduction of the voclosporin+MMF regime in Denmark. It has been estimated that approximately 10% of eligible patients will receive Voclosporin+MMF if made available, with 10% receiving belimumab, the remainder are assumed to receive MMF. Percentages remain are assumed the same in the current scenario where Voclosporin+MMF is not available, but with those patients now assumed to have belimumab instead (20% belimumab and 80% MMF). The patient numbers are based on the data presented in section 5.1.3.

The budget impact model was linked through the Markov traces in the cost-effectiveness model, and therefore, any changes in the settings of the cost-effectiveness model would affect the results of the budget impact model. The analysis was developed by comparing the costs for the Danish healthcare system per year over five years in the scenario where the voclosporin+MMF regime is recommended as standard treatment and the scenario where the voclosporin+MMF regime is not recommended as standard treatment. The total budget impact per year is the difference between the two scenarios.

Number of patients

Table 89: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Voclosporin+MMF	21.4	22.3	23.3	24.2	25.2

	Year 1	Year 2	Year 3	Year 4	Year 5
MMF	171.2	178.7	186.3	193.8	201.4
Belimumab+MMF/ CYC	21.4	22.3	23.3	24.2	25.2
Total number of patients	**214***	**223***	**233***	**242***	**252***

Abbreviations: CYC = cyclophosphamide; MMF = mycophenolate mofetil

*Numbers are rounded to nearest whole number.

Table 90: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Voclosporin+MMF	0.0	0.0	0.0	0.0	0.0
MMF	171.2	178.7	186.3	193.8	201.4
Belimumab+MMF/CYC	42.8	44.7	46.6	48.5	50.3
Total number of patients	**214***	**223***	**233***	**242***	**252***

Abbreviations: CYC = cyclophosphamide; MMF = mycophenolate mofetil

*Numbers are rounded to nearest whole number.

Expenditure per patient

Table 91: Costs per patient per year

	Year 1	Year 2	Year 3	Year 4	Year 5
Voclosporin+MMF	DKK 128,286	DKK 95,414	DKK 85,160	DKK 51,524	DKK 35,496
MMF	DKK 58,860	DKK 42,194	DKK 39,616	DKK 52,070	DKK 38,022
Belimumab+MMF/CYC	DKK 178,077	DKK 144,367	DKK 141,791	DKK 50,109	DKK 36,579

Abbreviations: CYC = cyclophosphamide; DKK = Danish Kroner; MMF = mycophenolate mofetil

Budget impact

Table 92: Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Voclosporin+MMF is recommended	16,633,084	13,088,147	12,916,739	12,880,041	12,880,041
Of which: Drug costs initial treatment	4,894,803	4,380,975	4,210,412	567,325	567,325
Of which: Administrative costs	350,592	262,823	270,159	676,248	65,275
Of which: Background treatment	700,117	173,075	177,881	183,734	189,615
Of which: Drug costs subsequent treatment	-	-	-	3,085,647	803,963
Of which: Adverse events	311,861	13,746	13,746	13,746	13,746
Of which: Health state specific costs	10,375,711	8,257,528	8,244,540	8,353,341	8,691,425
Minus: Voclosporin+MMF is NOT recommended	17,698,602	14,182,708	14,221,791	12,996,331	12,996,331
Of which: Drug costs initial treatment	5,492,847	5,124,897	5,158,226	664,535	664,535
Of which: Administrative costs	701,184	525,647	540,318	681,703	100,983
Of which: Background treatment	781,204	180,876	185,705	191,723	197,771
Of which: Drug costs subsequent treatment	-	-	-	3,046,527	782,167
Of which: Adverse events	312,377	13,769	13,769	13,769	13,769
Of which: Health state specific costs	10,410,989	8,337,519	8,323,773	8,398,074	8,740,524
Budget impact of the recommendation	-1,065,518	-1,094,561	-1,305,052	-116,290	-168,400

Abbreviations: DKK= Danish Kroner; MMF = mycophenolate mofetil

10. Discussion on the submitted documentation

Voclosporin is a next-generation CNI whose efficacy and safety are supported by three double-blind, randomised clinical trials in patients with LN (Phase 3 AURORA 1, Phase 3 24-month extension AURORA 2 and Phase 2 AURA-LV) (15, 139, 192).

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In AURORA 1, voclosporin + MMF demonstrated significantly higher CRR compared with placebo + MMF at Week 52 (primary endpoint: 40.8% vs. 22.5%; OR 2.65; p<0.0001) and Week 24 (secondary endpoint: 32.4% vs 19.7%; OR 2.23; p=0.002) (192); as well as significant improvements in PRR, median time to UPCR ≤ 0.5 mg/mg and median time to 50% reduction in UPCR (secondary endpoints) (192). Rapid UPCR reduction is particularly important, as the level of proteinuria is a well-established prognostic factor for further kidney deterioration in the form of renal flares, ESRD, and also death in patients with LN (193). Long-term efficacy was also demonstrated in the Phase 3 follow-up study, AURORA 2, whereby voclosporin + MMF achieved significantly greater CRR and PRR (secondary endpoints) vs. placebo + MMF, despite the fact that AURORA 2 was not powered to detect superior efficacy for voclosporin (15). ITC results based on AURORA 1 and AURA-LV data further confirmed voclosporin + MMF to be more effective at achieving CRR than belimumab+MMF/CYC. A tolerable safety profile for voclosporin has also been demonstrated across AURORA 1 and AURORA 2 over a three-year period, with similar TEAE incidence to placebo. Notably, there was no evidence of safety risks associated with voclosporin, such as diabetes, renal toxicity, neurotoxicity or malignancy (14, 15, 136). Furthermore, the efficacy of voclosporin was demonstrated without the need for high-dose corticosteroids, that are otherwise associated with side-effects and morbidity (14).

A model was developed to assess the cost-effectiveness of voclosporin in combination with MMF as a treatment for adult patients with active class III, IV, or V (including mixed class III/V and IV/V) LN compared to MMF and belimumab+MMF/CYC. MMF is considered to be the most commonly used first-line initial treatment of LN in Danish clinical practice, while belimumab may be included in Danish clinical practice soon. Further treatments are also used in Danish practice with rituximab and tacrolimus often used in more severe patients and AZA typically limited to maintenance therapy; these have been applied as potential second-line treatments in the cost-effectiveness model. As of the date of submission, no other DMC submissions have been completed for the indication of LN. Therefore, a de novo model was developed based on insights collected from published cost-effectiveness models in LN and KOL expert feedback. In line with feedback from KOL experts, the model accounted for all stages of LN-related CKD over a lifetime horizon to account for differing costs, outcomes, and mortality associated with LN patients with CKD stages 1-3a, CKD stages 3b-4, and CKD stage 5 (i.e., ESRD). Health state transitions between AD, PR, and CR were informed by patient-level Phase 3 response data collected across AURORA 1 and AURORA 2 trials for voclosporin + MMF and MMF alone arms (sections 8.2.1 and 8.3), while all other comparators were informed by response outputs of an ITC. Health state occupancy was further informed by patient-level treatment discontinuation rates collected in the AURORA 1 and AURORA 2 trials for voclosporin + MMF and MMF regimens, although other comparator regimens were assumed to have no discontinuation due to a lack of available TTD data.

In the absence of previous DMC applications for the indication of LN, it is important to note that this expert-informed economic evaluation of LN is both novel and innovative in its approach, and accounts for key limitations of other published LN models by considering both a patient's response to LN treatment and the long-term ramifications of kidney deterioration by modelling progression through CKD. Data limitations are expected for a novel model framework. However, there is a strong rationale for the approach taken over other published cost-effectiveness models which do not accurately reflect patients' transition through CKD health states. Other key strengths of the model include the fact that CKD 1-3a health state transition probabilities were directly informed by the patient-level response and TTD data collected across robust one-year Phase 3 (AURORA 1) and two-year Phase 3 extension (AURORA 2) studies which directly assessed voclosporin + MMF against the current standard of care LN treatment in Denmark, MMF. In the absence of other head-to-head data, all other comparator transition probabilities needed to be informed by ITC response data.

LN-related CKD 1-3a utility values were also informed by data collected directly within AURORA 1 and AURORA 2 using the SF-36 patient questionnaire. Although neither AURORA 1 nor AURORA 2 included Denmark-based patients, the studies were conducted internationally across Europe, North America, Latin America, South Africa, and Asia. It is however noteworthy that the mapping algorithm used to generate utility values by conversion to EQ-5D scores is associated with an overprediction of severe health states (163, 194) and there is a risk that "active disease", being the most severe health state, will have a slightly inflated average due to the most severe patients being overpredicted. However, the Rowen et al. 2009 (163) study indicates that this bias is only present in health states with an average EQ-5D score below approximately 0.5, which is not what is observed in the AURORA trials.

In accordance with the DMC guidelines, the evaluation was conducted from a Danish-restricted societal perspective, and can therefore be considered relevant to all patients with class III, IV, or V (including mixed class III/V and IV/V) in Denmark. The base-case economic analysis demonstrated voclosporin + MMF a discounted ICER of DKK 211,530 QALY vs. MMF (the current standard of care in the treatment of LN) and dominant result vs. belimumab. In conclusion, the clinical and economic evaluations presented within this submission demonstrate that voclosporin (in combination with background immunosuppressive therapies) offers both a clinically effective, and likely cost-effective treatment option for all patients with active class III, IV or V (including mixed class III/V and IV/V) LN.

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Version log

Version	Date	Change
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.
1.1	9 February 2022	Appendix K and onwards have been deleted (company specific appendices) Colour scheme for text highlighting table added after table of contents Section 6: Specified requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described Section 8.3.1: Listed the standard parametric models Section 8.4.1: Added the need for description of quality of life mapping Appendix A: Specified that the literature search needs to be specific for the Danish context and the application Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices

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Appendix A Literature search for efficacy and safety of intervention and comparator(s)

The objective of the SLR is to identify all relevant RCTs for the treatment of LN. A parent SLR (Search date 01 June 2021) and a SLR update (after approximately 6 months - search date 24 January 2022) were conducted using the same methodology and search strategies. The full search strategies used and number of references retrieved from each of these searches for the clinical SLR is presented below.

The focus will be RCT evidence, as this is the strongest type of evidence, and it is believed to be widely available for LN treatment options based on previously published SLRs. This review will follow the requirements set out by the NICE (195). Once the relevant studies have been identified, the outcomes investigated will be characterised, and an appropriate data extraction sheet will be developed to capture outcome data. The results of the SLR will be used to provide evidence for comparative effectiveness and support further market access activities.

Search strategy

The Embase/Medline search terms for the indication "lupus nephritis" were searched in title/abstract and as indexed terms (i.e., Emtree and MeSH). Search terms for the list of interventions with the generic name as well as brand name were searched in title/abstract and as indexed terms. The search terms for RCTs are based on the filters provided by the Scottish Intercollegiate Guidelines Network (SIGN) (196). Search strategy and number of results for both parent SLR and SLR update are listed in Table 93.

Table 93: Search strategy Embase, Medline (using ProQuest)

[redacted]

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[redacted]

Note: * Duplicates are removed from the search but included in the result count. ° Duplicates are removed from the search and from the result count.

Abbreviations: SLR = systematic literature review

In the Cochrane Library, to search the CENTRAL and CSDR databases, a comprehensive list of search terms for "lupus nephritis" were used to identify relevant literature. The Cochrane search terms for "Lupus nephritis" consist of words searched in title/abstract and as indexed terms (i.e., MeSH). Search strategy and number of results for both the parent SLR and the SLR update are listed in Table 94.

Table 94: Search strategy Cochrane Library

[redacted]

Abbreviations: SLR = systematic literature review

Search strategy and number of results for conference search of European Renal Association - European Dialysis and Transplant Association (annual congress) for both parent SLR and SLR update are listed in Table 95.

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Table 95: Conference hand search

Conference name	Month and year	Query	Parent SLR results (01.06.2021)	Included
European Renal Association - European Dialysis and Transplant Association (annual congress)	June 2019	"lupus nephritis"	17	0
	June 2020		33	1
	June 2021		12	0

Abbreviations: SLR = systematic literature review

Methods

The scope of this literature review was defined by the criteria for the relevant population, intervention, comparators, outcomes, and study design (PICOS). These eligibility criteria are specified in Table 96. The scope as defined by the eligibility criteria was used as a guide for developing search strategies. For a publication to be included, it had to match all the criteria from each PICOS component. Any study that did not match criteria in at least one of the PICOS components was excluded.

The parent SLR (Search date 01 June 2021) and the first SLR update (after approximately 6 months - search date 24 January 2022) were conducted using the same methodology and search strategies. The full search strategies that were used for each search are presented in Table 93. SLRs were conducted in line with DMC submission guidelines, and therefore provide a robust evidence base from which the analysis is underpinned.

Table 96: PICOS inclusion/Exclusion Criteria

Patient population	Inclusion: Patients 18 years or above, with active LN defined as: • Class III • Class IV-S, IV-G • Class V • (and/or) UPCR of ≥1.5 mg/mg Exclusion: • Class I and Class II LN • Current medical history of human immunodeficiency virus, tuberculosis, severe cardiovascular disease, liver dysfunction, kidney transplant, chronic obstructive pulmonary disease or other overlapping autoimmune condition
Interventions[2](197)	Inclusion: • Cyclophosphamide • Immunosuppressants (for example, azathioprine, voclosporin, cyclosporin A, tacrolimus, pimecrolimus, mycophenolate mofetil, mycophenolate acid) • Monoclonal antibodies (for example, rituximab, belimumab, obinutuzumab, anifrolumab, guselkumab, deucravacitinib, iscalimab) • Angiotensin-converting enzyme (ACE) inhibitors (for example, benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril) • Corticosteroids (for example, beclomethasone, bethamethasone, prednisone) Exclusion: • Interventions not listed in inclusion criteria • Relevant intervention but not investigated for LN treatment

[2] Interventions are based on the recommendations of EULAR ERA/EDTA guidelines

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	• Complementary and alternative medicine
Comparators	Inclusion: Placebo or SOC or active comparator Exclusions: No comparator
Outcomes	Efficacy: • Renal response (or complete remission) • Partial renal response (or partial remission) • Time to and duration of renal response • Time to and duration of partial response • Time to and duration of UPCR of ≤0.7 mg/mg • Time to 50% reduction in UPCR • Occurrence of ESRD • ESRD-free survival • Serum creatinine, urine protein and eGFR • SELENA-SLEDAI Safety and treatment patterns: • Occurrence of severe adverse events (grade 3-4) • Adverse events that led to discontinuation of the study therapy • Treatment-related severe adverse events (grade 3-4) • Occurrence of renal failure, transplant, and dialysis • Mortality Exclusions: Reporting only outcomes that were not listed as inclusion criteria
Study design	Inclusion: • RCTs with results • RCTs without results[3] Exclusions: • Non-randomised studies, cohorts, and case series[4] • Narrative reviews • Systematic reviews and meta-analyses[5] • Preclinical studies • Prognostic studies • Case reports • Commentaries and letters • Consensus reports
Language	No restrictions
Countries	No restrictions
Publication year	No restrictions

Abbreviations: ACE = angiotensin-converting enzyme; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; IV-G = diffuse global; IV-S = diffuse segmental; LN = lupus nephritis; RCT = randomised controlled trial; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index; SOC = standard of care; UPCR = urine protein creatinine ratio

To identify relevant evidence published in peer-reviewed journals, the electronic databases presented in Table 97 were searched for both parent SLR and the SLR update. The searches in Embase and Medline were performed using ProQuest, a database tool which enables OPEN Health to search these databases simultaneously, automatically removing duplicates

[3] RCTs without results (e.g., ongoing trials) will be included but not extracted. An overview will be created to track new published results during updates of this review.

[4] During the review process, publications on large cohort studies and disease registries will be flagged and shared with Otsuka.

[5] Up to 5 systematic literature reviews/meta-analysis publications will be used for citation review.

between the databases. The searches in CENTRAL and the Cochrane Database of Systematic Reviews (CDSR) were conducted via the Cochrane website.

Table 97: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion – Parent SLR	Date of search completion – SLR update
Embase	ProQuest	-	01.06.2021	24.01.2022
Medline	ProQuest	-	01.06.2021	24.01.2022
Medline in-Process	ProQuest	-	01.06.2021	24.01.2022
CENTRAL	Cochrane Library	-	01.06.2021	24.01.2022
CDSR	Cochrane Library	-	01.06.2021	24.01.2022

Note: No time frame was added for the clinical efficacy and safety literature search

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; SLR = systematic literature review

The searches for conference proceedings (Table 98) were independent of that conducted for peer-reviewed publications. Conference proceedings that are indexed in Embase were searched electronically. Conference proceedings not indexed in Embase were hand-searched using the term "lupus nephritis" in whichever format was provided by the conference (e.g., PDF booklet, online search portal).

Table 98: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched
LUPUS	Embase.com	For conference proceedings with abstracts indexed in electronic literature databases Embase was	See the search strategy in (section Search strategy)
SLEuro	Embase.com	For conference proceedings with abstracts indexed in electronic literature databases Embase was searched using the strategy detailed in the search strategy below.	See the search strategy in (section Search strategy)
EULAR	Embase.com	For conference proceedings with abstracts indexed in electronic literature databases Embase was searched using the strategy detailed in the search strategy below.	See the search strategy in (section Search strategy)
WCN	Embase.com	For conference proceedings with abstracts indexed in electronic literature databases Embase was searched using the strategy detailed in the search strategy below.	See the search strategy in (section Search strategy)
European renal association -	https://www.era-online.org/	Hand-searched	"lupus nephritis"

Conference	Source of abstracts	Search strategy	Words/terms searched
European dialysis and transplant association			

Abbreviations: EULAR = European Congress of Rheumatology; LUPUS = International Congress on Systemic Lupus Erythematosus; SLEuro = European Lupus Congress/ Meeting; WCN = World Congress of Nephrology

Systematic selection of studies

Peer-reviewed publications

Once the electronic searches were run, all retrieved references were downloaded and imported into an EndNote database and duplicates were removed. The references were then exported into a reference screening software (DistillerSR) that was used for title and abstract screening.

Inclusion or exclusion of articles was based on the eligibility criteria specified in Table 96. Title/abstract review of all references was performed independently by two reviewers, with any discrepancies resolved by a third reviewer. The same process was applied for articles that were selected for full-text review. During both the title/abstract and full-text screening phases, reasons for excluding an article were documented (as per criteria listed in Table 96).

A PRISMA for each of the two SLRs (parent SLR, SLR update) diagram detailing the inclusion/exclusion of articles at each stage of the review is presented in Figure 27: PRISMA diagram (Parent SLR)) and Figure 28: PRISMA diagram (SLR update).

Conference proceedings

Searches of conference proceedings were performed by a single reviewer and checked by a second one. Conference abstracts published after January 1, 2019, were screened based on the eligibility criteria specified in Table 96. Conference abstracts meeting the eligibility criteria were collated in a Microsoft Excel database and were matched up to included peer-reviewed publications where relevant to determine if any additional information is provided in them. If the data presented in a conference abstract were available from an included peer-reviewed publication, the conference's abstract were excluded. If duplicate data were presented in multiple conference abstracts, only the most recent abstract was included.

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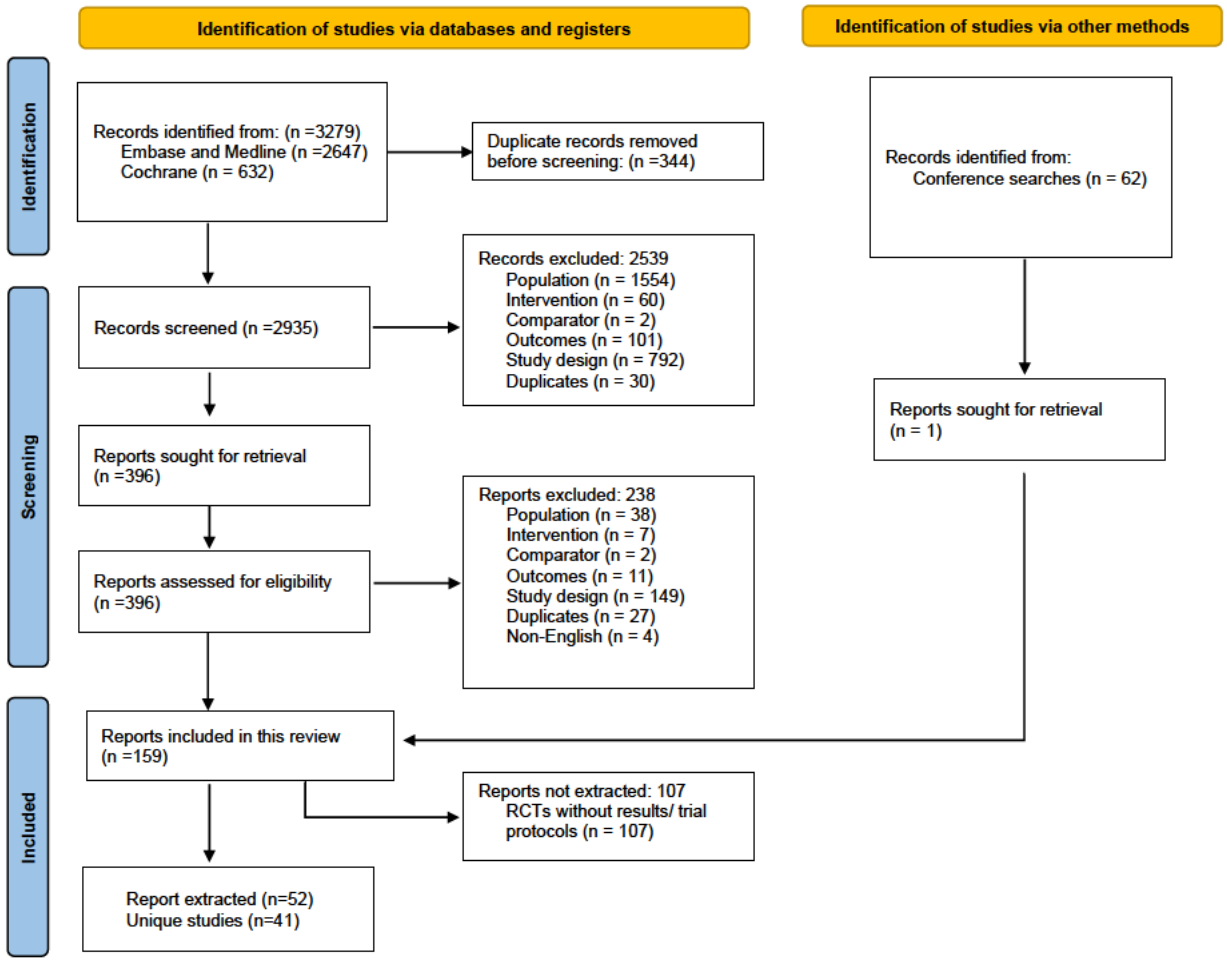
Parent SLR

Figure 27: PRISMA diagram (Parent SLR)



Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR = systematic literature review

Table 99: Excluded reports assessed for eligibility (Parent SLR) (n= 238)

Bibliography	Reason of exclusion
Abd-Elhady El-Sehemy, et al., Cyclosporine but not cyclophoshamide is a rescue therapy in resistant lupus nephritis even in class iv proliferative gn, 2004	Study Design
Amoura, et al., Alternative Renal Response Definitions in a Randomized, Controlled Trial of Obinutuzumab for Proliferative Lupus Nephritis, 2020	Study Design
Amoura, et al., Alternative renal response definitions in a randomized, controlled trial of obinutuzumab for proliferative lupus nephritis, 2020	Duplicate
An, et al., Combined immunosuppressive treatment (CIST) in lupus nephritis: a multicenter, randomized controlled study, 2019	Population
Appel, et al., Cyclophosphamide therapy of severe lupus nephritis, 1997	Study Design
Appel, et al., Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis, 2009	Population

Aranow, et al., Phase 2 trial of induction therapy with anticd20 (rituximab) followed by maintenance therapy with anti-BAFF (belimumab) in patients with active lupus nephritis, 2019	Duplicate
Arends, et al., Cyclophosphamide versus azathioprine/methylprednisolone: Long-term follow-up of the first dutch lupus nephritis study, 2011	Study Design
Arriens, et al., Aurora phase 3 study demonstrates voclosporin statistical superiority over standard of care in lupus nephritis (LN), 2020	Duplicate
Atsumi, et al., Voclosporin has demonstrated efficacy in Asian patients with lupus nephritis, 2020	Duplicate
Austin Iii, et al., Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy, 2009	Population
Baker, et al., Phase II, randomised, double-blind, multicentre study evaluating the safety and efficacy of filgotinib and lanraplenib in patients with lupus membranous nephropathy, 2020	Intervention
Balletta, et al., Ciclosporin plus steroids versus steroids alone in the treatment of lupus nephritis, 1992	Population
Balow, et al., Management of lupus nephritis, 1996	Study Design
Bao, et al., Successful treatment of class V+IV lupus nephritis with multitarget therapy, 2008	Population
Bargman, et al., How did cyclophosphamide become the drug of choice for lupus nephritis?, 2009	Study Design
Barron, et al., Pulse methylprednisolone therapy in diffuse proliferative lupus nephritis, 1982	Population
Belmont, et al., Initial management of proliferative lupus nephritis: to cytotoxic or not to cytotoxic?, 1999	Study Design
Bharati, et al., Comparison of two steroid regimens in induction therapy of proliferative lupus nephritis: a randomised controlled trial, 2018	Study Design
Boletis, et al., Intravenous immunoglobulin compared with cyclophosphamide for proliferative lupus nephritis, 1999	Intervention
Burch, et al., How do mycophenolate mofetil and cyclophosphamide compare with each other and with alternative induction therapies for people with lupus nephritis?, 2018	Study Design
Cade, et al., Comparison of azathioprine, prednisone, and heparin alone or combined in treating lupus nephritis, 1973	Study Design
Cardiel, et al., Abetimus sodium: A new therapy for delaying the time to, and reducing the incidence of, renal flare and/or major systemic lupus erythematosus flares in patients with systemic lupus erythematosus who have a history of renal disease, 2005	Study Design
Cardiel, et al., Abetimus sodium for renal flare in systemic lupus erythematosus: Results of a randomized, controlled phase III trial, 2008	Population
Carette, et al., Controlled studies of oral immunosuppressive drugs in lupus nephritis. A long-term follow-up, 1983	Population
Chan, et al., Mycophenolate mofetil in the treatment of lupus nephritis: 7 years on, 2008	Study Design
Chan, et al., Mycophenolate mofetil in the treatment of lupus nephritis--7 years on, 2008	Study Design

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Chan, et al., Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group, 2000	Duplicate
Chen, et al., Outcomes of maintenance therapy with tacrolimus versus azathioprine for active lupus nephritis: A multicenter randomized clinical trial, 2012	Population
Chen, et al., Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: A multicenter randomized clinical trial, 2011	Population
Chowdhary, et al., To study the effectivity of tacrolimus and azathioprine combination during induction phase of lupus nephritis: a single-center prospective study, 2019	Study Design
Clancy, et al., Vascular biomarkers and risk of treatment failure in the maintenance phase of a randomized multicenter trial comparing mycophenalate mofetil and azathioprine for lupus nephritis, 2011	Study Design
Cui, et al., Efficacy and safety of leflunomide in the treatment of proliferative lupus nephritis: preliminary results from a randomized, cyclophosphamide-controlled study, 2003	Study Design
Cui, et al., Treatment of proliferative lupus nephritis with leflunomide and steroid: a prospective multi-center controlled clinical trial, 2005	Study Design
Dai, et al., Big dose cyclophosphamide pulse therapy in lupus nephritis with oral Chinese herbal drugs, 1998	Study Design
Dall'Era, et al., Comparison of standard of care treatment with a low steroid and mycophenolate mofetil regimen for lupus nephritis in the ALMS and AURA studies, 2019	Study Design
Dall'Era, et al., Phase 2 trial of induction therapy with anti-CD20 (rituximab) followed by maintenance therapy with anti-BAFF (belimumab) in patients with active lupus nephritis, 2018	Study Design
Dall'Era, et al., Identification of biomarkers that predict response to treatment of lupus nephritis with mycophenolate mofetil or pulse cyclophosphamide, 2011	Population
Daza, et al., Captopril effect on prostaglandin E2, thromboxane B2 and proteinuria in lupus nephritis patients, 2005	Outcomes
D'Cruz, et al., Systemic lupus erythematosus, 2006	Intervention
Dinant, et al., Alternative modes of cyclophosphamide and azathioprine therapy in lupus nephritis, 1982	Population
Dinant, et al., Randomized trial of oral cyclophosphamide plus azathioprine and intravenous cyclophosphamide in lupus nephritis, 1980	Study Design
Dobronravov, et al., 48 week complete remission of active lupus nephritis with voclosporin, 2017	Study Design
Donadio, et al., Chemotherapy of lupus nephropathy, 1985	Study Design
Donadio, et al., Treatment of lupus nephritis with prednisone and combined prednisone and azathioprine, 1972	Population
Donadio, et al., Further observations on the treatment of lupus nephritis with prednisone and combined prednisone and azathioprine, 1974	Outcomes
Dooley, et al., Aspreva lupus management study (ALMS): maintenance results analysis by racial subgroup, 2011	Study Design

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Dooley, et al., Speed of remission with the use of voclosporin, MMF and low dose steroids: results of a global lupus nephritis study, 2016	Study Design
Dooley, et al., Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis, 2011	Population
Doria, et al., Treatment of lupus nephritis with enteric-coated mycophenolate sodium (EC-MPS) MyLupus exploratory study, 2010	Study Design
Dostal, et al., Cyclofa-Lune (2002) lupus nephritis - randomized controlled multicentric therapeutic comparative study with cyclosporin A versus cyclophosphamide: running evaluation, 2004	Study Design
Drinkard, et al., Azathioprine and prednisone in the treatment of adults with lupus nephritis. Clinical, histological, and immunological changes with therapy, 1970	Population
El Shafey, et al., Is mofetil superior to pulse intravenous cyclophosphamide for induction therapy of proliferative lupus nephritis in Egyptian patients?, 2010	Duplicate
Elliott, et al., Induction therapy for active lupus nephritis: mycophenolate mofetil is superior to cyclophosphamide, 2006	Study Design
El-Mohsen, et al., Value of Urinary Neutrophil Gelatinase-Associated Lipocalin versus Conventional Biomarkers in Predicting Response to Treatment of Active Lupus Nephritis, 2020	Study Design
El-Shafey, et al., Is mycophenolate mofetil superior to pulse intravenous cyclophosphamide for induction therapy of proliferative lupus nephritis in Egyptian patients?, 2010	Population
Farahat, et al., Comparative study of mycophenolate mofetil (MFF) versus cyclophosphamide (CYC) in treatment of lupus nephritis, 2011	Study Design
Feng, et al., Mizoribine versus mycophenolate mofetil or intravenous cyclophosphamide for induction treatment of active lupus nephritis, 2014	Population
Flores-Suarez, et al., Preliminary results of an open randomised clinical trial comparing mycophenolate mofetil (MMF) vs intravenous cyclophosphamide (IV-CYC) as induction therapy for severe lupus nephritis, 2004	Study Design
Fregoso, et al., Treatment of lupus nephritis with anti-CD20 followed by anti-BAFF: impact on B cell reconstitution, B cell subsets, and autoreactivity, 2019	Duplicate
Fu, et al., Leflunomide versus azathioprine for maintenance therapy of lupus nephritis: a prospective, multicenter, randomized, open-label clinical trial, 2018	Study Design
Furie, et al., Efficacy and safety of rituximab in patients with proliferative lupus nephritis: results from the randomized, double-blind phase III LUNAR study, 2010	Study Design
Furie, et al., Efficacy and safety of rituximab in subjects with active proliferative lupus nephritis (LN): results from the randomized, double-blind phase III LUNAR study, 2009	Study Design
Furie, et al., Efficacy and safety of rituximab in subjects with active proliferative lupus nephritis (LN): Results from the randomized, double-blind phase III lunar study, 2009	Study Design
Furie, et al., Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study, 2014	Intervention
Furie, et al., BLISS-LN: a randomised, double-blind, placebo-controlled phase 3 trial of intravenous belimumab in patients with active lupus nephritis, 2020	Population

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Furie, et al., Trial design and baseline characteristics of patients in the randomized double-blind, placebo-controlled phase III lupus nephritis assessment with rituximab study (LUNAR), 2009	Study Design
Furie, et al., Effect of rituximab (RTX) On anti-dsDNA and C3 levels and relationship to response: Results from the LUNAR trial, 2009	Study Design
Furie, et al., Effect of rituximab (RTX) on anti -double-stranded DNA antibody and c3 levels and relationship to response: results from the LUNAR trial, 2010	Study Design
Furie, et al., Effects of Belimumab on Renal Outcomes, Overall SLE Control and Biomarkers: findings from a Phase 3, Randomized, Placebo-controlled 104-week Study in Patients with Active Lupus Nephritis, 2020	Population
Furie, et al., Phase 2, Randomized, Placebo-Controlled Trial of Dapirolizumab Pegol in Patients with Moderate-to-Severe Active Systemic Lupus Erythematosus, 2021	Population
Furie, et al., Efficacy and safety of rituximab (RTX) in patients (Pts) with proliferative lupus nephritis (LN): Results from randomized, double-blind phase III LUNAR study at week 52, 2010	Study Design
Furie, et al., Efficacy and safety of abatacept over 12 months in patients with lupus nephritis: Results from a multicenter, randomized, double-blind, placebo-controlled phase II/III study, 2011	Study Design
Furie, et al., Effect of rituximab (RTX) on anti-dsDNA and C3 levels and relationship to response: Results from the LUNAR trial, 2010	Study Design
Gandhi, et al., Early and intensive treatment of lupus nephritis with pulse cyclophosphamide, 1993	Study Design
Ginzler, et al., The natural history and response to therapy of lupus nephritis, 1980	Study Design
Ginzler, et al., Atacicept with newly initiated mmf and corticosteroids in lupus nephritis patients, 2011	Study Design
Ginzler, et al., Aspreva lupus management study (ALMS): Maintenance results, 2010	Study Design
Ginzler, et al., Atacicept in combination with MMF and corticosteroids in lupus nephritis: results of a prematurely terminated trial, 2012	Outcomes
Ginzler, et al., Nonrenal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induction treatment for lupus nephritis: Findings in a multicenter, prospective, randomized, open-label, parallel-group clinical trial, 2010	Outcomes
Goglin, et al., Reduction in proteinuria and normalization of C4 complement levels predict response to treatment of lupus nephritis with low-dose pulse cyclophosphamide and abatacept, 2014	Study Design
Gomez Mendez, et al., Measures of peripheral blood B-cell depletion predict renal response in patients with lupus nephritis treated with rituximab, 2017	Study Design
Gonzalez-Diaz, et al., Adjusted methylprednisolone dosing to serum albumin levels plus cyclophosphamide in patients with lupus nephritis. A pilot study, 2011	Study Design
Gorman, et al., This house believes that low-dose intravenous cyclophosphamide is superior to standard high-dose regimes for treatment of lupus nephritis, 2005	Study Design
Goyal, et al., Randomized controlled trial of low dose intravenous cyclophosphamide versus oral mycophenolate mofetil in treatment of lupus nephritis, 2013	Study Design
Grootscholten, et al., Is azathioprine an alternative for cyclophosphamide in the treatment of patients with proliferative lupus nephritis? Two year results of the Dutch Lupus Nephritis Study, 2004	Study Design

Grootscholten, et al., Randomized controlled trial comparing cyclophosphamide pulse therapy with azathioprine/methylprednisolone in proliferative lupus nephritis, 2004	Study Design
Gupta, et al., A study to compare the efficacy of cyclophosphamide versus multi-drug therapy in the treatment of lupus nephritis, 2017	Duplicate
Hein, et al., Follow-up after cyclophosphamide bolus therapy in lupus nephritis, 1994	Study Design
Hermanova, et al., Anti C1q and antinucleosome antibodies (Ab) in the clinical trial in lupus nephritis, 2010	Study Design
Hohol, et al., Treatment of progressive multiple sclerosis with pulse cyclophosphamide/methylprednisolone: Response to therapy is linked to the duration of progressive disease, 1999	Population
Houssiau, et al., RING, an investigator-initiated trial aimed at testing the efficacy of rituximab in refractory lupus nephritis: Rationale, trial design and call for participation, 2015	Study Design
Houssiau, et al., Lupus nephritis, 2007	Study Design
Houssiau, et al., Azathioprine versus mycophenolate mofetil for maintenance immunosuppression of proliferative lupus nephritis: results of a randomized trail (MAINTAIN), 2009	Study Design
Houssiau, et al., The Euro-Lupus Nephritis Trial: comparison between a low-dose and a high-dose cyclophosphamide regimen, 1999	Study Design
Houssiau, et al., The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide, 2010	Population
Houssiau, et al., Azathioprine versus mycophenolate mofetil for maintenance immunosuppression of proliferative lupus nephritis: Results of a randomized trial (MAINTAIN), 2009	Study Design
Houssiau, et al., Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: Results from the MAINTAIN Nephritis Trial, 2010	Population
Houssiau, et al., Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: Lessons from long-term followup of patients in the euro-lupus nephritis trial, 2004	Population
Houssiau, et al., Immunosuppressive therapy in lupus nephritis: The Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide, 2002	Population
Hu, et al., Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis, 2002	Study Design
Hu, et al., Effect of rituximab on serum levels of anti-c1q antibodies and antineutrophil cytoplasmic autoantibodies in refractory severe lupus nephritis, 2015	Study Design
Huizinga, et al., Early renal response biomarkers in lupus nephritis: data from the aurion and aura trials, 2017	Study Design
Illei, et al., Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: Long-term followup of a cohort of 145 patients participating in randomized controlled studies, 2002	Study Design
Isenberg, et al., Mycophenolate mofetil (MMF, Cellcept) for induction and maintenance treatment of lupus nephritis (LN): baseline demographics of patients from the phase III randomized , controlled ASPREVA Lupus Management Study (ALMS), 2007	Study Design

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Isenberg, et al., Aspreva lupus management study (ALMS): Extra-renal activity results from the maintenance phase, 2010	Study Design
Isenberg, et al., Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study, 2010	Population
Ivanova, et al., Controlled trial of cyclophosphamide, azathioprine and chlorambucil in lupus nephritis (the double-blind method), 1981	Duplicate
Ivanova, et al., Cyclophosphamide, azathioprine, or chlorambucil for systemic lupus erythematosus nephritis, 1979	Population
Jayne, et al., A randomized controlled study of laquinimod in active lupus nephritis patients in combination with standard of care, 2013	Study Design
Jigui, et al., Clinical study on 18 patients lupus nephritis (ln) with low dose and long time for mycophenolate mofetil (cellcept), 2000	Study Design
Kaballo, et al., Mycophenolate mofetil versus azathioprine for maintenance treatment of lupus nephritis, 2016	Population
Kamanamool, et al., Comparison of disease activity between tacrolimus and mycophenolate mofetil in lupus nephritis: a randomized controlled trial, 2017	Duplicate
Karassa, et al., Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis.[erratum appears in N Engl J Med 2001 Apr 12;344(15): 1176], 2001	Study Design
Khan, et al., Intravenous pulse Cyclophosphamide in renal lupus: Comparison of low dose fortnightly and conventional monthly regimen, 2002	Study Design
Kiriakidou, et al., Systemic lupus erythematosus, 2013	Comparator
Klippel, et al., Cyclophosphamide (CY) and azathioprine (AZ) in lupus glomerulonephritis. Results of a randomized trial at 28 months, 1975	Study Design
Klippel, et al., Randomized study of intravenous cyclophosphamide (IVCY) and cyclophosphamide plus azathioprine (CY + AZ) in lupus nephritis, 1978	Study Design
Korbet, et al., Factors predictive of outcome in severe lupus nephritis. Lupus Nephritis Collaborative Study Group, 2000	Study Design
Korbet, et al., Factors predictive of outcome in severe lupus nephritis, 2000	Duplicate
Levey, et al., Progression and remission of renal disease in the Lupus Nephritis Collaborative Study. Results of treatment with prednisone and short-term oral cyclophosphamide, 1992	Study Design
Lewis, et al., A controlled trial of plasmapheresis therapy in severe lupus nephritis, 1992	Intervention
Li, et al., Controlled trial of tacrolimus (FK506) vs intravenous cyclophosphamide (IVC) as induction therapy for sever lupus nephritis, 2005	Study Design
Li, et al., Mycophenolate mofetil treatment for diffuse proliferative lupus nephritis: a multicenter clinical trial in China, 2002	Comparator
Li, et al., Induction therapies for proliferative lupus nephritis: mycophenolate mofetil, tacrolimus and intravenous cyclophosphamide, 2009	Study Design

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Liebling, et al., A double-blind placebo controlled trial of pulse-methylprednisolone in SLE nephritis: a preliminary report, 1980	Study Design
Ligtenberg, et al., Treatment of nephritis in systemic lupus erythematodes, 1996	Study Design
Lin, et al., A comparison of response between mycophenolate mofetil and cyclophosphamide therapy for lupus nephritis, 2002	Population
Martin, et al., A multiple dose study of AMG 811 (anti-IFN-gamma) in subjects with systemic lupus erythematosus and active nephritis, 2015	Study Design
McDonald, et al., Developing predictors of global bilag treatment response in patients with lupus nephritis: more lessons from the aspreva lupus management study group (ALMS) data, 2020	Study Design
Mehra, et al., To compare the efficacy of low dose versus high dose cyclophosphamide regimen as induction therapy in the treatment of proliferative lupus nephritis, 2016	Study Design
Mejía-Vilet, et al., Immunosuppressive treatment for pure membranous lupus nephropathy in a Hispanic population, 2016	Study Design
Mendez, et al., Elevated baff following rituximab for lupus nephritis (LN) is associated with higher anti-DSDNA titers in patients with b cell recovery, 2017	Study Design
Mendonca, et al., Mycophenolate mofetil or cyclophosphamide in indian patients with lupus nephritis: Which is better? A single-center experience, 2017	Population
Miyasaka, et al., Efficacy and safety of tacrolimus for lupus nephritis: A placebo-controlled double-blind multicenter study, 2009	Population
Mok, et al., Clinical presentation, treatment and outcome of membranous nephropathy in SLE: A comparison with proliferative lupus glomerulonephritis in 141 patients, 2013	Study Design
Mok, et al., Long-term outcome of a randomized controlled trial comparing tacrolimus with mycophenolate mofetil as induction therapy of severe lupus nephritis, 2020	Outcomes
Mok, et al., Long-term outcome of a randomized controlled trial comparing tacrolimus with mycophenolate mofetil as induction therapy of severe lupus nephritis, 2019	Duplicate
Mok, et al., Factors determining response in patients with active lupus nephritis treated with glucocorticoids and mycophenolate mofetil (MMF), 2009	Study Design
Mok, et al., Mycophenolate mofetil versus tacrolimus for active lupus nephritis: an extended observation of a randomized controlled trial, 2008	Study Design
Mok, et al., Response to: 'Correspondence on 'Long-term outcome of a randomised controlled trial comparing tacrolimus with mycophenolate mofetil as induction therapy for active lupus nephritis'' by Xu, 2020	Study Design
Mok, et al., Factors associated with renal remission, relapse and long-term renal function decline in lupus nephritis treated with combined prednisolone and mycophenolate mofetil (MMF) or tacrolimus (TAC), 2015	Study Design
Mok, et al., Factors associated with long-term renal function deterioration in lupus nephritis treated initially with combined prednisolone and mycophenolate mofetil (MMF) or tacrolimus (Tac), 2013	Study Design
Mok, et al., Risk of renal flares and decline in renal function in patients with active lupus nephritis treated with mycophenolate mofetil (MMF), 2010	Study Design

Mok, et al., Factors determining response in patients with active lupus nephritis treated with glucocorticoids and mycophenolate mofetil (MMF), 2010	Study Design
Mok, et al., Tacrolimus (Tac) versus mycophenolate mofetil (MMF) for the treatment of membranous lupus nephritis: A randomized controlled trial, 2010	Study Design
Mok, et al., Factors determining response in patients with active lupus nephritis treated with glucocorticoids and mycophenolate mofetil (MMF), 2009	Study Design
Mosca, et al., Induction therapy with oral cyclophosphamide in lupus nephritis, 2002	Study Design
Mysler, et al., Efficacy and safety of ocrelizumab, a humanized antiCD20 antibody, in patients with active proliferative lupus nephritis (LN): Results from the randomized, double-blind phase III BELONG study, 2010	Study Design
Mysler, et al., Study design and baseline patient characteristics of BELONG, the randomized double-blind, placebo-controlled phase III trial of ocrelizumab, A humanized anti-CD20 antibody, in lupus nephritis, 2010	Study Design
Nct, et al., Cyclophosphamide Versus Mycophenolate Mofetil in Lupus Nephritis, 2017	Duplicate
Nct, et al., Comparison of Low Dose Versus High Dose Cyclophosphamide as Induction Therapy in the Treatment of Lupus Nephritis, 2015	Duplicate
NR, et al., Cyclophosphamide versus azathioprine for proliferative lupus nephritis therapy, 2006	Study Design
NR, et al., Cytotoxic drugs and lupus nephritis, 1973	Study Design
NR, et al., Lupus nephritis: Negative results for the LUNAR phase III study of rituximab, 2012	Study Design
NR, et al., AURORA PHASE 3 TRIAL DEMONSTRATES VOCLOSPORIN STATISTICAL SUPERIORITY OVER STANDARD OF CARE IN LUPUS NEPHRITIS (LN), 2020	Duplicate
NR, et al., Aurora phase 3 trial demonstrates voclosporin statistical superiority over standard of care in lupus nephritis (LN), 2020	Duplicate
NR, et al., Remission of active lupus nephritis with voclosporin: asian subgroup analysis from the aura study, 2017	Study Design
NR, et al., Histologic findings from paired renal biopsies: single-site results from the allure study of abatacept for lupus nephritis, 2019	Study Design
NR, et al., Integrated Efficacy of the AURORA 1 and AURA-LV Trials Confirms Voclosporin Rapid Proteinurea Reduction in the Presence of Low-Dose Steroids, 2020	Study Design
Onno Teng, et al., Aurora phase 3 study demonstrates voclosporin statistical superiority over standard of care in lupus nephritis (LN), 2020	Duplicate
Pal, et al., Novel tacrolimus-azathioprine combination regimen as induction therapy in proliferative lupus nephritis, 2017	Study Design
Pal, et al., Comparison of tacrolimus-azathioprine combination versus cyclophosphamide for induction treatment of proliferative lupus nephritis, 2017	Study Design
Pendergraft, et al., AURA-LV: successful treatment of active lupus nephritis with voclosporin, 2016	Study Design
Pešičková, et al., Cyclosporin a versus intravenous cyclophosphamide in the treatment of lupus nephritis: The Cyclofa-lune study, 2010	Study Design

Petri, et al., Baseline laboratory characteristics from the combined placebo groups in the phase 3 belimumab trials are predictive of severe flare at 52 weeks, 2012	Study Design
Pohl, et al., Plasmapheresis does not increase the risk for infection in immunosuppressed patients with severe lupus nephritis, 1991	Intervention
Ponticelli, et al., Treatment of diffuse proliferative lupus nephritis, 1992	Study Design
Radhakrishnan, et al., Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class v lupus nephritis, 2010	Study Design
Rathi, et al., Randomized controlled trial of low-dose intravenous cyclophosphamide versus oral mycophenolate mofetil in treatment of lupus nephritis, 2014	Study Design
Rathi, et al., Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis: long term follow-up data, 2018	Study Design
Rathi, et al., Randomized controlled trial of low-dose intravenous cyclophosphamideversus oral mycophenolate mofetil in treatment of lupus nephritis, 2014	Study Design
Rathi, et al., Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis, 2016	Population
Rathi, et al., Outcomes in lupus nephritis patients previously randomized to receive either low dose cyclophosphamide versus oral mycophenolate mofetil on azathioprine maintenance, 2015	Study Design
Rijnink, et al., Long-term preserved renal function in class III or IV lupus nephritis without aggressive immunosuppression, 2015	Study Design
Rovin, et al., Efficacy and safety of rituximab (RTX) in subjects with proliferative lupus nephritis (LN): results from the randomized, double-blind phase III LUNAR study, 2009	Study Design
Rovin, et al., Belimumab (BEL) improves renal outcomes in active lupus nephritis (LN): a phase 3 randomized, placebo (PBO)-controlled trial, 2020	Duplicate
Rovin, et al., Two-year results from a randomized, controlled study of obinutuzumab for proliferative lupus nephritis, 2020	Duplicate
Rovin, et al., Efficacy and safety of belimumab in patients with active lupus nephritis: a phase 3, randomised, placebo-controlled trial, 2020	Duplicate
Roychowdhury, et al., IV cyclophosphamide vs tacrolimus and azathioprine as induction in proliferative lupus nephritis: a randomized controlled trial, 2017	Study Design
Ruan, et al., Lupus nephritis treated with impact therapy of cyclophosphamide and traditional Chinese medicine, 1994	Study Design
Sahin, et al., Mycophenolate mofetil treatment for therapy-resistant glomerulopathies, 2007	Study Design
Schaumann, et al., Intravenous cyclophosphamide (cp) pulse therapy for lupus nephritis - duration of induction therapy, 1992	Study Design
Schmalzing, et al., Mycophenolate mofetil seems to be superior to azothioprine in maintenance therapy of lupus nephritis, 2012	Study Design

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Schwartz, et al., Response to MMF therapy for lupus nephritis is independent of genetic variation of inosine monophosphate dehydrogenase, 2012	Study Design
Sedhain, et al., Effect of cyclophosphamide versus mycophenolate mofetil in induction therapy of lupus nephritis in Nepalese population, 2016	Study Design
Sedhain, et al., Low dose mycophenolate mofetil versus cyclophosphamide in the induction therapy of lupus nephritis in Nepalese population: A randomized control trial, 2018	Population
Silva-Fernandez, et al., Efficacy, toxicity and tolerability of mycophenolate mofetil in patients with lupus nephritis, based on dose/weight ratio, 2007	Study Design
Sin, et al., An evaluation of voclosporin for the treatment of lupus nephritis, 2018	Study Design
Solomons, et al., Aurion study: multi-target therapy with voclosporin, MMF and steroids for lupus nephritis, 2016	Study Design
Specker, et al., The LUNAR study: rituximab for lupus nephritis?, 2013	Study Design
Steinberg, et al., A double blind controlled trial comparing cyclophosphamide, azathioprine and placebo in the treatment of lupus glomerulonephritis, 1974	Outcomes
Steinberg, et al., A double-blind controlled trial comparing cyclophosphamide, azathioprine and placebo in the treatment of lupus glomerulonephritis, 1974	Duplicate
Steinberg, et al., Cyclophosphamide in lupus nephritis: a controlled trial, 1971	Population
Stoenoiu, et al., Repeat kidney biopsies fail to detect differences between azathioprine and mycophenolate mofetil maintenance therapy for lupus nephritis: Data from the MAINTAIN Nephritis Trial, 2010	Study Design
Stone, et al., Identification of biomarkers that predict response to treatment of lupus nephritis with mycophenolate mofetil (MMF) or pulse cyclophosphamide (IVC), 2009	Study Design
Sun, et al., Efficacy and safety of cyclophosphamide combined with mycophenolate mofetil for induction treatment of class IV lupus nephritis, 2015	Population
Suryawanshi, et al., Abatacept exposure-response analysis and its impact on dose selection in lupus nephritis, 2013	Study Design
Suttichet, et al., Urine tweak protein is a novel biomarker for resistant-to-treat lupus nephritis, 2017	Study Design
Tamirou, et al., A low and promptly tapered steroid regimen can achieve excellent results in lupus nephritis, with less adverse events, 2019	Study Design
Tamirou, et al., The 10-year followup of nephritis trial comparing azathioprine and mycophenolate mofetil for longterm immunosuppression of lupus nephritis, 2014	Study Design
Tamirou, et al., Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis, 2016	Outcomes
Tanaka, et al., Long-term mizoribine intermittent pulse therapy for young patients with flare of lupus nephritis, 2006	Study Design
Tanaka, et al., Efficacy and safety of rituximab in Japanese patients with systemic lupus erythematosus and lupus nephritis who are refractory to conventional therapy, 2016	Study Design

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Vital, et al., Biomarkers of B-cell Depletion and Response in a Randomized, Controlled Trial of Obinutuzumab for Proliferative Lupus Nephritis, 2020	Outcomes
Walsh, et al., Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis with poor kidney function: A subgroup analysis of the aspreva lupus management study, 2013	Study Design
Wang, et al., The GSTA1 polymorphism and cyclophosphamide therapy outcomes in lupus nephritis patients, 2015	Outcomes
Weiner, et al., Combination of tacrolimus and MMF for treatment of proliferative lupus nephritis, 2016	Study Design
Wentworth, et al., Systemic lupus erythematosus, 2009	Outcomes
Witte, et al., Pulse cyclophosphamide treatment of lupus nephritis, 1993	Duplicate
Witte, et al., Pulse cyclophosphamide treatment of lupus nephritis. CYCLOPHOSPHAMID-BOLUSTHERAPIE BEI LUPUSNEPHRITIS, 1993	Duplicate
Wofsy, et al., Mycophenolate mofetil compared with intravenous cyclophosamide in the treatment of lupus nephritis: predictors of response, 2008	Study Design
Wofsy, et al., Treatment of lupus nephritis with abatacept plus low-dose pulse cyclophosphamide followed by azathioprine (the Euro-Lupus regimen): twenty-four week data from a double-blind controlled trial, 2013	Study Design
Wofsy, et al., 48-Week complete remission by ethnic, sex and age subgroups in patients with active lupus nephritis treated with voclosporin, 2017	Study Design
Wofsy, et al., Treatment of lupus nephritis with abatacept: The abatacept and cyclophosphamide combination efficacy and safety study, 2014	Intervention
Wofsy, et al., Aspreva Lupus Management Study maintenance results, 2010	Study Design
Wofsy, et al., Treatment of lupus nephritis with abatacept plus low-dose pulse cyclophosphamide followed by azathioprine (the euro-lupus regimen): Twenty-four week data from a double-blind controlled trial, 2013	Study Design
Wofsy, et al., Comparison of alternative primary outcome measures for use in lupus nephritis clinical trials, 2013	Study Design
Wofsy, et al., Abatacept for lupus nephritis: Alternative outcome measures support opposing interpretations of data from a multicenter, randomized, double-blind, placebo-controlled phase II/III study, 2011	Study Design
Xu, et al., Correspondence on â € Long-term outcome of a randomised controlled trial comparing tacrolimus with mycophenolate mofetil as induction therapy for active lupus nephritis', 2020	Study Design
Yap, et al., A prospective randomized study on preemptive immunosuppressive therapy in lupus nephritis patients with asymptomatic serological reactivation, 2020	Outcomes
Yap, et al., A prospective randomized study on pre-emptive immunosuppressive treatment in lupus nephritis patients with asymptomatic serological reactivation, 2020	Population
Yin, et al., A clinical study on low dose cyclosporin A in the treatment of lupus nephritis, 1994	Study Design
Yu, et al., The long-term outcomes of leflunomide in patients with lupus nephritis, 2010	Study Design
Yu, et al., Belimumab improves renal outcomes in lupus nephritis: pre-specified analyses of a phase 3 randomized trial in an East Asian population, 2020	Study Design

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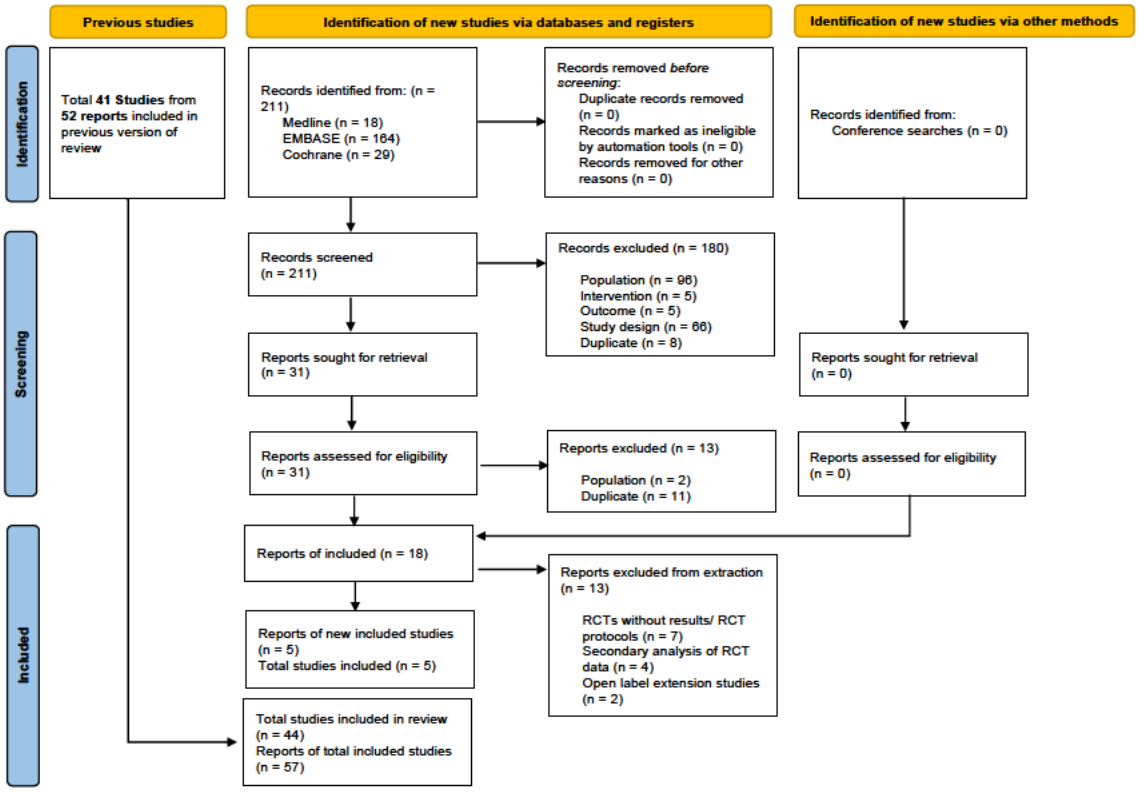
Zanetti, et al., Hydroxychloroquine blood levels in stable lupus nephritis under low dose (2–3 mg/kg/day): 12-month prospective randomized controlled trial, 2021	Population
Zavada, et al., Extended follow-up of a investigator-initiated trial comparing two sequential induction and maintenance treatment regimens for proliferative lupus nephritis based either on cyclophosphamide or cyclosporine, 2013	Study Design
Zavada, et al., Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the Cyclofa-Lune study, 2010	Duplicate
Zeher, et al., Efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS) in combination with two corticosteroid regimens for the treatment of lupus nephritis flare – results of the MYLUPUS study, 2010	Study Design
Zhang, et al., Multitarget therapy for maintenance treatment of lupus nephritis, 2017	Population
Zhang, et al., Cyclophosphamide (ctx) pulse therapy in lupus nephritis (ln): short term is better, 1995	Study Design
Zhang, et al., Leflunomide versus cyclophosphamide in the induction treatment of proliferative lupus nephritis in Chinese patients: a randomized trial, 2018	Duplicate
Ivanova, et al., Controlled trial of cyclophosphamide, azathioprin and chlorambucil in lupus nephritis (a double-blind trial), 1981	Non-Eng
Aranow, et al., Phase 2 trial of induction therapy with anticd20 (rituximab) followed by maintenance therapy with anti-BAFF (belimumab) in patients with active lupus nephritis, 2019	Duplicate
Honma, et al., Double blind trial of pulse methylprednisolone versus conventional oral prednisolone in lupus nephritis, 1994	Non-Eng
Witte, et al., Cyclophosphamide bolus therapy in lupus nephritis--status of the clinical study, 1993	Non-Eng
Hein, et al., Cyclophosphamide pulse therapy of systemic lupus erythematosus with renal involvement, 1991	Non-Eng
Fregoso, et al., Treatment of lupus nephritis with anti-CD20 followed by anti-BAFF: impact on B cell reconstitution, B cell subsets, and autoreactivity, 2019	Duplicate

Abbreviations: SLR = systematic literature review

SLR update

Figure 28: PRISMA diagram (SLR update)



Note: 5 news studies were included in the first SLR update – two publications linked to two studies (AURORA and NOBILITY) from the parent SLR, with the remaining three representing three unique studies. Together with the 41 unique studies identified in the parent SLR 44 total studies were included in the review.

Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR = systematic literature review

Table 100: Excluded reports assessed for eligibility (SLR update) (n= 13)

Bibliography	Reason of exclusion
Rubioet al., Journal Club: Efficacy and Safety of Voclosporin Versus Placebo for Lupus Nephritis (AURORA 1): A Double-Blind, Randomized, Multicenter, Placebo-Controlled, Phase 3 Trial, ACR Open Rheumatology, 2021	Duplicate
Rovinet al., Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial, Lancet (London, England), 2021	Duplicate
Furieet al., B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial, Annals of the rheumatic diseases, 2021	Duplicate
Anderset al., Effects of belimumab (BEL) on renal outcomes in patients (PTS) with relapsed and newly diagnosed active lupus nephritis (LN), Journal of the American Society of Nephrology, 2021	Duplicate
Furieet al., B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial, Annals of the rheumatic diseases, 2022	Duplicate
Jayneet al., A randomised dose ranging, placebocontrolled, phase ii study assessing the efficacy and safety of BI 655064, an antagonistic anti-CD40 antibody, in patients with lupus nephritis, Annals of the Rheumatic Diseases, 2021	Duplicate

Nctet al., Phase 3 Study of Anifrolumab in Adult Patients With Active Proliferative Lupus Nephritis, https://clinicaltrials.gov/show/NCT05138133, 2021	Duplicate
Jayneet al., Randomized, controlled, phase 2 trial of type 1 IFN inhibitor anifrolumab in patients with active proliferative lupus nephritis, Annals of the rheumatic diseases, 2021	Duplicate
Rubioet al., Journal Club: efficacy and Safety of Voclosporin Versus Placebo for Lupus Nephritis (AURORA 1): a Double-Blind, Randomized, Multicenter, Placebo-Controlled, Phase 3 Trial, ACR open rheumatology, 2021	Duplicate
Rovinet al., Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial, Lancet, 2021	Duplicate
Yanet al., Comparison of iguratimod and conventional cyclophosphamide with sequential azathioprine as treatment of active lupus nephritis: study protocol for a multi-center, randomized, controlled clinical trial (iGeLU study), Trials, 2021	Duplicate
Furieet al., Phase 2, Randomized, Placebo-Controlled Trial of Dapirolizumab Pegol in Patients with Moderate-to-Severe Active Systemic Lupus Erythematosus, Rheumatology (Oxford, England), 2021	Population
Ginzleret al., EMBRACE: phase 3/4, Randomized, 52-Week Study of Belimumab Efficacy and Safety in Patients of Black African Ancestry With Systemic Lupus Erythematosus, Arthritis & rheumatology (hoboken, N.J.), 2021	Population

Abbreviations: SLR = systematic literature review

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Included studies

Table 101: Summary of included studies (efficacy outcome: Complete renal response)

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Study ID	Author, Year	Aim	Primary outcome/ measurements	Study design	Intervention / Comparator	Minimum follow-up
Anutrakulchai, S 2016 (NCT01015456)	Anutrakulchai, S 2016(113)	To investigate the efficacy and safety of enteric-coated mycophenolate sodium as compared to intravenous cyclophosphamide (CYC) in the treatment of active nephritis. The primary outcomes are complete and partial renal remission, as assessed by renal function, urinary sediment and proteinuria in patients with International Society of Nephrology/ Renal Pathology Society (ISN/RPS) class III or IV lupus nephritis (LN).	Efficacy of enteric-coated Myfortic at 12 months in the treatment of LN [Time Frame: 12 months]	12-month period of multicentre, open-label randomised controlled study	Intervention - enteric-coated mycophenolate sodium Comparator- CYC IV	12 M (entire study duration)
AURA-LV (NCT02141672)	Rovin, B 2019(87)	To assess the efficacy of 2 doses of voclosporin compared to placebo in achieving complete remission after 24 weeks of therapy in subjects with active LN.	Number of Subjects Achieving Complete Renal Remission at 24 Weeks [Time Frame: week 24]	Phase 2, multicentre, randomised, double-blind, placebo-controlled trial	Intervention- voclosporin 23.7 mg Comparator- voclosporin 39.5 mg placebo	48 Wk (entire study duration)
AURORA 1 (NCT03021499)	Rovin J 2021(88)	The purpose of this study is to assess the efficacy of voclosporin compared with placebo in achieving renal response after 52 weeks of therapy in subjects with active LN.	Number of Participants With Adjudicated Renal Response at Week 52 [Time Frame: 52 Weeks]	Double-blind, randomised, multicentre, placebo-controlled	Intervention- voclosporin 23.7 mg Comparator- Placebo	52 Wk
AURORA 2 (NCT03021499)	Saxena A, 2021 (95)	The purpose of this study is to assess the efficacy of voclosporin compared with placebo in achieving renal response after 52 weeks of therapy in subjects with active LN.	Number of Participants With Adjudicated Renal Response at Week 52 [Time Frame: 52 Weeks]			52+52 WK
BLISS LN (NCT01639339)	Furie, R 2020(80) Yu 2020(91)	The purpose of this study is to evaluate the efficacy, safety, and tolerability of	• Double-blind Period: Percentage of Participants With Primary Efficacy			28 Wk open-label extension

	Rovin 2020(79)	belimumab in adult patients with active LN.	Renal Response at Week 104 [Time Frame: Week 104] • Open-label Period: Number of Participants Reporting adverse events (AEs) and serious adverse events (SAEs) [Time Frame: From first open-label dose (Day 1) up to open-label Week 32 (8 weeks after last dose)] • Open-label Period: Number of Participants Reporting AEs of Special Interest [Time Frame: From first open-label dose (Day 1) up to open-label Week 32 (8 weeks after last dose)]	Randomised, double-blind, placebo-controlled	Intervention - belimumab 10 mg Comparator - placebo	
Bandhan, 2021 (NCT04146220)	Bandhan, 2021 (127)	Assess Efficacy of Lower Dose Prednisolone in the Induction of Remission of LN	Number of participants achieving complete renal remission [Time Frame: At the end of 24th week]	open-label, randomized clinical trial	Intervention - Low-dose prednisolone 0.5 mg/kg/d (maximum 30 mg/d) Comparator - high-dose (HD) prednisolone 1 mg/kg/d (maximum 60 mg/d).	24 Wk
CALIBRATE (NCT02260934)	Atisha-Fregoso, Y 2021(108)	In this experimental study, researchers will try to find out if treatment of LN with a combination of rituximab (RTX) and CYC, or a combination of RTX and CYC followed by treatment with belimumab is safe and if this drug combination can block the immune system attacks.	Percentage of Participants With At Least One Grade 3 or Higher Infectious AE By Week 24, Week 48 and Week 96 [Time Frame: Week 0 to Week 96]	Phase II multicentre, randomised, controlled, open-label trial	Intervention - belimumab IV 10 mg/kg with RTX and CYC Comparator - RTX and CYC	96 Wk
Chan, T 2000	Chan, T 2000(115)	Purpose of the study was to compare the efficacy of the immunosuppressive regimens in controlling acute disease activity	Complete remission [Time frame: one-year]	Randomised	Intervention - MMF 1.0 g PO + prednisolone PO Comparator - CYC 2.5 mg/kg/day PO + prednisolone PO	12 M (entire study duration)
Chan, T 2005	Chan, T 2005	This extended study aimed to define the role of this MMF-based regimen in the treatment of DPLN, with a bigger sample size and prolonged follow-up.	Complete remission [Time frame: approximately 5 years]	Randomised	Intervention - MMF plus prednisolone for induction/maintenance Comparator - CYC plus prednisolone for induction; AZA plus prednisolone as maintenance	Median follow-up of 63 months

Contreras, G 2004	Contreras, G 2004(198)	Comparison of low-dose intravenous CYC with oral mycophenolate mofetil (MMF) in the treatment of LN	Treatment response, defined as a decrease in the uPCR to <3 in subjects with a baseline ratio ≥3 or a decrease in uPCR by ≥50% in those with a baseline ratio <3, along with stabilization or improvement in serum creatinine	Single-centre, randomised, open- label, controlled trial	Intervention - AZA Comparator - CYC, MMF	NR
Cyclofa-Lune (NCT00976300)	Zavada, J 2010(93)	In a randomized, multicenter, open-label, controlled trial the investigators sought to compare the efficacy of oral cyclosporine A with intravenous pulse CYC to induce durable remission in patients with LN III-IV.	Renal remission and renal response [Time Frame: at the end of induction (month 9) and maintenance (month 18) phase]	Multicentre, randomised, open-label, controlled trial	Intervention - cyclosporine Comparator - CYC	Mean 40 M
	Zavada, J 2014(92)					Median 7.7 years (range 5.0–10.3)
Dinant, H 1982	Dinant, H 1982(129)	Investigate Alternative Modes of CYC and AZA Therapy in LN	Renal function	Randomised	Intervention - CYC IV Comparator - CYC PO + AZA PO, prednisone	The mean observation period was 42 months (range 1 to 6.5 years)
Doria, A 1994	Doria, A 1994(117)	The aim of our study was to compare the efficacy of 3 different therapeutic protocols in the treatment of patients with WHO class IV LN and normal renal function	Decrease in 24-hour urinary protein excretion to < or = 0.5 g and < or = 0.2 g per day.	Randomised, prospective study	Intervention - methylprednisolone pulse IV Comparator - standard Therapy alone, plasmapheresis, followed by slow prednisone taper (added to standard therapy)	Until October 1993
DUTCH LN	Grootscholten, C 2006(123)	Access AZA/methylprednisolone versus CYC in proliferative LN	Renal response	Open label, randomised, controlled trial	Intervention - AZA 2 mg/kg/day IV plus methylprednisolone IV Comparator- CYC 750 mg/m^2 plus oral prednisone	Median follow-up of 5.7 years (interquartile range 4.1–7.2 years)

	Grootscholten, C 2007(124)	To study prospectively the effect of treatment with CYC pulses or AZA with methylprednisolone, both for 24-month periods, on health-related quality of life (HRQOL) in patients with proliferative LN in a randomized controlled trial. We expected better HRQOL during AZA treatment.	HRQOL and disease activity were measured at start and after 12 and 24 months. Generic questionnaires [patient's visual analog scale, Medical Outcomes 36-Item Short Form Survey (SF-36), Profile of Mood States] and a disease-specific measure [Systemic Lupus Erythematosus (SLE) Symptom Checklist] were used. Treatment burden was assessed at 24 months. Disease activity was measured with the SLE Disease Activity Index (SLEDAI) and physician's patient's visual analog scale.			
	Arends, S 2012 (199)	The objectives of this study are to analyse the long-term follow-up of a randomised controlled trial (RCT) of induction treatment with azathioprine/methylprednisolone (AZA/MP) versus HD intravenous CYC in patients with proliferative LN and to evaluate the predictive value of clinical, laboratory and renal biopsy parameters regarding renal outcome	The primary study end point was sustained doubling of serum creatinine. Secondary end points included renal relapse, end-stage renal disease and mortality.			Median follow-up of 9.6 years
Feng XB 2014	Feng XB 2014(97)	The aim of this study was to evaluate the efficacy and safety of mizoribine, a novel selective inhibitor of inosine monophosphate dehydrogenase, as induction treatment for active LN in comparison with MMF and intravenous CYC.	Therapeutic effects and AEs were evaluated at the end of 24-week treatment	Randomised, open label	Intervention- Mizoribine 300 mg every other day Comparator- MMF 2 g CYC 0.5g	NA
Ginzler, E 1976	Ginzler, E 1976(81)	Comparing prednisone and AZA to prednisone plus low-dose AZA and CYC	Renal disease activity	Double-blind, crossover	Intervention- AZA and CYC 1.25 mg/kg/day Comparator- AZA 2.5 mg/kg/day	12 M (entire study duration)
Ginzler, E 2005	Ginzler, E 2005(82)	Comparing oral MMF (initial dose, 1000 mg per day, increased to 3000 mg per day) with monthly intravenous CYC (0.5 g per square meter of body-surface area, increased to 1.0 g per square meter) as induction therapy for active LN	The primary end point was complete remission at 24 weeks (normalization of abnormal renal measurements and maintenance of baseline normal measurements). A secondary end point was partial remission at 24 weeks.	24-week randomised, open-label, noninferiority trial	Intervention- MMF PO Comparator- CYC IV	24 Wk (entire study duration)

Gourley, M 1996	Gourley, M 1996(109)	To determine 1) whether intensive bolus therapy with methylprednisolone is an adequate substitute for bolus therapy with CYC and 2) whether the combination of methylprednisolone and CYC is superior to bolus therapy with methylprednisolone or CYC alone.	• Renal remission (defined as < 10 dysmorphic erythrocytes per high-power field, the absence of cellular casts, and excretion of < 1 g of protein per day without doubling of the serum creatinine level) • prevention of doubling of the serum creatinine level, and • prevention of renal failure requiring dialysis.	Randomised, parallel study	Intervention - methylprednisolone 1g/m2 IV Comparator - CYC bolus, combination methylprednisolone + CYC	A total of 4656 patient-months of follow-up were accumulated
Illei, G 2001	Illei, G 2001(200)	To define the long-term risk and benefit of monthly treatment with boluses of methylprednisolone, CYC, or both.	Rates of treatment failure (defined as need for supplemental immunosuppressive therapy or doubling of serum creatinine concentration, or death) and AEs.	Extended follow-up (median, 11 years) of a randomized, controlled trial.	Patients were randomly assigned to receive one of three regimens: • intravenous methylprednisolone, 1 g/m2 of body surface area, • intravenous CYC, targeting 1 g/m2 of body surface area • the combination of these two regimens.	11 Y (median)
Jayne, 2021 (NCT02770170)	Jayne, 2021 (133)	The overall purpose of the study is to assess the efficacy of three different doses of BI 655064 against placebo as add-on therapy to standard of care (SOC) treatment for active LN in order to characterize the dose-response relationship within the therapeutic range, and select the target dose for phase III development.	Percentage of Patients With Complete Renal Response (CRR) at Week 52 [Time Frame: At week 52.]	Double blind, randomised dose ranging, placebo controlled, Phase 2	Intervention - BI 655064 120 mg Comparator - BI 655064 180 mg, BI 655064 240 mg, Placebo	52 Wk
Li, E 2009	Li, E 2009(116)	To assess if combination RTX and CYC is more effective than RTX monotherapy as an induction therapy for proliferative LN.	The clinical, laboratory and renal histological changes were assessed after 48 weeks of treatment.	Randomised, open-label pilot study	Intervention - RTX 1000 mg IV Comparator - RTX 1000 mg IV and CYC 750 mg IV	48 Wk

Li, X 2012 (ChiCTR-TRC-10000896)	Li, X 2012(98)	The objective of this study is to assess the efficacy and safety of MMF and tacrolimus compared with intravenous CYC as induction therapies for active LN.	CR or PR at 24 weeks was the primary endpoint.	Randomised, open-label, 24-week prospective study	Intervention- MMF 1.5-2.0 g/day PO Comparator - tacrolimus 0.08-0.1 mg/kg/day PO, CYC 0.5-0.72 g/m^2 IV	24 Wk (entire study duration)
Liebling, M 1982	Liebling, M 1982(110)	Assess Efficacy of Monthly pulses of methylprednisolone in SLE nephritis.	Improvement in serum creatinine	Placebo-controlled, double-blind trial	Intervention - methylprednisolone pulse IV Comparator - placebo IV	Methylprednisolone: 35.0 +/- 7.8 months Placebo: 26.5 +/- 3.5 months
Liu, Z 2015 (NCT00876616)	Liu, Z 2015(99)	The purpose of this study is to assess the efficacy and safety of multi-target therapy in the treatment of class Ⅲ,Ⅳ,Ⅴ,Ⅲ+Ⅴ and Ⅳ+Ⅴ LN.	To assess the efficacy of FK506 combined with MMF vs intravenous CTX pulses in treatment of class Ⅲ, Ⅳ, Ⅴ, Ⅲ+Ⅴ and Ⅳ+Ⅴ LN. [Time Frame: 24 weeks]	Randomised, open-label, multicentre study	Intervention - MMF + tacrolimus Comparator - CYC IV	24 Wk (entire study duration)
LUNAR (NCT00282347)	Rovin, B 2012(86)	This was a Phase III, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of RTX in combination with MMF compared with placebo in combination with MMF in subjects diagnosed with International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Class III or IV LN.	Percentage of Participants Who Achieved a CRR, a Partial Renal Response (PRR), or no Renal Response at Week 52 [Time Frame: Week 52]	Randomised, double-blind, placebo- controlled phase III trial	Intervention - RTX 1000 mg IV Comparator - placebo	78 Wk
Mehra, S 2018 (NCT02645565)	Mehra, S 2018(120)	This study will be conducted to find out whether low dose or HD-CYC therapy is effective in the treatment of proliferative LN.It will also compare the side effects and risks of infection in low dose and HD-CYC group. Half of the participants will receive a low dose CYC for 3 months and half will receive HD-CYC therapy monthly for 6 months followed by AZA 2 mg/kg.	Assessment of Primary Renal Response [Time Frame: 12 months]	Investigator-initiated, open label, parallel group RCT	Intervention - CYC 500 mg IV (low-dose) Comparator - CYC 750 mg/m^2 IV (high-dose)	52 Wk (entire study duration)
Mitwalli, A 2011	Mitwalli, A 2011(121)	To evaluate the outcome of low doses of CYC therapy in LN patients, we studied 117 biopsy-proven, de novo LN WHO class IV patients double-blinded and randomized in December 1997 to receive Cyclo in different doses; Group I (n=73) received Cyclo 10 mg/kg monthly for six months then every two months for 12 months.	The following parameters were measured monthly during induction therapy and quarterly thereafter: serum creatinine, urea, albumin, cholesterol, triglycerides, anti-nuclear antibodies, anti-double strands DNA, complements (C3 and C4), and hematological indices, in addition to 24-hour urinary protein and complete urine analysis.	Single-centre, randomised, double-blinded, prospective, controlled trial	Intervention - CYC 5 mg/kg IV Comparator - CYC 10 mg/kg	Mean follow up: 6.77 ± 3.3 years
Mok, C 2016 (NCT00371319)	Mok, C 2016(101) Mok, C 2020(100)	The purpose of this study is comparing the efficacy of tacrolimus and MMFl for the initial therapy of active lupus glomerulonephritis.	Remission rate [Time Frame: month 6]	Open randomised controlled parallel group study	Intervention - MMF 2-3 g/day Comparator - tacrolimus 0.06-0.1 mg/kg/day	5 Y 10 Y

Moroni, G 2006	Moroni, G 2006(118)	Comparing the safety and efficacy of cyclosporine and AZA	The primary outcome measure was the incidence of disease flares.	Multicentre, prospective, randomised, open, blinded–end point, controlled trial	Intervention - cyclosporine Comparator - AZA	Patients who met the inclusion criteria were studied for 2 Y (core study). At the end of core study, the patients were invited to continue to be followed up to 4 Y
MyLupus	Zeher, M 2011(94)	Investigating the Efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS) in combination with two glucocorticoid regimens for the treatment of active LN	The primary efficacy endpoint was the proportion of patients showing complete response at week 24	24-week, randomised, multicentre, open-label, parallel-group study	Intervention - reduced-dose oral glucocorticoids + EC-MPS Comparator - standard-dose oral glucocorticoids + EC-MPS	24 Wk (entire study duration)
Mysler, E.F. 2013 (NCT00626197)	Mysler, E.F. 2013(85)	This is a Phase III, randomized, double-blind, placebo-controlled, multicentre, parallel-group study designed to evaluate the efficacy and safety of ocrelizumab added to SOC (corticosteroid plus one of two immunosuppressant regimens) compared with placebo added to SOC in patients with WHO or ISN Class III or IV LN.	• Number of Participants Who Achieved CRR [Time Frame: Week 48] • Percentage of Participants Who Achieved Overall Response [Time Frame: Week 48]	Multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase III study	Intervention - ocrelizumab 400 mg Comparator - ocrelizumab 1000 mg placebo	48 Wk (entire study duration)
NOBILITY (NCT02550652)	Furie, R 2019(130) Furie, R 2020(84) Furie, R 2020(131) Amoura, Z 2020(128) Furie R.A., 2021 (96)	This Phase II study will compare the efficacy and safety of obinutuzumab plus MMF/mycophenolic acid with placebo plus MMF/MPA in participants with proliferative LN.	Percentage of Participants Who Achieve Protocol Defined CRR at Week 52 [Time Frame: From baseline to Week 52]	Phase II, randomised, double-blind, placebo-controlled study	Intervention - obinutuzumab 1000 mg IV Comparator - placebo IV	104 Wk (entire study duration) Abstract reports data at 76 Wk

Ong, L 2005	Ong, L 2005(125)	The aim of the present study was to evaluate the efficacy of MMF in the induction therapy of proliferative LN.	The primary outcome was remission of nephritis (combined partial and complete remission) at 6 months defined as stabilization or improvement in renal function, urinary red blood cell of less than 10 per high power field and reduction of proteinuria to less than 3 g/day if baseline proteinuria was more than 3 g/day and at least a 50% reduction in proteinuria or to less than 1 g/day if the baseline proteinuria was in the subnephrotic range.	Prospective, randomised, open-labelled clinical trial	Intervention - MMF 1.0 g PO Comparator - CYC 0.75-1 g/m^2 IV	6 M (entire study duration)
Rathi, M 2020	Rathi, M 2020(132)	The present study was aimed at comparing the efficacy and safety of these treatment options in subjects with less severe LN.	The primary end point was treatment response at 24 weeks, while secondary end points were complete remission, SLE Disease Activity Index and AEs	RCT	Intervention - MMF Comparator - CYC low-dose IV	Median 76 months
Rovin BH 2016 (NCT01273389)	Rovin BH 2016(89)	The purpose of this study is to evaluate the efficacy and safety of CNTO 136 administered intravenously in patients with active, International Society of Nephrology/Renal Pathology Society Class III and IV LN.	Number of patients with reduction in proteinuria (measurement of total urine protein greater than 0.5 g/24-hours, or a urine protein to creatinine ratio greater than 0.5 mg/mg) [Time Frame: Baseline to Week 24]	Multicentre, randomised, double-blind, placebo-controlled, parallel group study	Intervention - sirukumab 10 mg Comparator - placebo	16 Wk
Sabry, A 2009	Sabry, A 2009(126)	To compare between efficacy, potential toxicity and outcome of parenteral HD-CYC versus HD-CYC therapy for severe LN.	The primary end point of the study was treatment failure. It was defined as urinary protein excretion that remained at or above 3 g per 24 h, and/or doubling of serum creatinine or severe flare that was resistant to increased glucocorticoid dose.	Randomised, prospective study	Intervention - low-dose remission-inducing IV CYC Comparator - HD IV CYC	1 Y
Sesso, R 1994	Sesso, R 1994(83)	Assess pulse methylprednisolone versus two regimens of pulse CYC in severe LN	The primary study outcome was renal insufficiency defined as sustained doubling (for more than 1 month) of serum creatinine over the lowest value reached during the study period	Prospective randomised trial	Intervention - CYC 0.5-1.0 g/m^2 IV Comparator - methylprednisolone 10-20 mg/kg IV	The mean follow-up was 15 months.
Steinberg, A 1991	Steinberg, A 1991(111)	The purpose of this study was to assess long-term preservation of renal function in 111 patients with SLE and active glomerulonephritis who participated in a randomized treatment trial.	Preservation of renal function	Randomised, prospective study	Intervention - AZA PO Comparator - AZA PO + CYC PO, CYC IV, CYC PO, prednisone PO	The cut-off date for the present analysis was October 31, 1989 (1969 to 1989)

TULIP-LN (NCT02547922)	Jayne 2021(112)	The purpose of this study is to evaluate the efficacy and safety of an intravenous treatment regimen of two doses of anifrolumab versus placebo in adult subjects with active proliferative LN.	Change From Baseline in 24-hour Urine Protein to Creatinine Ratio (UPCR) [Time Frame: From Week 1 (Baseline) up to Week 52]	Phase 2 double-blind trial	Intervention - Anifrolumab basic regimen (BR, 300 mg, based on SLE dosing) Comparator - Anifrolumab intensified regimen (IR, 900 mg for 3 doses, 300 mg thereafter), Placebo	NR
TTT (NCT01580865)	Kamanamool, N 2018(114)	Comparison Between Tacrolimus and MMF for Induction of Remission in LN	Complete remission [Time Frame: 1 year]	Multicenter, open-label, parallel, randomised, controlled trial	Intervention - Tacrolimus Comparator - MMF	12 M (entire study duration)
Wang, J 2007	Wang, J 2007(102)	In this study, the efficacy and safety of MMF plus corticosteroids were compared with that of i.v. CTX plus corticosteroids for inducing remission of patients with class IV LN and NNV in an open-label, randomized study design.	The primary endpoint was complete remission.	Single-centre, randomised, open-label, controlled trial	Intervention - MMF 0.75 or 1 g Comparator - CYC 0.75-1.0 g/m2 IV	6 M (entire study duration)
Yap, D 2012	Yap, D 2012(103)	This pilot study compared MMF and tacrolimus in the treatment of severe membranous LN.	The primary endpoint was response to treatment at 24 months. Complete response	Prospective, randomised, open-label study	Intervention - MMF Comparator - Tacrolimus	24 M (entire study duration)
Yee, C-S 2004	Yee, C-S 2004(90)	To compare the efficacy and side effects of intermittent pulse CYC plus methylprednisolone with continuous oral CYC plus prednisolone, followed by AZA, in patients with proliferative glomerulonephritis caused by SLE.	The primary end points were doubling of serum creatinine and renal failure requiring dialysis. Secondary end points were withdrawal from treatment, complications from treatment (infection, malignancy, haemorrhagic cystitis, amenorrhoea, alopecia, or nausea and vomiting), and death.	Open-label, multicentre, RCT	Intervention - CYC PO Comparator - CYC intermittent pulse	Mean duration of follow up was 3.7 years in the continuous group (range 0 to 5.6) and 3.3 years in the pulse group (range 0.25 to 6).
Zhang M 2019	Zhang M 2019(105)	A prospective, multi-center, randomized controlled study was conducted to evaluate the efficacy and safety of a 24-week course low-dose leflunomide combined with prednisone in the induction treatment of proliferative LN in Chinese patients.	The primary endpoints were complete remission and partial remission at 24 weeks.	Randomised, Open label	Intervention - leflunomide PO 20 mg/day Comparator - CYC 0.8 - 1.0 g monthly	NI
Zhang, J 2015	Zhang, J 2015(104)	The objective of this study was to analyze and compare the effects of RTX and CYC on the serum levels of anti-C1q antibodies and antineutrophil cytoplasmic autoantibodies (ANCA) in assessing the prognosis of severe and refractory LN.	Measurement of Anti-C1q and ANCA Antibodies in the Serum	Randomised	Intervention - RTX 275 mg/m^2 IV + CYC 800 mg IV Comparator - CYC 800 mg IV	12 M (entire study duration)

Zhang, X 2014	Zhang, X 2014(107)	The objective of this study was to assess the efficacy and safety of short-interval lower-dose (SILD) intravenous CYC in the treatment of SLE	The primary end point was the remission of LN (includes complete and partial remission) at the 6th month	Prospective, randomised observational study	Intervention - Short-interval lower-dose (SILD) CYC IV Comparator – HD-CYC IV	1 Y (entire study duration)
Zhang, X 2020	Zhang, X 2020(106)	Here, we aimed to compare the clinical effects of MMF combined with either tacrolimus or with CYC on LN and to analyze their influence on the expression of cystatin C and on transforming growth factor-1 (TGF-β1).	Expression levels of serum TGF-β1 and cystatin C before and after treatment.	Randomised	Intervention - MMF + tacrolimus Comparator - MMF + CYC	6 M (entire study duration)

Note: The population for all studies were: Patients 18 years or above, with active LN defined as Class III, Class IV-S, IV-G, Class V (and/or) UPCR of ≥1.5 mg/mg

Abbreviations: AEs = adverse events; ANCA = Antineutrophil Cytoplasmic Autoantibodies; AZA = azathioprine; BI = twice; CR = Complete Remission; CRR = complete renal response; CTX = cyclophosphamide; CYC = cyclophosphamide; DPLN = diffuse proliferative lupus nephritis; EC-MPS = Enteric-Coated Mycophenolate Sodium; HD = High-Dose; HD-CYC = High-Dose Cyclophosphamide; HRQOL = Health-Related Quality Of Life; ISN/RPS = International Society of Nephrology/Renal Pathology Society; IV = intravenous; LN = lupus nephritis; MMF = mycophenolate mofetil; NA = Not Applicable; NR = Not reported; PO = orally; PR = partial response; PRR = Partial Renal Response; RCT = randomised controlled trial; RTX = rituximab; SAEs = Serious Adverse Events; UPCR = Protein To Creatinine Ratio; SF-36 = 36-Item Short Form Survey; SILD = Safety Of Short-Interval Lower-Dose; SLE = Systemic Lupus Erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SOC = Standard Of Care; WHO = World Health Organization; Wk = week

Quality assessment

Quality assessment (QA) was performed for all publications except for conference proceedings (44 publications – 2 conference proceedings = 42), as there would be insufficient methodological data to assess the quality of included study publication. The QA for RCTs was conducted using the Cochrane risk of bias tool (201). The Cochrane risk of bias tool is a qualitative tool, leaving room for interpretation. The Cochrane risk of bias tool consists of six elements: random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, complete outcome assessment, and selective reporting (201). Results of the QA using the checklist for RCTs from the CRD Guidance for Undertaking Reviews in Health Care (2009 (201)) are presented in Table 102. The table has been colour coded to indicate those areas with high (red), low (green) or unclear (orange) risk of bias.

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Table 102: Quality assessment of included studies (n = 42)

Study ID	Was the method used to generate random allocations adequate?	Was the allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Anutrakulchai 2016(113)	Yes	Not clear	Yes	No	Yes	No	Not clear
AURA-LV(202)	Yes	Yes	Yes	Yes	Yes	No	Yes
AURORA 1(12)	Yes	Yes	Yes	Yes	Yes	No	Yes
BLISS LN(154)	Yes	Yes	Yes	Yes	No	No	Yes
Bandhan 2021(127)	No	No	Yes	No	Yes	Yes	Yes
CALIBRATE(108)	Yes	Yes	Yes	No	Yes	No	Yes
Chan 2000(115)	Not clear	Yes	Yes	No	No	No	Yes
Contreras 2004(198)	Yes	Yes	Yes	No	Yes	No	No
Cyclofa-Lune(92, 93)	Yes	Yes	Yes	No	No	No	Yes
Dinant 1982(129)	Not clear	Not clear	Not clear	Not clear	No	No	Not clear

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Study ID	Was the method used to generate random allocations adequate?	Was the allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Doria 1994(117)	Not clear	Not clear	Yes	Not clear	No	No	Not clear
DUTCH LN(123, 124)	Yes	Yes	Not clear	No	No	No	Not clear
Feng XB(97)	Yes	Not clear	Not clear	No	Yes	No	No
Ginzler 1976(81)	Not clear	Not clear	Yes	Not clear	No	No	No
Ginzler 2005(82)	Yes	Yes	Yes	No	Yes	No	Yes
Gourley 1996(109)	Yes	Yes	Yes	Not clear	No	No	Yes
Li 2009(116)	Yes	Yes	Yes	No	No	No	Yes
Li 2012(98)	Not clear	Not clear	Yes	No	No	No	Yes
Liebling 1982(110)	Not clear	Not clear	Not clear	Yes	No	No	No
Liu 2015(190)	Yes	Yes	Yes	No	No	No	No
LUNAR(203)	Not clear	Not clear	Yes	Yes	Yes	No	Yes
NOBILITY(96)	Yes	Yes	Yes	Yes	Yes	No	Yes
Mehra 2018(204)	Yes	Yes	Yes	No	No	No	Yes

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Study ID	Was the method used to generate random allocations adequate?	Was the allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Mitwalli 2011(121)	Not clear	Not clear	Yes	Yes	Not clear	No	Not clear
Mok 2016(101)	Yes	Yes	Yes	No	Not clear	No	Yes
Moroni 2006(118)	Yes	Yes	Yes	No	No	No	No
MyLupus(205)	Yes	Yes	Yes	No	No	No	Not clear
Mysler 2013(85)	Not clear	Not clear	Yes	Yes	No	No	No
Ong 2005(125)	Yes	Yes	No	No	No	No	No
Rathi 2020(206)	Not clear	Not clear	Not clear	Not clear	Not clear	No	No
Rovin BH(89)	Not clear	Not clear	Not clear	Not clear	Yes	No	No
Sabry 2009(126)	No	No	Not clear	Not clear	No	No	Yes
Sesso 1994(83)	Not clear	Not clear	Yes	Not clear	No	No	Yes
Steinberg 1991(111)	Yes	Yes	Yes	No	Not clear	No	Not clear
TTT(114)	Yes	Yes	Yes	No	No	No	No
Wang 2007(102)	Not clear	Yes	Yes	No	No	No	Yes
Yap 2012(103)	Not clear	Not clear	Yes	No	No	No	Not clear

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Study ID	Was the method used to generate random allocations adequate?	Was the allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in dropouts between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Yee 2004(90)	Yes	Not clear	Yes	No	No	No	No
Zhang 2014(107)	Not clear	Not clear	Yes	Not clear	No	No	No
Zhang 2015(104)	Not clear	Not clear	Yes	Not clear	No	No	Yes
Zhang 2019(105)	Yes	Yes	Yes	No	No	No	Yes
Zhang 2020(106)	Not clear	Not clear	Yes	Not clear	Not clear	No	Not clear

Unpublished data

No unpublished data were included for either of the SLR reports.

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Economic models used for the current model structure

Table 103: Economic model identified and used to build the structure of the current model

Study	Summary of model	Population (age [yrs])	Time horizon and perspective	Health states	Treatment	QALYs	Costs	ICER
Wilson et al., (2007)(146)	Short-term patient-level simulation model of 6 months (cycle length: 3 months)	Patients with active LN receiving initial treatment with CYC or MMF (mean: NR)	6 months time horizon equal to the induction period with a UK National Health Service perspective	Active disease, complete remission, partial remission, minor infection, major infection	Initial MMF	0.3	£1,388	Initial MMF dominant vs CYC
					Initial CYC	0.2	£2,994	
Mohara et al., (2014)(145)	Lifetime Markov (cycle length: 6 months in first year; then 12 months)	Patients with LN and "active, severe disease" (mean: 40)	Lifetime with Thailand's societal perspective	Active disease, complete remission, partial remission, ESRD and death (with the first three divided into three substates)	Initial CYC/maint. CYC	9.4	3,979,910 baht	Reference
					Initial CYC/maint. AZA	9.7	3,966,611 baht	-49,167 baht /QALY gained
					Initial CYC/maint. MMF	9.7	4,118,461 baht	+618,014 baht /QALY gained
					Initial MMF/maint. MMF+AZA	9.7	4,072,513 baht	+349,029baht /QALY gained
Nee et al., (2015)(144)	Mixed: short-term Markov model of 3 years (cycle length: 6 months) followed by lifetime Markov model (cycle length: 12 months)	Patients with class III/IV LN who responded to initial therapy (range: 20–40)	Lifetime (3 years short-term and 40 years long-term) with a US healthcare system perspective	Short-term: Remission, relapse MMF, relapse IV CYC, ESRD due to LN, death. Long-term: Remission, relapse, ESRD due to LN, death	Maint. AZA	14.2	$478,333	Reference
					Maint. MMF	15.1	$484,310	+$6,454 /QALY gained
Kim et al., (2019)(143)	Mixed: decision tree for induction phase, followed by Markov model for maintenance (cycle length: 3 months)*	Patients with class III/IV LN, ± class V (mean: 18)	Lifetime – 20 years with a Chinese Payer perspective	Active disease, complete remission, partial remission, ESRD, kidney transplant, post-kidney transplant and death	Initial TAC/maint. TAC	11.9	CN¥180,448	Initial TAC/maint. TAC dominant vs all other comparators
					Initial TAC/maint. AZA	11.4	CN¥272,007	
					Initial TAC/maint. MMF	11.5	CN¥704,959	
					Initial CYC/maint. TAC	11.9	CN¥292,085	
					Initial CYC/maint. AZA	11.3	CN¥291,206	
					Initial CYC/maint. MMF	11.5	CN¥721,084	
					Initial MMF/maint. TAC	11.8	CN¥298,252	
					Initial MMF/maint. AZA	11.3	CN¥297,568	
					Initial MMF/maint. MMF	11.4	CN¥728,080	
ICER report (2021)(147)	Mixed: short-term Markov model of 3 years and lifetime PSM	SLE patients with class III, IV, or V LN (mean: 35)	Lifetime with a modified societal perspective analysis, indirect costs considered were costs of unemployment, absenteeism and caregiving	Complete response, partial response, active disease, kidney failure	Initial placebo + MMF	11.7	$784,416	Reference
					Initial VCS + MMF	12.6	$928,486	$149,260 /QALY gained

*3-month cycle length based on clinical feedback to reflect how often treatment was evaluated

Abbreviations: AZA = azathioprine; CN¥ = Chinese Yuan; CYC = cyclophosphamide; ESRD = end-stage renal disease; ICER = incremental cost-effectiveness ratio; IV = intravenous; LN = lupus nephritis; maint. = maintenance; MMF = mycophenolate mofetil; NR = not reported; PSM = partitioned survival model; SLE = systemic lupus erythematosus; TAC = tacrolimus; QALYs = quality-adjusted life years; VCS = voclosporin; yrs = years

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Appendix B Main characteristics of included studies

Table 104: AURORA characteristics

Trial name: Aurinia Renal Response in Active Lupus With Voclosporin (AURORA)	NCT number: NCT03021499	
Objective	The aim of the current study is to investigate whether voclosporin, added to the standard of care treatment in active lupus nephritis (LN), is able to reduce disease activity over a treatment period of 52 weeks. The background therapy will be mycophenolate mofetil (MMF) and initial treatment with IV methylprednisolone, followed by a reducing course of oral corticosteroids. Subjects with active, flaring LN will be eligible to enter the study. They are required to have a diagnosis of LN according to established diagnostic criteria and clinical and biopsy features suggestive of active nephritis. Efficacy will be assessed by the ability of the drug combination to reduce the level of proteinuria (as measured by Urine Protein Creatinine Ratio (UPCR)) while demonstrating an acceptable safety profile.	
Publications – title, author, journal, year	A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active LN (73) AURORA 1 reports efficacy of voclosporin in LN (207) Efficacy and safety of voclosporin versus placebo for LN (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial (14)	
Study type and design	Phase 3, multicenter, randomized, prospective, double-blind, parallel-group, placebo-controlled, 2-arm comparison study of voclosporin versus matching placebo. Subjects were randomized in a ratio of 1:1 to receive either voclosporin or matching placebo.	
Sample size (n)	358 participants	
	Inclusion	**Exclusion**

Inclusion and exclusion criteria

- Written informed consent before any study-specific procedures were performed.
- Male or female subjects with a minimum age of 18 (or legal age of consent if >18 years) to 75 years of age, inclusive, at the time of screening (Visit 1).
- Previous diagnosis of systemic lupus erythematosus (SLE) (Table 108: International Society of Nephrology and the Renal Pathology Society (ISN/RPS) 2003 Classification of Lupus Nephritis)
- Subjects with evidence of active nephritis, defined as follows:
    - Kidney biopsy result within 2 years prior to screening indicating Class III, IV-S, IV-G (alone or in combination with Class V), or Class V with a doubling or greater increase of UPCR within the previous 6 months to a minimum of ≥1.5 mg/mg for Class III/IV or to a minimum of ≥2 mg/mg for Class V at screening. Biopsy results over 6 months prior to screening had to be reviewed with a medical monitor to confirm eligibility

      OR
    - Kidney biopsy result within 6 months prior to screening indicating Class III, Class IV-S, or Class IV-G (alone or in combination with Class V) LN with a UPCR of ≥1.5 mg/mg at screening.

      OR
    - Kidney biopsy result within 6 months prior to screening indicating Class V LN and a UPCR of ≥2 mg/mg at screening.

  A biopsy could be performed during screening, if not available. The above criteria had to be fulfilled at baseline.
- In the opinion of the Investigator, subject required high-dose corticosteroids and immunosuppressive therapy.
- Subjects unable or unwilling to give written informed consent and/or to comply with study procedures.
- Estimated glomerular filtration rate (eGFR) as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation of ≤45 mL/min/1.73 m^2 at screening confirmed before randomization.
- Currently taking or known need for any of the following medications or food items during the study.
    - IV corticosteroids unless approved by the Medical Monitor
    - Enteric coated oral corticosteroids during the study were not allowed. No other use of non-enteric coated oral corticosteroids, other than administration required as per protocol, was allowed
    - IV immunoglobulin treatment
    - Cyclophosphamide
    - Cholestyramine or other drugs that may interfere with enterohepatic recirculation of MMF
    - Initiation of new treatment or change in dosage of Angiotensin Receptor Blockers and/or angiotensin-converting enzyme (ACE) inhibitors
    - Calcineurin inhibitors (CNIs) (e.g., cyclosporine and tacrolimus)
    - Immunosuppression biologic agents (e.g., abatacept, belimumab, infliximab, adalimumab, etanercept, or rituximab)
    - Vaccines using live organisms, viral or bacterial
    - MMF dose other than 2 g/day without prior discussion with the Medical Monitor
    - Concomitant therapy with other immunosuppressants after consent, other than MMF administered per protocol
    - Azathioprine or mycophenolate sodium

- Subject was willing to take oral MMF for the duration of the study, either by continuing current MMF therapy or by initiating it on or before the baseline visit.
- Women of childbearing potential had to have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline. Two effective forms of contraception had to be used simultaneously unless abstinence was the chosen method. Subjects had to use effective contraception during the study.
    - Ketoconazole or rifampin
    - Concomitant use of other CYP3A4/5 inhibitors and inducers was to be discussed with the Medical Monitor
- A previous kidney transplant or planned transplant within study treatment period
- Was currently requiring renal dialysis (hemodialysis or peritoneal dialysis) or was expected to require dialysis during the study period.
- Any known hypersensitivity or contraindication to MMF, mycophenolic acid, cyclosporine, corticosteroids, or any components of these drug products.
- Current or medical history of:
    - Congenital or acquired immunodeficiency.
    - In the opinion of the Investigator, clinically significant drug or alcohol abuse within 2 years prior to screening.
    - Malignancy within 5 years of screening, with the exception of basal and squamous cell carcinomas treated by complete excision. Subjects with cervical dysplasia that was cervical intraepithelial neoplasia 1 but had been treated with conization or loop electrosurgical excision procedure and had a normal repeat Papanicolaou test were allowed.
    - Lymphoproliferative disease or previous total lymphoid irradiation.
    - Severe viral infection (e.g., cytomegalovirus, hepatitis B virus, hepatitis C virus) within 3 months of screening; or known human immunodeficiency virus infection. Severe viral infection was defined as active disease requiring antiviral therapy
    - Active tuberculosis or known history of tuberculosis/evidence of old tuberculosis if not taking prophylaxis with isoniazid.
- Other known clinically significant active medical conditions, such as:

- Severe cardiovascular disease including congestive heart failure, history of cardiac dysrhythmia or congenital long QT syndrome. QTcF exceeding 480 msec in the presence of a normal QRS interval (<110 msec) at time of screening resulted in exclusion.
- Liver dysfunction (aspartate aminotransferase, alanine aminotransferase, or bilirubin ≥2.5 times the upper limit of normal) at screening and, if abnormal at screening, then confirmed that the levels had returned to <2.5 times upper limit of normal before randomization.
- Chronic obstructive pulmonary disease or asthma requiring oral steroids.
- Bone marrow insufficiency unrelated to active SLE (according to Investigator judgment) with white blood cell count <2,500/mm3 ; absolute neutrophil count <1.3 × 103 /µL; thrombocytopenia (platelet count <50,000/mm3).
- Active bleeding disorders.
- Had current infection requiring IV antibiotics.

- Any overlapping autoimmune condition for which the condition or the treatment of the condition may have affected the study assessments or outcomes (e.g., scleroderma with significant pulmonary hypertension; any condition for which additional immunosuppression was indicated). Overlapping conditions for which the condition or treatment was not expected to affect assessments or outcomes (e.g., Sjögren's syndrome) were not excluded.
- No vaccines using live organisms, virus or bacterial, were allowed during screening and while taking the study treatment.
- Other major physical or psychiatric illness or major traumatic injury within 6 months prior to screening that may have affected study conduct or interfered with study assessments or outcome.
- Any other medical condition which, in the Investigator's judgment, may have been associated with increased risk to the subject or may have interfered with study assessments or outcomes.

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Trial name: Aurinia Renal Response in Active Lupus With Voclosporin (AURORA)	NCT number: NCT03021499
	• Subjects who were pregnant, breast feeding or, if of childbearing potential, not using adequate contraceptive precautions. • Participation in another clinical study within 4 weeks prior to screening and/or receipt of investigational drugs within 4 weeks or 5 half-lives of the drug (whichever was longer) prior to screening. • Subject was randomized and treated in a previous voclosporin clinical study.
Intervention	23.7 mg Voclosporin (3 capsules) given orally twice daily (total 47.4 mg/day, 6 capsules) for 52 weeks. Subjects were also to receive 2 g/day MMF; subjects who were not already taking MMF prior to randomization received 1 g/day for the first week, increasing to 2 g/day on Day 8. In addition, all subjects were to receive 0.5 g/day intravenous methylprednisolone on Days 1 and 2 (0.25 g/day for subjects weighing <45 kg) before changing to a reducing course of oral corticosteroid therapy on Day 3. **(N= 179)**
Comparator(s)	Matching placebo softgel capsules (3 capsules) given orally twice daily (6 capsules) for 52 weeks. Subjects were also to receive 2 g/day MMF; subjects who were not already taking MMF prior to randomization received 1 g/day for the first week, increasing to 2 g/day on Day 8. In addition, all subjects were to receive 0.5 g/day intravenous methylprednisolone on Days 1 and 2 (0.25 g/day for subjects weighing <45 kg) before changing to a reducing course of oral corticosteroid therapy on Day 3. **(N= 178)**
Follow-up time	52 weeks
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints	**Key primary endpoint:** • Renal response at Week 52 as adjudicated by the Clinical Endpoints Committee based on the following parameters: o UPCR of ≤0.5 mg/mg, and o eGFR ≥60 mL/min/1.73 m2 or no confirmed decrease from baseline in eGFR of >20%, and o Received no rescue medication for LN, and o Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44-52, just prior to the renal response assessment. Subjects who withdrew from the study prior to the Week 52 assessment were defined as non-responders. **Key secondary endpoints:** • Time to UPCR of ≤0.5 mg/mg • Renal response at Week 24 (based on definition of primary endpoint) • Partial renal response, defined as 50% reduction from baseline in UPCR, at Weeks 24 and 52 • Time to 50% reduction in UPCR from baseline. **Other secondary outcomes:** • Duration of UPCR ≤0.5 mg/mg • Proportion of subjects experiencing a confirmed >30% decrease from baseline in eGFR at each time point • Change from baseline in UPCR at each time point • Change from baseline in urine protein, serum creatinine and eGFR • Change from baseline in immunology parameters (C3, C4 and anti-dsDNA) at Weeks 24 and 52 • Renal response with low-dose steroids (defined as renal response in the presence of corticosteroids of ≤2.5 mg/day between Weeks 16 to 24 and Weeks 44 to 52) • Change from baseline in Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score at Weeks 24 and 52 • Change from baseline in health-related quality of life (HRQoL) at Weeks 12, 24, and 52 Health Resource Utilization at Weeks 24 and 52
Method of analysis	All statistical analyses were undertaken at study closure and incorporated all Week 24 and Week 52 endpoints.

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	Populations: The efficacy analysis was based on the intention-to-treat (ITT) principles and consisted of all randomized subjects. The per-protocol set was a subset of subjects in the ITT population who did not have any major protocol violations (defined prior to unblinding). The safety analysis set consisted of all subjects who received at least 1 dose of study treatment. Methods: The analysis of the primary endpoint, renal response at Week 52, was conducted on the ITT population using a logistic regression model with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline, region, and renal response as the response variable. The results were displayed as odds ratios (OR) and two-sided 95% confidence interval (CI) for voclosporin compared to placebo. Sensitivity and supplementary analyses based on the primary endpoint were also performed. The impact of withdrawals on the primary endpoint was investigated with a tipping point analysis. Other binary endpoints were analysed in a similar manner to the primary endpoint. Secondary time-to-event endpoints were estimated using Kaplan-Meier methodology. Voclosporin was compared to placebo using a Cox's proportional hazards model including terms for treatment and appropriate baseline assessments. Estimates of the treatment effects were expressed as hazard ratios (HR) and associated 95% CIs for voclosporin relative to placebo. Other secondary endpoints were summarized by treatment and visit. Differences between baseline and on-treatment values at weeks up to and including Week 52, and differences between treatment arms were analysed using a Mixed Effect Model Repeated Measures (MMRM) analysis including terms for treatment, visit, treatment by visit interaction and baseline assessments. Results were expressed as LS means along with associated 95% CIs.
Subgroup analyses	All subgroup analyses were prespecified in the statistical analysis plan. The primary endpoint was analysed controlling in turn for each the following factors: **Age (≥30 years vs < 30 years)**, **Sex (Female, Male)**, **Race (White, Asian, Other)**, **Biopsy class (Pure Class V, Other)**, **Region (Asia Pacific, Europe+ South Africa, Latin America, North America)**, **Prior MMF Use? (No, Yes)**, **Maximum MMF Dose (≥2 mg, >2 mg)**. An interaction between the factor and treatment group was added to the model, and a p-value for the main effect of the covariate in question along with the p-value for the interaction between treatment and covariate are reported.
Other relevant information	NA

Abbreviations: ACE = angiotensin-converting enzyme; CI = confidence interval; CNI = calcineurin inhibitor; eGFR = estimated glomerular filtration rate; ISN/RPS = International Society of Nephrology and the Renal Pathology Society; ITT = intention-to-treat; IV = intravenous; IV-G = diffuse global; IV-S = diffuse segmental; LN = lupus nephritis; MMF = mycophenolate mofetil; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index; SOC = standard of care; UPCR = urine protein creatinine ratio

Table 105: AURORA 2 characteristics

Trial name: AURORA 2: Aurinia Renal Response in Lupus With Voclosporin	NCT number: NCT03597464
Objective	The aim of the Phase 3 continuation study (AURORA 2) is to assess the long-term safety and tolerability of voclosporin, added to the standard of care treatment in lupus nephritis (LN), for an additional 24 months, following a treatment period of 52 weeks in the AURORA 1 study [see Appendix B Main characteristics of included studies]. All subjects will continue to receive background therapy of mycophenolate mofetil (MMF) and/or oral corticosteroids starting at the same dose as at the end of the AURORA 1 study. Subjects with LN, who have completed 52 weeks of treatment with study drug in the AURORA 1 study, will be eligible to enter the study. The long-term safety and tolerability of the drug combination will be assessed from its safety profile while demonstrating the continued ability to achieve and maintain long-term renal response.
Publications – title, author, journal, year	Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial (14)
Study type and design	Phase 3, randomized, prospective, placebo-controlled, double-blind, parallel-group, 24-month continuation study to the AURORA 1 study (see Appendix B Main characteristics of included studies).
Sample size (n)	216 participants
Inclusion	**Exclusion**

Main inclusion and exclusion criteria	• Written informed consent before any study-specific procedures were performed. • Male or female subjects who completed 52 weeks of treatment with study drug in the AURORA 1 study (see Appendix B Main characteristics of included studies,Table 104), including subjects who had a temporary interruption and successfully restarted study drug during the AURORA 1 study. Male or female subjects who completed 52 weeks of treatment with study drug in the AURORA 1 study (see Appendix B Main characteristics of included studies, Table 104, including subjects who had a temporary interruption and successfully restarted study drug during the AURORA 1 study. • In the opinion of the investigator, subject required continued immunosuppressive therapy. • Women of childbearing potential must continue to use effective contraception and have a negative urine pregnancy test at Month 12. Two effective forms of contraception must be used simultaneously unless abstinence is the chosen method. Subjects must use effective contraception during the study. • Subject willing to continue taking oral MMF for the duration of the study • Subjects unable or unwilling to give written informed consent and/or to comply with study procedures. • Currently taking or known need for any of the following medications or food items during the study. o IV corticosteroids unless approved by the Medical Monitor o Enteric coated oral corticosteroids during the study were not allowed. No other use of non-enteric coated oral corticosteroids, other than administration required as per protocol, was allowed o IV immunoglobulin treatment o Cyclophosphamide o Cholestyramine or other drugs that may interfere with enterohepatic recirculation of MMF o Initiation of new treatment or change in dosage of Angiotensin Receptor Blockers and/or angiotensin-converting enzyme (ACE) inhibitors o Calcineurin inhibitors (CNIs) (e.g., cyclosporine and tacrolimus) o Immunosuppression biologic agents (e.g., abatacept, belimumab, infliximab, adalimumab, etanercept, or rituximab) o Vaccines using live organisms, viral or bacterial o MMF dose other than 2 g/day without prior discussion with the Medical Monitor

Trial name: AURORA 2: Aurinia Renal Response in Lupus With Voclosporin	NCT number: NCT03597464
	o Concomitant therapy with other immunosuppressants after consent, other than MMF administered per protocol o Azathioprine or mycophenolate sodium o Ketoconazole or rifampin o Concomitant use of other CYP3A4/5 inhibitors and inducers was to be discussed with the Medical Monitor • Subjects currently requiring renal dialysis (hemodialysis or peritoneal dialysis) or expected to require dialysis during the study period • A planned kidney transplant within study treatment period. • Subjects with any medical condition which, in the investigator's judgment, may be associated with increased risk to the subject or may interfere with study assessments or outcomes. • Subjects who were pregnant, breast feeding or, if of childbearing potential, not using adequate contraceptive precautions. • Vaccines using live organisms, virus or bacterial, while taking the study treatment.
Intervention	23.7 mg voclosporin (3 capsules) given orally twice daily (total 47.4 mg/day, 6 capsules) for 52 weeks. Subjects were also to receive 2 g/day MMF; subjects who were not already taking MMF prior to randomization received 1 g/day for the first week, increasing to 2 g/day on Day 8. In addition, all subjects were to receive 0.5 g/day intravenous methylprednisolone on Days 1 and 2 (0.25 g/day for subjects weighing <45 kg) before changing to a reducing course of oral corticosteroid therapy on Day 3. **(N= 116)**

Trial name: AURORA 2: Aurinia Renal Response in Lupus With Voclosporin	NCT number: NCT03597464
Comparator(s)	Matching placebo softgel capsules (3 capsules) given orally twice daily (6 capsules) for 52 weeks. Subjects were also to receive 2 g/day MMF; subjects who were not already taking MMF prior to randomization received 1 g/day for the first week, increasing to 2 g/day on Day 8. In addition, all subjects were to receive 0.5 g/day intravenous methylprednisolone on Days 1 and 2 (0.25 g/day for subjects weighing <45 kg) before changing to a reducing course of oral corticosteroid therapy on Day 3. **(N= 100)**
Follow-up time	24 months (from end of AURORA 1 (36 months in total))
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Key primary endpoint:** • AE profile and routine biochemical and haematological assessments. **Key secondary endpoints:** • Proportion of subjects in renal response defined as: o Urine protein creatinine ratio (UPCR) of ≤0.5 mg/mg, and o Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m2 or no confirmed decrease from baseline in eGFR of >20%, and o Received no rescue medication for LN, and o Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during the 8 weeks prior to the renal response assessment. Subjects who withdrew from the study prior to the response assessment were defined as non-responders • Proportion of subjects in partial renal response, defined as 50% reduction from AURORA 1 baseline in UPCR • Renal flare as adjudicated by the Clinical Endpoints Committee (CEC) • Non-renal flare as adjudicated by the CEC • Change from AURORA 1 baseline in UPCR, urine protein, serum creatinine and eGFR • Change from AURORA 1 baseline in Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score

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Trial name: AURORA 2: Aurinia Renal Response in Lupus With Voclosporin	NCT number: NCT03597464
Method of analysis	AEs were aggregated by System Organ Class and Preferred Term and presented as summary tables. A treatment-emergent adverse event (TEAE) was defined as an AE occurring on or after the first dose of voclosporin/placebo up to and including 30 days after the last dose of voclosporin/placebo. Laboratory values (based on results from the central laboratory), vital signs and other safety parameters were summarized by visit as absolute values and change from baseline. Laboratory values outside of defined normal ranges were summarized as shifts from baseline at each visit. Secondary endpoints were summarized by treatment and visit. Differences between baseline and on-treatment values by visit, and differences between treatment arms were analysed using a Mixed Effect Model Repeated Measures (MMRM) analysis including terms for treatment, visit, treatment by visit interaction and baseline assessments. Results were expressed as least squares (LS) means along with associated 95% confidence intervals (CIs).
Subgroup analyses	No subgroup analyses
Other relevant information	NA

Abbreviations: ACE = angiotensin-converting enzyme; CEC = Clinical Endpoints Committee; CI = confidence interval; CNI = calcineurin inhibitor; eGFR = estimated glomerular filtration rate; IV = intravenous; LN = lupus nephritis; LS = least squares; MMF = mycophenolate mofetil; MMRM = Mixed Effect Model Repeated Measures; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index; TEAE = treatment-emergent adverse event; UPCR = urine protein creatinine ratio

Table 106: AURA-LV characteristics

Trial name: AURA-LV: Aurinia Urinary Protein Reduction Active - Lupus With Voclosporin (AURA-LV) (AURA-LV)	**NCT number: NCT02141672**
Objective	To assess the efficacy of 2 doses of voclosporin compared to placebo in achieving complete remission after 24 weeks of therapy in subjects with active lupus nephritis (LN).
Publications – title, author, journal, year	Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, Eitner F, Appel GB, Contreras G, Lisk L, Solomons N; ALMS Group. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med. 2011 Nov 17;365(20):1886-95. doi: 10.1056/NEJMoa1014460.(152) Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, Li LS, Mysler E, Sánchez-Guerrero J, Solomons N, Wofsy D; Aspreva Lupus Management Study Group. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol. 2009 May;20(5):1103-12. doi: 10.1681/ASN.2008101028. Epub 2009 Apr 15.(208)
Study type and design	Randomized, Controlled Double-blind Phase 2 Study
Sample size (n)	265 participants
Inclusion	Exclusion

Main inclusion and exclusion criteria

- Male or female subjects aged 18 to 75 years.
- Diagnosis of systemic lupus erythematosus (SLE) according to the American College of Rheumatology criteria.
- Kidney biopsy within 6 months prior to Screening (Visit 1) with a histologic diagnosis of LN (International Society of Nephrology/Renal Pathology Society 2003 classification of lupus nephritis) Classes III, IV-S or IV-G, (A) or (A/C); or Class V, alone or in combination with Class III or IV.
- Laboratory evidence of active nephritis at screening, defined as:
    - Class III, IV-S or IV-G: Confirmed proteinuria ≥1,500 mg/24 hours when assessed by 24 hour urine collection, defined by a UPCR of ≥1.5 mg/mg assessed in a first morning void urine specimen (2 samples).
    - Class V (alone or in combination with Class III or IV): Confirmed proteinuria ≥2,000 mg/24 hours when assessed by 24 hour urine collection, defined by a UPCR of ≥2 mg/mg assessed in a first morning void urine specimen (2 samples).
- Estimated glomerular filtration rate (eGFR) as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation of ≤45 mL/min/1.73 m2.
- Currently requiring renal dialysis (hemodialysis or peritoneal dialysis) or expected to require dialysis during the study period.
- A previous kidney transplant or planned transplant within study treatment period.
- In the opinion of the Investigator, subject does not require long-term immunosuppressive treatment (in addition to corticosteroids).
- Current or medical history of:
    - Pancreatitis or gastrointestinal hemorrhage within 6 months prior to screening.
    - Active unhealed peptic ulcer within 3 months prior to screening. If an ulcer has healed and the subject is on adequate therapy, the subject may be randomized.
    - Congenital or acquired immunodeficiency.
    - Clinically significant drug or alcohol abuse 2 years prior to screening.
    - Malignancy within 5 years of screening, with the exception of basal and squamous cell carcinomas treated by complete excision. Subjects with cervical dysplasia that is cervical intraepithelial neoplasia 1, but have been treated with conization or loop electrosurgical excision procedure, and have had a normal repeat PAP are allowed.
    - Lymphoproliferative disease or previous total lymphoid irradiation.
    - Severe viral infection (such as CMV, HBV, HCV) within 3 months of screening; or known human immunodeficiency virus infection.
    - Active tuberculosis (TB), or known history of TB/evidence of old TB if not taking prophylaxis with isoniazid.

Trial name: AURA-LV: Aurinia Urinary Protein Reduction Active - Lupus With Voclosporin (AURA-LV) (AURA-LV)	NCT number: NCT02141672

- Other known clinically significant active medical conditions, such as:
    - Severe cardiovascular disease including congestive heart failure, history of cardiac dysrhythmia or congenital long QT syndrome.
    - Liver dysfunction (aspartate aminotransferase, alanine aminotransferase, or bilirubin greater than 2.5 times the upper limit of normal) at screening and confirmed before randomization.
    - Chronic obstructive pulmonary disease or asthma requiring oral steroids.
    - Bone marrow insufficiency unrelated to active SLE (according to Investigator judgment) with white blood cell count <2,500/mm3; absolute neutrophil count <1.3 x 103/µL; thrombocytopenia (platelet count <50,000/mm3).
    - Active bleeding disorders.
    - Current infection requiring IV antibiotics.
- Any overlapping autoimmune condition for which the condition or the treatment of the condition may affect the study assessments or outcomes. Overlapping conditions for which the condition or treatment is not expected to affect assessments or outcomes are not excluded.
- Subjects who are pregnant, breast feeding or, if of childbearing potential, not using adequate contraceptive precautions.

Intervention	**Experimental arm 1**: voclosporin Low Dose	**Experimental arm 2**: voclosporin High Dose

Trial name: AURA-LV: Aurinia Urinary Protein Reduction Active - Lupus With Voclosporin (AURA-LV) (AURA-LV)	NCT number: NCT02141672	
	Voclosporin, oral, 23.7 mg BID	Voclosporin, oral 23.7 mg BID until Week 2, then voclosporin, oral, 39.5 mg BID
Comparator(s)	**Comparator arm 1**: Placebo	**Comparator arm 2**: Placebo
	Voclosporin placebo, oral, 3 capsules BID	Voclosporin placebo, oral, 3 capsules BID until Week 2 then voclosporin placebo, oral, 5 capsules BID
Follow-up time	24 weeks	
Is the study used in the health economic model?	No	

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Primary, secondary and exploratory endpoints

Primary outcome:

- Number of Subjects Achieving Complete Renal Remission at 24 Weeks [Time Frame: week 24]

Complete remission is defined as:

  - Confirmed protein/creatinine ratio of ≤0.5 mg/mg and
  - eGFR ≥60 mL/min/1.73m2 or no confirmed decrease from baseline in eGFR of ≥20%. Subjects who received rescue medication for LN or >10 mg prednisone for >3 consecutive days or >7 days total from 56 days prior to remission assessment until the time of the remission assessment were considered not achieving complete remission.

Secondary outcome:

- Number of Subjects Achieving Complete Renal Remission at 48 Weeks [Time Frame: Week 48]

  Complete remission is defined as:

  - Confirmed protein/creatinine ratio of ≤0.5 mg/mg and
  - eGFR ≥60 mL/min/1.73m2 or no confirmed decrease from baseline in eGFR of ≥20%. Subjects who received rescue medication for LN or >10 mg prednisone for >3 consecutive days or >7 days total from 56 days prior to remission assessment until the time of the remission assessment were considered not achieving complete remission.

- Number of Subjects Achieving Complete Renal Remission at 24 and 48 Weeks in the Presence of Low Dose Steroids [Time Frame: Weeks 24 and 48]

  Complete remission is defined as:

  - Confirmed protein/creatinine ratio of ≤0.5 mg/mg and
  - eGFR ≥60 mL/min/1.73m2 or no confirmed decrease from baseline in eGFR of ≥20%. Subjects who received rescue medication for LN or >10 mg prednisone for >3 consecutive days or >7 days total from 56 days prior to remission assessment until the time of the remission assessment were considered not achieving complete remission.

  Low-dose steroids is defined as use of ≤5 mg prednisone for 8 weeks leading up to the Week 24 visit date or for 12 weeks leading up to the Week 48 visit date.

- Time to Complete Remission (Number of Weeks) [Time Frame: week 48]

  Time to Complete Remission is defined as time from first dose of voclosporin/placebo to UPCR ≤ 0.5mg in the absence of rescue medication.

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- Time to Sustained Early Complete Remission (Number of Weeks) [Time Frame: week 48]

  Time to Sustained Complete Remission is defined as time from first dose of voclosporin/placebo to UPCR ≤ 0.5mg occurring at week 24 or earlier and sustained until week 48 in the absence of rescue medication.

- Number of Subjects Achieving Sustained Early Complete Remission [Time Frame: week 48]

  Sustained early complete remission defined as complete remission that occurred on or before Week 24 and was sustained through Week 48

- Time to Partial Remission (Number of Weeks) [Time Frame: week 48]

  Time to partial Remission is defined as time from first dose of voclosporin/placebo to 50% UPCR reduction sustained until week 48 in the absence of rescue medication.

- Number of Subjects Achieving Partial Remission [Time Frame: week 48]

  Partial remission is defined as a 50% reduction in UPCR from baseline at Week 24 and Week 48.

- Number of Subjects Achieving, and Remaining in, Complete Remission [Time Frame: week 48]

  Sustained complete remission defined as the first occurrence of complete remission that was sustained through Week 48

- Duration of Complete Remission (Number of Weeks) [Time Frame: week 48]

  Duration of Complete Remission is defined as time of first occurrence of UPCR ≤ 0.5 mg/mg until the second increase above 0.5 mg/mg (i.e., a single occurrence above 0.5 is permitted) or use of rescue medication.

- Number of Subjects Achieving Partial Renal Remission at 24 and 48 Weeks [Time Frame: week 24 and 48]

  Number of patients with partial Remission is defined as time from first dose of voclosporin/placebo to 50% UPCR reduction at week 24 or week 48 in the absence of rescue medication.

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- Time to Sustained Partial Remission (Number of Weeks) [Time Frame: week 48]

  Time to sustained partial Remission is defined as time from first dose of voclosporin/placebo to 50% UPCR reduction sustained until week 48 in the absence of rescue medication.

- Number of Subjects Achieving Sustained Partial Remission [Time Frame: week 48]

  Sustained partial remission defined as the first occurrence of partial remission that was sustained through Week 48

- Time to Sustained Early Partial Remission (Number of Weeks) [Time Frame: week 48]

  Time to sustained early partial Remission is defined as time from first dose of voclosporin/placebo to 50% UPCR reduction occurring at week 24 or earlier and sustained until week 48 in the absence of rescue medication.

- Number of Subjects Achieving Sustained Early Partial Remission [Time Frame: week 48]

  Early partial remission defined as partial remission that occurred on or before Week 24 and was sustained through Week 48

- Change From Baseline in UPCR at Weeks 24 and 48 [Time Frame: Baseline, Week 24 and Week 48]

  Change from baseline in urine protein creatinine ratio at weeks 24 and 48

- Change From Baseline in Safety of Estrogens in Systemic Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) Score [Time Frame: Baseline, Week 24 and Week 48]

  The SELENA-SLEDAI assesses disease activity within the last 10 days. Twenty-four items are scored for nine organ systems, and summed to a maximum of 105 points. A score of 6 is considered clinically significant and indicates active disease. For analysis purposes, a score ≥6 was categorized as "high". The 24 items are as follows: seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident, vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, pyuria, new rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA binding, fever, thrombocytopenia, and leukopenia.

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Trial name: AURA-LV: Aurinia Urinary Protein Reduction Active - Lupus With Voclosporin (AURA-LV) (AURA-LV)	NCT number: NCT02141672
Method of analysis	The primary efficacy analysis was an intention-to-treat analysis that included all patients who were randomly assigned to the maintenance study and underwent at least one efficacy assessment. The safety population comprised all patients who received at least one dose of study medication and underwent at least one safety assessment. Treatment groups were compared with the use of Kaplan–Meier survival estimates for the time to treatment failure for each patient, with censoring of data for patients who withdrew before the end of the study. Between-group differences in survival curves were assessed with the use of a log-rank test. The magnitude of the treatment effect was estimated by means of the hazard ratio (HR) obtained from an unadjusted Cox model. HRs were also estimated in subgroups stratified according to induction therapy, race, and geographic region. The overall incidence of events and the event rates per 100 person-years for both treatments are presented within subgroups. Secondary efficacy variables were analysed by calculating HRs from unadjusted Cox models. Sensitivity analyses for the primary end point were conducted, with adjustment for covariates. Testing at the significance level of 0.05 was applied to the primary efficacy analysis and to any key secondary efficacy analyses (with no adjustments for multiple comparisons). Safety variables were analyzed descriptively, with a between-group comparison of proportions of patients with adverse events.
Subgroup analyses	Subgroups stratified according to: • Induction therapy • Race • Geographic region
Other relevant information	NA

Abbreviations: BID = twice daily; eGFR = estimated glomerular filtration rate; HR = hazard ratio; IV = intravenous; IV-G = diffuse global; IV-S = diffuse segmental; LN = lupus nephritis; TB = tuberculosis; SLE = systemic lupus erythematosus; UPCR = urine protein creatinine ratio

Table 107: BLISS-LN characteristics

Trial name: Efficacy and Safety of Belimumab in Patients With Active Lupus Nephritis	NCT number: NCT01639339	
Objective	The purpose of this study is to evaluate the efficacy, safety, and tolerability of belimumab in adult patients with active lupus nephritis.	
Publications – title, author, journal, year	Rovin BH, Furie R, Teng YKO, Contreras G, Malvar A, Yu X, Ji B, Green Y, Gonzalez-Rivera T, Bass D, Gilbride J, Tang CH, Roth DA. A secondary analysis of the Belimumab International Study in Lupus Nephritis trial examined effects of belimumab on kidney outcomes and preservation of kidney function in patients with lupus nephritis. Kidney Int. 2022 Feb;101(2):403-413. doi: 10.1016/j.kint.2021.08.027. Epub 2021 Sep 22.(135) Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, Amoura Z, Yu X, Mok CC, Santiago MB, Saxena A, Green Y, Ji B, Kleoudis C, Burriss SW, Barnett C, Roth DA. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med. 2020 Sep 17;383(12):1117-1128. doi: 10.1056/NEJMoa2001180.(154)	
Study type and design	Phase 3, Randomized, Double-Blind, Placebo-Controlled Study	
Sample size (n)	448 participants	
Main inclusion and exclusion criteria	**Inclusion**	**Exclusion**

Trial name: Efficacy and Safety of Belimumab in Patients With Active Lupus Nephritis	NCT number: NCT01639339	
	• Clinical diagnosis of SLE by American College of Rheumatology criteria. • Biopsy confirmed active lupus nephritis. • Clinically active lupus renal disease at screening requiring /receiving induction therapy with Standard of Care medications. • Autoantibody-positive.	• Pregnant or nursing. • On dialysis within the past year. • Treatment with belimumab within the past year . • Receipt of induction therapy with cyclophosphamide within 3 months prior to induction therapy for the study. • Receipt of any B cell targeted therapy (for example, rituximab), investigational biological agent within the past year. • Severe active central nervous system lupus. • Required management of acute or chronic infections within the past 60 days. • Current drug or alcohol abuse or dependence. • Tested positive for human immunodeficiency virus, hepatitis B, or hepatitis C. • History of severe allergic reaction to contrast agents or biological medicines.
Intervention	Belimumab 10 mg/kg plus standard therapy*	
Comparator(s)	Placebo plus standard therapy*	
Follow-up time	104 weeks	
Is the study used in the health economic model?	Yes	

Primary, secondary and exploratory endpoints

Primary outcome

- Double-blind Period: Percentage of Participants With Primary Efficacy Renal Response (PERR) at Week 104 [Time Frame: Week 104]

  PERR is defined as urinary protein creatinine ratio <=0.7, estimated glomerular filtration rate (eGRF) was not more than 20 percent (%) below the pre-flare value or >=60 milliliters per minute per 1.73 square meter (mL/min/1.73m^2) and was not a treatment failure. Analysis was performed using a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), Baseline urine protein-creatinine ratio (uPCR), and Baseline eGFR. Modified Intent-to-treat Population consisted of all randomized participants who received at least one dose of study treatment and were not excluded due to Good Clinical Practice (GCP) non-compliance. Percentage of participants with PERR at Week 104 has been presented.

- Open-label Period: Number of Participants Reporting AEs and serious adverse events (SAEs) [Time Frame: From first open-label dose (Day 1) up to open-label Week 32 (8 weeks after last dose)]

  An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. A SAE is any untoward medical occurrence that, at any dose: resulting in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, any other situation according to medical or scientific judgment or all events of possible drug-induced liver injury with hyperbilirubinemia were categorized as SAE. Number of participants with AEs and SAEs have been reported.

- Open-label Period: Number of Participants Reporting Adverse Events of Special Interest (AESI) [Time Frame: From first open-label dose (Day 1) up to open-label Week 32 (8 weeks after last dose)]

  An AESI is one of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by investigator to sponsor can be appropriate. A summary of protocol defined AESIs include malignant neoplasms including and excluding non-melanoma skin cancer, post-infusion systemic reactions, all infections of special interest (opportunistic infections, Herpes Zoster, tuberculosis, and sepsis), depression (including mood disorders and anxiety)/suicide/self-injury and deaths.

Secondary outcome:

- Double-blind Period: Percentage of Participants With Complete Renal Response (CRR) at Week 104 [Time Frame: Week 104]

  CRR is defined as urinary protein creatinine ratio <0.5, eGRF was not more than 10% below the pre-flare value or >=90 mL/min/1.73m^2 and was not a treatment failure. Analysis was performed using a logistic regression model for the comparison between belimumab and placebo with covariates of induction regimen (CYC vs. MMF), race (Black vs. Non-Black), Baseline uPCR and Baseline eGFR. Percentage of participants with CRR at Week 104 has been presented.

- Double-blind Period: Percentage of Participants With PERR at Week 52 [Time Frame: Week 52]

  PERR is defined as urinary protein creatinine ratio <=0.7, eGRF was not more than 20% below the pre-flare value or >=60 mL/min/1.73m^2 and was not a treatment failure. Analysis was performed using a logistic regression model for the comparison between belimumab and placebo with covariates of induction regimen (CYC vs. MMF), race (Black vs. Non-Black), uPCR, and Baseline eGFR. Percentage of participants with PERR at Week 52 has been presented.

- Double-blind Period: Number of Participants With Time to Death or Renal Related Event [Time Frame: Up to Week 104]

  Events are defined as the first event experienced among the following: death, progression to end stage renal disease, doubling of serum creatinine from Baseline, renal worsening or renal-related treatment failure. Participants who discontinued randomized treatment, withdrew from the study, were lost to follow-up, or had a non renal-related treatment failure were censored. Participants who completed the 104-week treatment period were censored at the Week 104 visit. Time to event is defined as event date minus treatment start date plus one. Analysis was performed using Cox proportional hazards model for the comparison between belimumab and placebo adjusting for induction regimen, race, Baseline uPCR and Baseline eGFR. Number of participants with time to death or renal related event up to Week 104 has been presented.

- Double-blind Period: Percentage of Participants With Ordinal Renal Response (ORR) at Week 104 [Time Frame: Week 104]

  ORR is defined with respect to reproducible responses that included CRR, partial RR (PRR) and non responder. CRR is reported when uPCR was <0.5, eGFR was not more than 10% below pre-flare GFR or within normal range and not a treatment failure. PRR is >=50% decrease from Baseline in uPCR and one of the following: value <1 if Baseline <=3, or value <3 if the Baseline was >3, eGFR not more than

Trial name: Efficacy and Safety of Belimumab in Patients With Active Lupus Nephritis	NCT number: NCT01639339

10% below Baseline GFR or within normal range and not a treatment failure and not a CRR. Non responder is reported when neither CRR nor PRR criteria was met. Percentage of participants reporting CRR, PRR and non responders at Week 104 has been presented.

- Double-blind Period: Number of Participants Reporting On-treatment AEs and SAEs [Time Frame: Up to Week 104]

  An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. A SAE is any untoward medical occurrence that, at any dose: resulting in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, any other situation according to medical or scientific judgment or all events of possible drug-induced liver injury with hyperbilirubinemia were categorized as SAE. Number of participants with on-treatment AEs and SAEs has been reported.

- Double-blind Period: Number of Participants Reporting AESI [Time Frame: Up to Week 104]

An AESI is one of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by investigator to sponsor can be appropriate. A summary of protocol defined AESIs include malignant neoplasms including and excluding non-melanoma skin cancer, post-infusion systemic reactions (PISR), all infections of special interest (opportunistic infections, Herpes Zoster, tuberculosis, and sepsis), depression (including mood disorders and anxiety)/suicide/self-injury and deaths. On-treatment data is displayed.

Trial name: Efficacy and Safety of Belimumab in Patients With Active Lupus Nephritis	NCT number: NCT01639339
Method of analysis	Efficacy end points were analysed in the modified intention-to-treat population, which included all the patients who underwent randomization and received at least one dose of belimumab or placebo. Two patients from sites with compliance issues were excluded from the modified intention-to-treat population. Safety end points were analysed in all the patients who underwent randomisation and received at least one dose of belimumab or placebo. End points were analysed with the use of a step-down sequential testing procedure in a prespecified hierarchy to control overall type I error. The end points of a primary efficacy renal response (PERR) and CRR were analysed with logistic regression. The time to a renal-related event or death was analysed with the use of a Cox proportional-hazards regression. Ordinal renal response (ORR) without urinary sediment was analysed with a rank analysis of covariance. Statistical models controlled for induction regimen, race or ethnic group, baseline ratio of urinary protein to creatinine, and baseline eGFR. In the analyses of the PERR, CRR, and ORR, patients who discontinued belimumab or placebo, had treatment failure, or withdrew from the trial were considered to not have had a response. In the Cox proportional-hazards model, discontinuation of belimumab or placebo, treatment failure that was not related to a kidney event, or withdrawal from the trial before a renal-related event or death occurred were bases for censoring of patient data. Safety data were analysed while the patients were receiving belimumab or placebo.
Subgroup analyses	Subgroups stratified according to: • Induction therapy • Race
Other relevant information	NA

Note: * The standard therapies allowed in this study are: High-dose steroids (for example, methylprednisolone) plus cyclophosphamide for induction therapy followed by azathioprine for maintenance therapy OR High-dose steroids plus mycophenolate for induction therapy followed by mycophenolate for maintenance therapy

Table 108: International Society of Nephrology and the Renal Pathology Society (ISN/RPS) 2003 Classification of Lupus Nephritis

Classification	
Class I Minimal mesangial lupus nephritis	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II Mesangial proliferative lupus nephritis	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit

	May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscope
Class III Focal lupus nephritis	Active or inactive focal, segmental or global endo- or extra capillary glomerulonephritis involving
Class III (A)	Active lesions: focal proliferative lupus nephritis (LN)
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing LN
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing LN
Class IV Diffuse lupus nephritis	Active or inactive diffuse, segmental or global endo- or extra capillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) LN when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) LN when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
Class IV-S (A)	Active lesions: diffuse segmental proliferative LN
Class IV-G (A)	Active lesions: diffuse global proliferative LN
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing LN
Class IV-G (A/C)	Active and chronic lesions: diffuse global proliferative and sclerosing LN
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing LN
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing LN
Class V Membranous lupus nephritis	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alteration Class V LN may occur in combination with class II or IV in which case both will be diagnosed Class V LN show advanced sclerosis
Class VI Advanced sclerosis lupus nephritis	≥90% of glomeruli globally sclerosed without residual activity

Abbreviations: AE = adverse event; AESI = adverse events of special interest; CRR = complete renal response; CYC = cyclophosphamide; eGFR = estimated glomerular filtration rate; GCP = Good Clinical Practice; MMF = mycophenolate mofetil; ORR = ordinal renal response; PERR = primary efficacy renal response; PRR = partial renal response; SAE = serious adverse event; SLE = systemic lupus erythematosus; uPCR = urine protein creatinine ratio

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 109: Baseline characteristics for all studies

Baseline characteristic	AURORA n=357		AURORA 2 n=216		AURA-LV n=265			BLISS-LN n=446	
	Voclosporin n=179	Placebo n=178	Voclosporin n=116	Placebo n=100	Voclosporin		Placebo	Belimumab n= 223	Placebo n= 223
					Low-dose n=89	High-dose n=88	Placebo n=88		
Age, median (range), years	31 (18–62)	32 (18–72)	30.0 (18-59)	33.0 (18-72)	31.4 (NR) SD = 11.8	30.6 (NR) SD = 9.6	33.1 (NR) SD = 10.0	33.7 (NR)	33.1 (NR)
Female, n (%)	161 (90)	152 (85)	105 (90.5)	88 (88.0)	76 (85.4)	81 (92.0)	73 (83.0)	197 (88)	196 (88)
Weight, mean (SD), kg	66.49 (17.07)	66.55 (16.11)	66.8 (16.4)	64.9 (14.3)	62.5 (16.7)	66.3 (19.2)	65.0 (16.3)	NR	NR
Region, n (%)									
Asia Pacific	52 (29)	52 (29)	NR	NR	52 (58.4)	43 (48.9)	35 (39.8)	106 (48)	105 (47)
Europe and South Africa	52 (29)	52 (29)	NR	NR	25 (28.1)§	25 (28.4)§	34 (38.6)§	41 (18) §	45 (20) §
Latin America	49 (27)	48 (27)	NR	NR	12 (13.5)	20 (22.7)	19 (21.6)	38 (17)	35 (16)
North America	26 (15)	26 (15)	NR	NR				38 (17)	38 (17)
Race*, n (%)									
White	68 (38)	61 (34)	44 (37.9)	40 (40.0)	30 (33.7)	36 (40.9)	42 (47.7)	73 (33)	75 (34)
Black	26 (15)	19 (11)	18 (15.5)	7 (7.0)	3 (3.4)	6 (6.8)	5 (5.7)	30 (13)	31 (14)

Asian	53 (30)	56 (31)	30 (25.9)	30 (30.0)	52 (58.4)	44 (0.5)	36 (40.9)	114 (51)	109 (49)
Other†	32 (18)	42 (24)	24 (20.7)	23 (23.0)	4 (4.5)	2 (2.3)	5 (5.7)	6 (3)	8 (4)
Ethnicity*, n (%)									
Hispanic or Latino	57 (32)	59 (33)	39 (33.6)	33 (33.0)	9 (10.1)	13 (14.8)	13 (14.8)	NR	NR
Non-Hispanic or non-Latino	122 (68)	118 (66)	77 (66.4)	67 (67.0)	80 (89.9)	75 (85.2)	3.5 (4.0)	NR	NR
Unknown	0	1 (1)	0	0	0	0	0	NR	NR
Time since initial LN diagnosis, mean (SD), years	4.6 (5.1)	4.7 (4.9)	NR	NR	4.2 (5.1)	3.2 (4.4)	3.5 (4.0)	Median = 0.2	Median = 0.2
Time since SLE diagnosis, mean (SD), years	6.6 (6.4)	6.9 (6.1)‡	NR	NR	NR	NR	NR	Median = 3.3	Median = 3.3
Biopsy class, n (%)									
Pure class III	20 (11)	29 (16)	13 (11.2)	21 (21.0)	0	0	0	126 (56)	132 (59)
Pure class IV	91 (51)	77 (43)	64 (55.2)	37 (37.0)	0	0	0		
Pure class V	25 (14)	25 (14)	17 (14.7)	14 (14.0)	12 (13.5)	14 (15.9)	13 (14.8)	36 (16)	36 (16)
Class II and V only	0	1 (<1)	0	0	0	0	0	NR	NR
Class III and V only	24 (13)	20 (11)	11 (9.5)	12 (12.0)	56 (62.9)	63 (71.6)	59 (67.0)	61 (27)	55 (25)
Class IV and V only	19 (11)	26 (15)	10 (8.6)	16 (16.0)	21 (23.6)	11 (12.5)	16 (18.2)		
Baseline eGFR								NR	NR
Mean (SD), mL/min/1.73 m²	92.1 (30.6)	90.4 (29.0)	94.1 (31.4)	92.0 (28.0)	95.3 (28.4)	104.0 (27.3)	100.2 (27.1)	100.0 (NR)	101.0 (NR)
High (≥60 mL/min/1.73 m²), n (%)	146 (82)	144 (81)	NR	NR	NR	NR	NR	190 (85)	182 (82)
Mean (SD) baseline UPCR, mg/mg	4.14 (2.71)	3.87 (2.36)	3.9 (2.6)	3.9 (2.5)	5.16 (4.2)	4.48 (3.0)	4.43 (3.6) ‡	3.2 (NR)	3.5 (NR)
Anti-dsDNA									

Mean (SD), IU/mL	105.2 (127.7)	94.7 (124.4)	NR	NR	NR	NR	NR	NR	NR
Anti-dsDNA antibodies, n (%)	NR	NR	NR	NR	NR	NR	NR	194 (87)	197 (88)
High (>10 IU/mL), n (%)	133 (74)	118 (66)	NR	NR	NR	NR	NR	NR	NR
SELENA-SLEDAI, mean (SD); n	13.2 (6.5); n=177	11.8 (6.1); n=177			NR	NR	NR	12.5 (NR)	12.2 (NR)
MMF use at screening, n (%)									
Yes	100 (56)	96 (54)	NR	NR	31 (34.8)	29 (33.0)	32 (36.4)	NA	NA
No	79 (44)	82 (46)	NR	NR	58 (65.2)	59 (67.0)	56 (63.6)	NA	NA
Antinuclear antibodies — no. (%)	NR	NR	NR	NR	NR	NR	NR	194 (87)	197 (88)
Anti-C1q antibodies — no./total no. (%)	NR	NR	NR	NR	NR	NR	NR	181/223 (81)	172/221 (78)
Anti-Sm antibodies — no./total no. (%)	NR	NR	NR	NR	NR	NR	NR	73/223 (33)	72/219 (33)
Previous treatment — no. (%)									
Any antimalarial drug	NR	NR	NR	NR	NR	NR	NR	166 (74)	154 (69)
ACE inhibitor or ARB	NR	NR	NR	NR	NR	NR	NR	147 (66)	150 (67)

Note: *Analyses for race and ethnicity were post hoc; †Other include American Indian, Alaska Native, Native Hawaiian, Pacific Islander, and other or mixed races except mixed Black race; §Not including South Africa; ‡Data missing for 1 patient. Percentages might not add up to 100% because of rounding.

Abbreviations: ACE = angiotensin-converting enzyme; anti-dsDNA = anti-double-stranded deoxyribonucleic acid; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; MMF = mycophenolate mofetil; NR = not reported; SELENA-SLEDAI = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SD = standard deviation; UPCR = urine protein creatinine ratio.

Source: (150, 151)

Comparability of patients across studies

AURORA 2 is a continuation study of AURORA 1. As such, intrinsically, the two studies show similarities in baseline characteristics and inclusion/exclusion criteria. However, AURORA 1 and AURORA 2 have differences in study subjects enrolled. As such, some differences were noticed between the two trials concerning the proportion of participants classified in biopsy classes/groups. However, a review of the baseline characteristics and inclusion/exclusion criteria of the two trials demonstrated comparability of patients across the two studies.

The BLISS-LN and AURA-LV studies show demographical similarities (regards to age, female enrolment, weight, race) to the two studies AURORA 1 and AURORA 2. In addition, both studies share similarities in LN baseline characteristics (biopsy class, baseline eGFR, SELENA-SLEDAI (exclusively BLISS)) with the two studies AURORA 1 and AURORA 2.
However, the two studies show multiple baseline characteristic discrepancies from the two studies AURORA 1 and AURORA 2. Specifically, patients enrolled in the BLISS-LN study had much shorter (BLISS-LN; median, AURORA 1; mean, AURA-LV; mean) time from initial SLE or LN diagnosis to enrolment than the two other studies reporting on this metric. In addition, biopsy classes showed some discrepancies between the included studies. Lastly, a noticeable difference was observed between baseline characterises regarding prior MMF use between the two studies reporting on the metric (AURORA 1, AURA-LV).

Comparability of the study populations with Danish patients eligible for treatment

Though a large proportion of patients were recruited in the region of Asia and Asia-Pacific a larger proportion (majority in AURORA 1) of patients in the studies were recruited in North America and Europe, and the inclusion criteria and patient characteristics were consistent with the criteria for treatments in Denmark. Therefore, no important differences exist between the study populations and the Danish patient population. This was confirmed by a Danish key opinion leader (142).

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 110: Outcomes AURORA

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance(136)
Number of Participants With Adjudicated Renal Response at Week 52 [Time Frame: 52 Weeks]	The primary efficacy endpoint was the number of subjects showing renal response at Week 52. Renal response was adjudicated based on blinded data by an independent Clinical Endpoints Committee (CEC) based on meeting the following criteria: • UPCR of ≤0.5 mg/mg, and • Estimated Glomerular Filtration Rate (eGFR) ≥60 mL/min/1.73 m2 or no confirmed decrease from baseline in eGFR of >20%, and • Received no rescue medication for lupus nephritis (LN), and • Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44 through 52, prior to assessment study visits had their data assessed for response*	In severe LN, a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (209)	The binary endpoint analyses were conducted on the intention-to-treat (ITT) population using a logistic regression model with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region, and response (Yes/No) at as the response variables.

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance(136)
Time to Urine Protein Creatinine Ratio (UCPR) of ≤0.5 mg/mg (Number of Days) [Time Frame: 52 Weeks]	Time in days to reduction in UCPR to decrease to 0.5 mg/mg or less.	The American College of Rheumatology (ACR) lupus classification criteria define LN by proteinuria >0.5 g/day or a UPCR of >0.5 or urinary protein greater than 3+ by dipstick analysis or urinary cellular casts of more than five cells per high-power field (210)	Time to event endpoints for time to UPCR <0.5 mg/mg, 50% reduction in UPCR and duration of UPCR <0.5 mg/mg were measured from baseline as the number of weeks from day of randomization to the day of the event. Time-to-event was estimated using Kaplan-Meier methodology and analysed by comparing the survivor function between treatment arms. A Cox's proportional hazards model was performed to assess the significance of the differences between treatment arms. The model included terms for treatment, baseline UPCR, biopsy class, and MMF use at baseline.
Number of Participants With Renal Response at Week 24 [Time Frame: Week 24]	Number of subjects showing renal response at Week 24. Renal response was adjudicated based on blinded data by an Independent CEC based on the following criteria: UPCR of ≤0.5 mg/mg, & eGFR ≥60 mL/min/1.73 m2 or no confirmed decrease from baseline in eGFR of >20%, and Received no rescue medication for LN & Did not receive more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 16 through 24, just prior to the renal response assessment. †	In severe LN, a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (209)	The binary endpoint analyses were conducted on the ITT population using a logistic regression model with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region, and response (Yes/No) at as the response variables.

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance(136)
Number of Subjects With PRR at Weeks 24 & 52 [Time Frame: Weeks 24 and 52]	Number of subjects with PRR (defined as a 50% reduction in UPCR from baseline) at Week 24 and at Week 52. Baseline UPCR is the average of 2 pre-randomisation values.	In severe LN, a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (209)	The binary endpoint analyses were conducted on the ITT population using a logistic regression model with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region, and response (Yes/No) at as the response variables.
Duration of Renal Response (Number of Days) [Time Frame: Week 52]	Duration in days until second occurrence of UPCR >0.5 mg/mg in those subjects who achieve a reduction in UPCR to below 0.5 mg/mg	In severe LN, a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (209)	Time-to-event was estimated using Kaplan-Meier methodology and analysed by comparing the survivor function between treatment arms. A Cox's proportional hazards model was performed to assess the significance of the differences between treatment arms. The model included terms for treatment, baseline UPCR, biopsy class, and MMF use at baseline.
Time to 50% Reduction in UPCR (Number of Days) [Time Frame: 52 weeks]	Time in days to reduction in UCPR to decrease by 50% compared to baseline. Baseline is the average of two pre-randomisation values.	The ACR lupus classification criteria define LN by proteinuria >0.5 g/day or a urinary protein/creatinine ratio (UPCR) of >0.5 or urinary protein greater than 3+ by dipstick analysis or urinary cellular casts of more than five cells per high-power field (210)	Time-to-event was estimated using Kaplan-Meier methodology and analysed by comparing the survivor function between treatment arms. A Cox's PHs model was performed to assess the significance of the differences between treatment arms. The model included terms for treatment, baseline UPCR, biopsy class, and MMF use at baseline.
Change From Baseline in eGFR [Time Frame: Baseline and Weeks 2, 4, 8, 12, 16, 16, 20, 24, 30, 36, 42, 48 and 52.]	Change from baseline by visit in eGFR. eGFR is corrected to a maximum value of 90 mL/min/1.73 m2	The ACR lupus classification criteria define complete renal remission as an eGFR of >90mL/min/1.73 m2 (210)	Change from baseline endpoints were analysed using a mixed effect model repeated measures (MMRM) analysis with treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region, and baseline UPCR included as covariates in the model.

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance(136)
Change From Baseline in UPCR [Time Frame: Baseline and Weeks 2, 4, 8, 12, 16, 16, 20, 24, 30, 36, 42, 48 and 52.]	Change from baseline by visit in UCPR. Baseline is the average of two pre-randomisation values.	The ACR lupus classification criteria define LN by proteinuria >0.5 g/day or a urinary protein/creatinine ratio (UPCR) of >0.5 or urinary protein greater than 3+ by dipstick analysis or urinary cellular casts of more than five cells per high-power field (210)	Change from baseline endpoints were analysed using a MMRM analysis with treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region, and baseline UPCR included as covariates in the model.
Number of Subjects With Renal Response With Low Dose Steroids [Time Frame: Week 24 and Week 52]	Programmed Renal Response whilst on low dose steroids (<2.5 mg/day) for the preceding 8 Weeks at Weeks 24 and 52	In severe LN, a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (209)	The binary endpoint analyses were conducted on the ITT population using a logistic regression model with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region, and response (Yes/No) at as the response variables.
Change From Baseline in Safety of Estrogens in Systemic Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA - SLEDAI) [Time Frame: Week 24 and Week 52]	Change from baseline in Safety of Estrogens in Systemic Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI‡) score at Week 24 and 52.	The SELENA-SLEDAI tool is a cumulative and weighted index used to assess disease activity across 24 different disease descriptors in patients with lupus (211).	HRQoL [SF-36 and LupusPRO], and SELENA-SLEDAI score) were analysed using a mixed effect model repeated measures analysis with treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region, and baseline UPCR included as covariates in the model.
Change From Baseline in Patient Reported Outcomes [Time Frame: Week 24 and Week 52]	Health-related quality of life (HRQoL) information was collected using the Short Form Health Survey (SF-36) HRQoL assessment and the LupusPRO (v1.7) assessment.	LupusPro assessment is a patient-reported questionnaire regarding the effect of lupus or its treatment on the patient's health, quality of life, and the medical care received related to lupus (212).	HRQoL [SF-36 and LupusPRO], and SELENA-SLEDAI score) were analysed using a mixed effect model repeated measures analysis with treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region, and baseline UPCR included as covariates in the model.

Note: *To be disqualified from renal response, the subject had to fail both eGFR measures (i.e., confirmed eGFR <60 mL/min/1.73 m2 & confirmed >20% drop from baseline) & have an associated treatment-related or disease-related AE that impacted eGFR Withdrawals prior to Week 52 with insufficient Week 52 data to determine response were defined non responders. Subjects who discontinued study drug but continued to attend. †To be

disqualified from renal response, the subject had to fail both eGFR measures (i.e., confirmed eGFR <60 mL/min/1.73 m2 AND confirmed >20% drop from BL) & have an associated treatment-related or disease-related AE that impacted eGFR. Subjects who withdrew prior to the Week 24 assessment and provided insufficient Week 24 data to determine response were defined as non-responders. Subjects who discontinued study drug but continued to attend study visits had their data assessed for response.

Abbreviations: ACR = American College of Rheumatology; CEC = clinical endpoints committee; eGFR = estimated glomerular filtration rate; HRQoL = health-related quality of life; ITT = intention-to-treat; LN = lupus nephritis; MMF = mycophenolate mofetil; MMRM = mixed effect model repeated measures; PH = proportional hazard; PRR = partial renal response; SELENA-SLEDAI = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index; SF-36 = 36-Item Short Form Survey; UPCR = urine protein creatinine ratio

Table 111: AURORA 2 outcomes

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance(15)
AE profile and routine biochemical and haematological assessments. [Time Frame: 36 months]	Adverse event (AE) profile and routine biochemical and haematological assessments.	AE is a widely used and validated outcome measure (213)	A treatment-emergent adverse event (TEAE) was defined as any AE, including worsening of a pre-existing condition, with an onset day on or after the first dose of voclosporin/placebo in AURORA 2 up to and including 30 days after the last dose of voclosporin/placebo. In counting the number of TEAEs reported, a continuous event (i.e., which did not cease but was reported more than once) is counted only once for a subject; a non-continuous AE reported several times by the same subject is counted as multiple events. If a subject experienced the same TEAE multiple times, the highest severity was attributed and used in the by-severity summary tables. If a TEAE had a missing intensity assessment, it was assumed to be severe. If a TEAE had a missing relationship to study drug, it was assumed to be related to the study drug. Two time periods were used for the analysis of TEAEs. The primary analysis of AEs in the AURORA 2 study included all AEs from the day of first dose of study treatment in AURORA 2 to the last dose of study drug + 30 days. The analysis of AEs by year included all AEs recorded from the first dose

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance(15)
			of treatment in AURORA 1 to the last dose of study drug in AURORA 2 + 30 days; Year 1 included events starting on Days 1-365, Year 2 included events starting on Days 366-730 and Year 3 included events starting from Day 731 onwards. AEs that occurred more than 30 days post-last dose of voclosporin/placebo up to the Safety Follow-up Visit were defined as post-treatment AEs.
Proportion of subjects in renal response [Time Frame: Months 12, 18, 24, 30 and 36]	Proportion of subject in renal response	In severe lupus nephritis (LN), a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (209)	The numbers of subjects meeting the definition of renal response at Months 6, 12, 18, 24, 30 and 36 from the start of treatment in AURORA 1 were summarized by treatment group. The number of subjects who meet each of the four individual criteria were also summarized by treatment group.
Proportion of subjects in PRR [Time Frame: Months 12, 18, 24, 30 and 36]	50% reduction in baseline UPCR.	In severe LN, a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (209)	The numbers of subjects achieving PRR (defined as a 50% reduction in UPCR from the AURORA 1 baseline) at Months 6, 12, 18, 24, 30 and 36 from the start of treatment in AURORA 1 were summarized by treatment group.
Renal flare as adjudicated by the CEC. [Time Frame: Up to 37 months]	Renal flare and extra-renal flare	Flares represent a significant problem because of the potential for cumulative damage that may lead to deterioration of renal function as well as toxicity due to the additional immunosuppression (49).	The CEC was responsible for adjudicating renal and non-renal flares in subjects who entered the AURORA 2 study. For each subject, the CEC adjudicated whether the patient had responded to treatment, whether a renal or non-renal flare had occurred, and whether the flare resolved according to the guidance below; however, the CEC used their expertise and

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance(15)
			clinical judgment in assessing each case. The dates (study day) of response, flare and recovery and the severity of the flare (mild, moderate or severe) were also adjudicated.
Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) [Time Frame: Months 18, 24 and 36]	Assessment of Systemic Lupus Erythematosus (SLE) Disease Activity within the last 10 days. It scores 24 disease descriptors across 9 organ systems which are summed to a minimum of <2 (considered indicative of no activity) and maximum of 105 points. Scores are weighted and a score of 6 is considered clinically significant. Higher scores indicate worse disease activity.	The SELENA-SLEDAI tool is a cumulative and weighted index used to assess disease activity across 24 different disease descriptors in patients with lupus (211).	The following endpoints are summarized by treatment group using descriptive statistics for observed values and changes from AURORA 1 baseline: • Change in SELENA-SLEDAI at Months 6, 12, 18, 24 and 36. • Change in UPCR, eGFR, urine protein, and serum creatinine at Months 6, 12, 15, 18, 21, 24, 27, 30, 33 and 36. • Change in immunology parameters (C3, C4, and anti-dsDNA) at Months 6, 12, 15, 18, 21, 24, 27, 30, 33 and 36. • Change in HRQoL (SF-36) at Months 6, 12, 18, 24, 30 and 36. Changes from AURORA 1 baseline were analyzed using a mixed effect model repeated measures analysis with treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region, and baseline UPCR included as covariates in the model. Results are expressed as differences between treatment arms along with the associated 95% CI. The least squares means (LS means) and their corresponding 95% confidence intervals of the change
Change in Urine Protein to Creatinine Ratio (UPCR) [Time Frame: Up to 37 months]	Change from Aurinia Renal Response in Active Lupus With Voclosporin (AURORA) 1 baseline.	The ACR lupus classification criteria define LN by proteinuria >0.5 g/day or a UPCR of >0.5 or urinary protein greater than 3+ by dipstick analysis or urinary cellular casts of more than five cells per high-power field (210)	
Change in eGFR [Time Frame: Up to 37 months]	Change from AURORA 1 baseline.	The ACR lupus classification criteria define complete renal remission as an eGFR of >90mL/min/1.73 m2 (210)	
Change in urine protein [Time Frame: Up to 37 months]	Change from AURORA 1 baseline.	The ACR lupus classification criteria define LN by proteinuria >0.5 g/day or a UPCR of >0.5 or urinary protein greater than 3+ by dipstick analysis or urinary cellular casts of more than five cells per high-power field (210)	

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Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance(15)
Change in serum creatinine [Time Frame: Up to 37 months]	Change from AURORA 1 baseline.	ACR lupus Recommended outcome for Monitoring of LN (214).	from baseline values are also presented for each visit and for the overall change. For UPCR and eGFR, MMRM analyses were also performed for the change from the Month 12 (i.e., end of treatment in AURORA 1) by visit to show the effect of continued treatment in the AURORA 2 study. LS mean plots and mean change from AURORA 1 baseline by visit are presented for UPCR, urine protein, serum creatinine, eGFR, immunology parameters and selected laboratory parameters. In addition, LS mean plots are provided for change in urine protein and eGFR from Month 12 (end of AURORA 1) by AURORA 2 visit.
Change in immunology (Complement 3 (C3)) parameters from AURORA 1 baseline. [Time Frame: Up to 37 months]	Complement C3: mg/dL	ACR lupus Recommended outcome for Monitoring of LN (214).	
Change in immunology parameters (complement 4 (C4)) from AURORA 1 baseline. [Time Frame: Up to 37 months]	Complement C4: mg/dL	ACR lupus Recommended outcome for Monitoring of LN (214).	
Change in immunology parameters (anti-double-stranded deoxyribonucleic acid) from AURORA 1 baseline. [Time Frame: Up to 37 months]	Anti-dsDNA: IU/mL	ACR lupus Recommended outcome for Monitoring of LN (214).	
Change Health Related Quality of Life Assessments (HRQoL) Short Form Health Survey (SF-36) [Time Frame: Months 18,24,30,36]	A set of 36 generic questions assessing quality of life and health status across 8 health concepts (physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions) and is reliant upon patient self-reporting.	The SF-36 is a instrument for measuring health perception in a general population (215).	

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance(15)
Healthcare Resource Utilization (HRU) [Time Frame: Months 12, 15, 18, 21, 24, 27, 30, 33, 36]	Qualitative information gathered form the subjects via interview related to utilisation of healthcare resources e.g., visits to health care practitioners		HRU including number of visits to health care professionals (HCPs), types of HCP visited (specialists versus primary care) and diagnostic tests performed (Yes/No) was collected at Months 12, 15, 18, 21, 24, 27, 30, 33, and 36, and summarized by visit and changes over time.

Abbreviations: ACR = American College of Rheumatology; AE = adverse event; anti-dsDNA = anti-double-stranded deoxyribonucleic acid; CEC = clinical endpoints committee; eGFR = estimated glomerular filtration rate; HCPs = health care professionals; HRQoL = health-related quality of life; HRU = healthcare resource utilization; LN = lupus nephritis; LS = least squares; MMF = mycophenolate mofetil; MMRM = mixed effect model repeated measures; PRR = partial renal response; SELENA-SLEDAI = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index; SF-36 = 36-Item Short Form Survey; SLE = systemic lupus erythematosus; TEAE = treatment-emergent adverse event; UPCR = urine protein creatinine ratio

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Table 112: AURA-LV outcomes

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance
Number of Subjects Achieving Complete Renal Remission at 24 Weeks [Time Frame: week 24]	Complete remission is defined as: Confirmed protein/creatinine ratio of ≤0.5 mg/mg and	In severe LN, a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (203)	All statistical tests were two-sided with no adjustments for multiple comparisons (level of significance p<0.05) (139). Logistic regression models were used to conduct the primary efficacy analysis (CRR at Week 24) and secondary efficacy analyses of CRR at Week 48. PRR at Week 24/48, and CRR with low-dose steroids at Week 24/48. Logistic regression models incorporated baseline variables within the model as appropriate (139).
Number of Subjects Achieving Complete Renal Remission at 48 Weeks [Time Frame: Week 48]	eGFR ≥60 mL/min/1.73m2 or no confirmed decrease from baseline in eGFR of ≥20%. Subjects who received rescue medication for LN or >10 mg prednisone for >3 consecutive days or >7 days total from 56 days prior to remission assessment until the time of the remission assessment were considered not achieving complete remission.		
Number of Subjects Achieving Complete Renal Remission at 24 and 48 Weeks in the Presence of Low Dose Steroids [Time Frame: Weeks 24 and 48]	Complete remission as above. Low-dose steroids is defined as use of ≤5 mg prednisone for 8 weeks leading up to the Week 24 visit date or for 12 weeks leading up to the Week 48 visit date.		
Time to Complete Remission (Number of Weeks) [Time Frame: week 48]	Time to Complete Remission is defined as time from first dose of voclosporin/placebo to UPCR ≤ 0.5mg in the absence of rescue medication.		Time to CRR (UPCR <0.5 mg/mg) and PRR was measured from baseline as the number of days from randomisation to the day of the event. Time to sustained CRR/PRR and sustained early CRR/PRR (beginning ≤Week 24 assessment window) was measured from baseline to CRR/PRR that was sustained through the Week 48 visit. Each time to event endpoint was estimated using Kaplan-Meier methodology and Cox's proportion hazards model. A two-sided log-rank test was performed to assess the significance of differences between the two treatment groups (139).
Time to Sustained Early Complete Remission (Number of Weeks) [Time Frame: week 48]	Time to Sustained Complete Remission is defined as time from first dose of voclosporin/placebo to UPCR		

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance
	≤ 0.5mg occurring at week 24 or earlier and sustained until week 48 in the absence of rescue medication.		
Number of Subjects Achieving Sustained Early Complete Remission [Time Frame: week 48]	Sustained early complete remission defined as complete remission that occurred on or before Week 24 and was sustained through Week 48	In severe LN, a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (203)	All statistical tests were two-sided with no adjustments for multiple comparisons (level of significance p<0.05) (139). Logistic regression models were used to conduct the primary efficacy analysis (CRR at Week 24) and secondary efficacy analyses of CRR at Week 48. PRR at Week 24/48, and CRR with low-dose steroids at Week 24/48. Logistic regression models incorporated baseline variables within the model as appropriate (139).
Time to Partial Remission (Number of Weeks) [Time Frame: week 48]	Time to partial Remission is defined as time from first dose of voclosporin/ placebo to 50% UPCR reduction sustained until week 48 in the absence of rescue medication.		Time to CRR (UPCR <0.5 mg/mg) and PRR was measured from baseline as the number of days from randomisation to the day of the event. Time to sustained CRR/PRR and sustained early CRR/PRR (beginning ≤Week 24 assessment window) was measured from baseline to CRR/PRR that was sustained through the Week 48 visit. Each time to event endpoint was estimated using Kaplan-Meier methodology and Cox's proportion hazards model. A two-sided log-rank test was performed to assess the significance of differences between the two treatment groups (139).
Number of Subjects Achieving Partial Remission [Time Frame: week 48]	Partial remission is defined as a 50% reduction in UPCR from baseline at Week 24 and Week 48.		All statistical tests were two-sided with no adjustments for multiple comparisons (level of significance p<0.05) (139). Logistic regression models were used to conduct the primary efficacy analysis (CRR at Week 24) and secondary efficacy analyses of CRR at Week 48. PRR at Week 24/48, and CRR with low-dose steroids at Week 24/48. Logistic regression models incorporated baseline variables within the model as appropriate (139).
Number of Subjects Achieving, and Remaining in, Complete Remission [Time Frame: week 48]	Sustained complete remission defined as the first occurrence of complete remission that was sustained through Week 48		

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Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance
Duration of Complete Remission (Number of Weeks) [Time Frame: week 48]	Duration of Complete Remission is defined as time of first occurrence of UPCR ≤ 0.5 mg/mg until the second increase above 0.5 mg/mg (i.e., a single occurrence above 0.5 is permitted) or use of rescue medication.		Time to CRR (UPCR <0.5 mg/mg) and PRR was measured from baseline as the number of days from randomisation to the day of the event. Time to sustained CRR/PRR and sustained early CRR/PRR (beginning ≤Week 24 assessment window) was measured from baseline to CRR/PRR that was sustained through the Week 48 visit. Each time to event endpoint was estimated using Kaplan-Meier methodology and Cox's proportion hazards model. A two-sided log-rank test was performed to assess the significance of differences between the two treatment groups (139).
Number of Subjects Achieving Partial Renal Remission at 24 and 48 Weeks [Time Frame: week 24 and 48]	Number of patients with partial Remission is defined as time from first dose of voclosporin/placebo to 50% UPCR reduction at week 24 or week 48 in the absence of rescue medication.	In severe LN, a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (209)	All statistical tests were two-sided with no adjustments for multiple comparisons (level of significance p<0.05) (139). Logistic regression models were used to conduct the primary efficacy analysis (CRR at Week 24) and secondary efficacy analyses of CRR at Week 48. PRR at Week 24/48, and CRR with low-dose steroids at Week 24/48. Logistic regression models incorporated baseline variables within the model as appropriate (139).
Time to Sustained Partial Remission (Number of Weeks) [Time Frame: week 48]	Time to sustained partial Remission is defined as time from first dose of voclosporin/placebo to 50% UPCR reduction sustained until week 48 in the absence of rescue medication.		Time to CRR (UPCR <0.5 mg/mg) and PRR was measured from baseline as the number of days from randomisation to the day of the event. Time to sustained CRR/PRR and sustained early CRR/PRR (beginning ≤Week 24 assessment window) was measured from baseline to CRR/PRR that was sustained through the Week 48 visit. Each time to event endpoint was estimated using Kaplan-Meier methodology and Cox's proportion hazards model. A two-sided log-rank test was performed to assess the significance of differences between the two treatment groups (139).
Time to Sustained Early Partial Remission (Number of Weeks) [Time Frame: week 48]	Time to sustained early partial Remission is defined as time from first dose of voclosporin/placebo to 50% UPCR reduction occurring at week 24 or earlier and sustained until week 48 in the absence of rescue medication.		

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance
Number of Subjects Achieving Sustained Early Partial Remission [Time Frame: week 48]	Early partial remission defined as partial remission that occurred on or before Week 24 and was sustained through Week 48		All statistical tests were two-sided with no adjustments for multiple comparisons (level of significance p<0.05) (139). Logistic regression models were used to conduct the primary efficacy analysis (CRR at Week 24) and secondary efficacy analyses of CRR at Week 48. PRR at Week 24/48, and CRR with low-dose steroids at Week 24/48. Logistic regression models incorporated baseline variables within the model as appropriate (139).
Change From Baseline in UPCR at Weeks 24 and 48 [Time Frame: Baseline, Week 24 and Week 48]	Change from baseline in urine protein creatinine ratio at weeks 24 and 48	The ACR lupus classification criteria define LN by proteinuria >0.5 g/day or a urinary protein/creatinine ratio (UPCR) of >0.5 or urinary protein greater than 3+ by dipstick analysis or urinary cellular casts of more than five cells per high-power field (210)	Change from baseline endpoints (UPCR, eGFR, serum albumin, urine protein, and SELENA-SLEDAI score) were analysed using analysis of covariance (ANCOVA) models adjusted as appropriate (139).
Change From Baseline in Safety of Estrogens in Systemic Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) Score [Time Frame: Baseline, Week 24 and Week 48]	The SELENA-SLEDAI assesses disease activity within the last 10 days. Twenty-four items are scored for nine organ systems, and summed to a maximum of 105 points. A score of 6 is considered clinically significant and indicates active disease. For analysis purposes, a score ≥6 was categorized as "high". The 24 items are as follows: seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident, vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, pyuria, new rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low	The SELENA-SLEDAI tool is a cumulative and weighted index used to assess disease activity across 24 different disease descriptors in patients with lupus (205).	

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance
	complement, increased DNA binding, fever, thrombocytopenia, and leukopenia.		

Abbreviations: ACR = American College of Rheumatology; ANCOVA = analysis of covariance; CRR = complete renal response; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; LN = lupus nephritis; PRR = partial renal response; SELENA-SLEDAI = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index; UPCR = urine protein creatinine ratio

Table 113: BLISS-LN outcomes

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance
Double-blind Period: Percentage of Participants With Primary Efficacy Renal Response (PERR) at Week 104 [Time Frame: Week 104]	PERR is defined as urinary protein creatinine ratio <=0.7, eGRF was not more than 20 percent (%) below the pre-flare value or >=60 milliliters per minute per 1.73 square meter (mL/min/1.73m^2) and was not a treatment failure.	In severe lupus nephritis (LN), a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (209)	Analysis was performed using a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), Baseline urine protein-creatinine ratio (uPCR), and Baseline eGFR. Modified intention-to-treat (mITT) Population consisted of all randomized participants who received at least one dose of study treatment and were not excluded due to Good Clinical Practice (GCP) non-compliance. Percentage of participants with PERR at Week 104 has been presented.
Open-label Period: Number of Participants Reporting AEs and serious adverse events (SAEs) [Time Frame: From first open-label dose (Day 1) up to open-label Week 32 (8 weeks after last dose)]	An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. A SAE is any untoward medical occurrence that, at any	AE is a widely used and validated outcome measure (213)	Number of participants with AEs and SAEs was reported.

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance
	dose: resulting in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, any other situation according to medical or scientific judgment or all events of possible drug-induced liver injury with hyperbilirubinemia were categorized as SAE.		
Open-label Period: Number of Participants Reporting Adverse Events of Special Interest (AESI) [Time Frame: From first open-label dose (Day 1) up to open-label Week 32 (8 weeks after last dose)]	An AESI is one of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by investigator to sponsor can be appropriate. A summary of protocol defined AESIs include malignant neoplasms including and excluding non-melanoma skin cancer (NMSC), post-infusion systemic reactions (PISR), all infections of special interest (opportunistic infections [OI], Herpes Zoster [HZ], tuberculosis [TB], and sepsis), depression (including mood disorders and anxiety)/suicide/self-injury and deaths.	AE is a widely used and validated outcome measure (213)	Number of participants with AESI was reported.
Double-blind Period: Percentage of Participants With Complete Renal Response (CRR) at Week 104 [Time Frame: Week 104]	CRR is defined as urinary protein creatinine ratio <0.5, eGRF was not more than 10% below the pre-flare value or >=90 mL/min/1.73m^2 and was not a treatment failure.	In severe LN, a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (209)	Analysis was performed using a logistic regression model for the comparison between belimumab and placebo with covariates of induction regimen (CYC vs. MMF), race (Black vs. Non-Black), Baseline uPCR and Baseline eGFR. Percentage of participants with CRR at Week 104 has been presented.

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance
Double-blind Period: Percentage of Participants With PERR at Week 52 [Time Frame: Week 52]	PERR is defined as urinary protein creatinine ratio <=0.7, eGRF was not more than 20% below the pre-flare value or >=60 mL/min/1.73m^2 and was not a treatment failure.	In severe LN, a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (209)	Analysis was performed using a logistic regression model for the comparison between belimumab and placebo with covariates of induction regimen (CYC vs. MMF), race (Black vs. Non-Black), uPCR, and Baseline eGFR. Percentage of participants with PERR at Week 52 has been presented.
Double-blind Period: Number of Participants With Time to Death or Renal Related Event [Time Frame: Up to Week 104]	Events are defined as the first event experienced among the following: death, progression to end stage renal disease, doubling of serum creatinine from Baseline, renal worsening or renal-related treatment failure. Participants who discontinued randomized treatment, withdrew from the study, were lost to follow-up, or had a non renal-related treatment failure were censored. Participants who completed the 104-week treatment period were censored at the Week 104 visit.	AE is a widely used and validated outcome measure (213)	Time to event is defined as event date minus treatment start date plus one. Analysis was performed using Cox PHs model for the comparison between belimumab and placebo adjusting for induction regimen, race, Baseline uPCR and Baseline eGFR. Number of participants with time to death or renal related event up to Week 104 has been presented.
Double-blind Period: Percentage of Participants With Ordinal Renal Response (ORR) at Week 104 [Time Frame: Week 104]	ORR is defined with respect to reproducible responses that included CRR, partial RR (PRR) and non responder. CRR is reported when uPCR was <0.5, eGFR was not more than 10% below pre-flare GFR or within normal range and not a treatment failure. PRR is >=50% decrease from Baseline in uPCR and one of the following: value <1 if Baseline <=3, or value <3 if the Baseline was >3, eGFR not more than 10% below Baseline GFR or within normal	In severe LN, a significant correlation between response to treatment as measured by a reduction or remission in proteinuria and outcomes has been demonstrated. As a result, the use of remission as a short-term outcome has been suggested as a valid measure when designing studies. (209)	

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance
	range and not a treatment failure and not a CRR. Non responder is reported when neither CRR nor PRR criteria was met. Percentage of participants reporting CRR, PRR and non responders at Week 104 has been presented.		
Double-blind Period: Number of Participants Reporting On-treatment AEs and SAEs [Time Frame: Up to Week 104]	An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. A SAE is any untoward medical occurrence that, at any dose: resulting in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, any other situation according to medical or scientific judgment or all events of possible drug-induced liver injury with hyperbilirubinemia were categorized as SAE. Number of participants with on-treatment AEs and SAEs has been reported.	AE is a widely used and validated outcome measure (213)	
Double-blind Period: Number of Participants Reporting AESI [Time Frame: Up to Week 104]	An AESI is one of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by investigator to sponsor can be appropriate. A summary of protocol defined AESIs include malignant neoplasms including and excluding NMSC, PISR, all infections of special interest (OI, HZ, TB, and sepsis), depression (including	AE is a widely used and validated outcome measure (213)	

Outcome measure	Definition	Validity	How was the measure investigated?/Clinical relevance
	mood disorders and anxiety)/suicide/self-injury and deaths. On-treatment data is displayed.		

Abbreviations: AE = adverse event; AESI = adverse events of special interest; CRR = complete renal response; CYC = cyclophosphamide; eGFR = estimated glomerular filtration rate; GCP = good clinical practice; GFR = glomerular filtration rate; HZ = Herpes Zoster; LN = lupus nephritis; mITT = modified intention-to-treat; MMF = mycophenolate mofetil; NMSC = non-melanoma skin cancer; PRR = partial renal response; OI = opportunistic infections; ORR = ordinal renal response; PERR = primary efficacy renal response; PH = proportional hazard; PISR = post-infusion systemic reactions; SAEs = serious adverse events; TB = tuberculosis; UPCR = urine protein creatinine ratio

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Results per study

Table 114: The results from the AURORA trial

Results of AURORA NCT03021499 (136)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	**Study arm**	**N**	**Result (%) [CI]**	**Difference (%-points)**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
Primary endpoint: Complete renal response (CRR) at 52 weeks. n (%)	Voclosporin	179	73 (40.8)	18.3	NR	NR	OR: 2.65	1.6 to 4.3	<0.0001	The binary endpoint analyses were conducted on the intention-to-treat (ITT) population using a logistic regression model with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region, and response (Yes/No) at as the response variables (136).
	Placebo	178	40 (22.5)							
Composites of CRR										
UPCR ≤ 0.5 mg/mg. n (%)	Voclosporin	179	81 (45.2)				OR: 3.11	1.9 to 5.0	<0.0001	The binary endpoint analyses were conducted on the ITT population using a logistic regression model with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region, and response (Yes/No) at as the response variables (136).
	Placebo	178	41 (23.0)							
eGFR ≥60, eGFR <60 with no confirmed decrease of >20%, or eGFR <60 with confirmed decrease of >20% but with no disease-related or treatment-related eGFR associated AE present at time of assessment. n (%)	Voclosporin	179	147 (82.1)	6.3	NR	NR	OR: 1.50	0.9 to 2.5	0.129	
	Placebo	178	135 (75.8)							
Received no rescue medication for LN. n (%)	Voclosporin	179	163 (91.1)	4.6	NR	NR	OR: 1.62	0.8 to 3.2	0.164	
	Placebo	178	154 (86.5)							

Results of AURORA NCT03021499 (136)										
Did not receive > 10 mg/day prednisone for ≥ 3 consecutive days or for ≥ 7 days in total during Weeks 44 through 52 n (%)	Voclosporin	179	156 (87.2)	1.8	NR	NR	OR: 1.26	0.7 to 2.3	0.465	
	Placebo	178	152 (85.4)							
Partial renal response (PRR)										
PRR at 24 weeks, n (%)	Voclosporin	179	126 (70)	20	NR	NR	2.43	1.65 to 3.79	< 0.001	The binary endpoint analyses were conducted on the ITT population using a logistic regression model with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region, and response (Yes/No) at as the response variables (136).
	Placebo	178	89 (50)							
PRR at 52 weeks, n (%)	Voclosporin	179	125 (70)	18	NR	NR	2.26	1.45 to 3.51	< 0.001	
	Placebo	178	92 (52)							
Changes from baseline in disease activity (SELENA-SLEDAI)										
Change at 24 weeks	Voclosporin	179	-4.5 [-5.4, -3.7]	-0.5	-1.6 to 0.6	0.375	NR	NR	NR	Change from baseline endpoints (SELENA-SLEDAI score) were analysed using a mixed effect model repeated measures (MMRM) analysis with treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, region, and baseline UPCR included as covariates in the model (136).
	Placebo	178	-4.1 [-5.0, -3.2]							
Change at 52 weeks	Voclosporin	179	-6.0 [-6.7, -5.2]	-0.5	-1.4 to 0.4	0.277	NR	NR	NR	
	Placebo	178	-5.5 [-6.3, -4.7]							

Abbreviations: AE = adverse event; CI = confidence interval; CRR = complete renal response; eGFR = estimated glomerular filtration rate; LN = lupus nephritis; MMF = mycophenolate mofetil; MMRM = mixed effect model repeated measures; NR = not reported; OR = odds ratio; PRR = partial renal response; SELENA-SLEDAI = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index; UPCR = urine protein creatinine ratio

Table 115: The results of the AURORA 2 trial

Results of AURORA 2 NCT03597464 (15)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	**Study arm**	**N**	**Result (%) [CI]**	**Difference (%-points)**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
Complete renal response (CRR)										
CRR at 18 months. n (%)	Voclosporin	116	74 (63.8)	17.8	NR	NR	OR: 2.19	1.25 to 3.83	0.006	The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region. Subjects who withdrew from the study prior to the visit assessments and thus provide insufficient visit data were defined as non-responders.
	Placebo	100	46 (46.0)							
CRR at 24 months. n (%)	Voclosporin	116	65 (56.0)	13	NR	NR	OR: 1.81	1.04 to 3.16	0.035	
	Placebo	100	43 (43.0)							
CRR at 30 months. n (%)	Voclosporin	116	69 (59.5)	17.5	NR	NR	OR: 2.24	1.28 to 3.92	0.005	
	Placebo	100	42 (42.0)							
CRR at 36 months. n (%)	Voclosporin	116	59 (50.9)	11.9	NR	NR	OR: 1.74	1.00 to 3.03	0.051	
	Placebo	100	39 (39.0)							
Partial renal response (PRR)										
PRR at 18 months. n (%)	Voclosporin	116	96 (82.8)	14.8	NR	NR	OR: 2.50	1.28 to 4.88	0.008	The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, MMF use at baseline and region. Subjects who withdrew from the study prior to the visit assessments and thus provide insufficient visit data were defined as non-responders.
	Placebo	100	68 (68.0)							
PRR at 24 months. n (%)	Voclosporin	116	90 (77.6)	19.6	NR	NR	OR: 2.68	1.46 to 4.91	0.001	
	Placebo	100	58 (58.0)							
PRR at 30 months. n (%)	Voclosporin	116	85 (73.3)	12.3	NR	NR	OR: 1.86	1.03 to 3.34	0.040	
	Placebo	100	61 (61.0)							
PRR at 36 months. n (%)	Voclosporin	116	86 (74.1)	5.1	NR	NR	OR: 1.39	0.75 to 2.58	0.290	
	Placebo	100	69 (69.0)							
Adequate response* and renal flares from AURORA 1 baseline months 0 to 36										
Patients with adequate response. n (%)	Voclosporin	116	101 (87.1)	14.1	NR	NR	NR	NR	NR	The model is based on a logistic regression with terms for
	Placebo	100	73 (73.0)							

Results of AURORA 2 NCT03597464 (15)										
Patients with renal flares. n (%)	Voclosporin	101	24 (23.8)	22.2	NR	NR	OR: 0.85	0.42 to 1.73	0.662	treatment, baseline UPCR, biopsy class, MMF use at baseline and region.
	Placebo	73	19 (26.0)							
Patients with good renal outcomes (adequate response and without flares). n (%)	Voclosporin	116	77 (66.4)	11.6	NR	NR	OR: 0.56	0.32 to 0.99	0.045	
	Placebo	100	54 (54.0)							
Extra renal flares. n (%)	Voclosporin	116	21 (18.1)	4.1	NR	NR	OR: 1.33	0.63 to 2.81	0.448	
	Placebo	100	14 (14.0)							
SELENA-SLEDAI Least squares Mean change from baseline (AURORA 1 month 0) to 36 months	Voclosporin	116	-6.8 [-7.7, -5.9]	-0.7	-1.8 to 0.5	0.246	NR	NR	NR	Results are based on a Mixed Effect Model Repeated Measures (MMRM) analysis with Change from baseline at each visit as the response variable, while treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, Region and baseline UPCR are included effects in the model.
	Placebo	100	-6.1 [-7.1, -5.2]							
UPCR Mean change from baselin (AURORA 1 month 0) to 36 months	Voclosporin	116	-2.98 SD=2.6	-0.65	-0.98 to -0.24	0.001	NR	NR	NR	Results are based on a MMRM analysis with Change from baseline at each visit as the response variable, while treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, Region and baseline UPCR are included effects in the model
	Placebo	100	-2.33 SD=2.612							

*A CEC adjudicated the response status of each patient, percentages for patients who responded are based on AURORA 2 population; percentages for patients with renal flares are based on the number of patients who responded prior to visit.

Abbreviations: CEC = Clinical Endpoints Committee; CI = confidence interval; CRR = complete renal response; MMF = mycophenolate mofetil; MMRM = mixed effect model repeated measures; NR = not reported; OR = odds ratio; PRR = partial renal response; SELENA-SLEDAI = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index; UPCR = urine protein creatinine ratio

Source: AURORA 2 CSR(15)

Table 116: The results of the AURA-LV study

AURA-LV NCT02141672 (139)										
				Estimated absolute difference in effect			Estimated relative difference in effect [vs. placebo]			Description of methods used for estimation
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference (%- points)**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
Complete renal response at 24 weeks. n (%)	Low-dose voclosporin	89	29 (32.6)	13.3	NR	NR	OR: 2.03	1.01 to 4.05	0.046	Logistic regression models were used to conduct the primary efficacy analysis (CRR at Week 24) and secondary efficacy analyses of CRR at Week 48. PRR at Week 24/48, and CRR with low-dose steroids at Week 24/48. Logistic regression models incorporated baseline variables within the model as appropriate (139).
	High-dose voclosporin	88	24 (27.3)	8.0			OR: 1.59	0.78 to 3.27	0.204	
	Placebo	88	17 (19.3)							
Complete renal response at 48 weeks. n (%)	Low-dose voclosporin	89	44 (49.4)	25.5	NR	NR	OR: 3.21	1.68 to 6.13	<0.001	
	High-dose voclosporin	88	35 (39.8)	15.9			OR: 2.10	1.09 to 4.02	0.026	
	Placebo	88	21 (23.9)							
Partial renal response at 24 weeks. n (%)	Low-dose voclosporin	89	62 (69.7)	20.3	NR	NR	OR: 2.33	1.26 to 4.33	0.007	
	High-dose voclosporin	88	58 (65.9)	16.5			OR: 2.03	1.10 to 3.76	0.024	
	Placebo	88	43 (49.4)							
Partial renal response at 48 weeks. n (%)	Low-dose voclosporin	89	61 (68.5)	20.2	NR	NR	OR: 2.34	1.27 to 4.33	0.007	
	High-dose voclosporin	88	63 (71.6)	23.3			OR: 2.68	1.43 to 5.02	0.002	
	Placebo	88	42 (48.3)							

Median time to Complete renal response *	Low-dose voclosporin	89	19.7	NR	NR	NR	HR: 2.26	1.45 to 3.51	<0.001	Time to CRR (UPCR <0.5 mg/mg) and PRR was measured from baseline as the number of days from randomisation to the day of the event. Each time to event endpoint was estimated using Kaplan-Meier methodology and Cox's proportion hazards model. A two-sided log-rank test was performed to assess the significance of differences between the two treatment groups (139).
	High-dose voclosporin	88	23.4				HR: 2.25	1.46 to 3.47	<0.001	
	Placebo	88	NR*							
Median time to Partial renal response	Low-dose voclosporin	89	4.3	NR	NR	NR	HR: 1.63	1.16 to 2.27	0.005	
	High-dose voclosporin	88	4.4				HR: 1.74	1.25 to 2.43	0.002	
	Placebo	88	6.6							
Mean change from baseline in SELENA-SLEDAI week 24	Low-dose voclosporin	74	-6.3	1.8	NR	NR	-2.38**	-3.95 to -0.80	0.003	Change from baseline endpoints (UPCR, eGFR, serum albumin, urine protein, and SELENA-SLEDAI score) were analysed using analysis of covariance (ANCOVA) models adjusted as appropriate (139).
	High-dose voclosporin	82	-7.1	2.6			-2.35**	-3.88 to -0.82	0.003	
	Placebo	76	-4.5							
Mean change from baseline in SELENA-SLEDAI week 48	Low-dose voclosporin	77	-7.9	2.6	NR	NR	-2.95**	-4.44 to -1.45	<0.001***	
	High-dose voclosporin	82	-8.3	3.0			-2.58**	-4.05 to -1.11	<0.001***	
	Placebo	79	-5.3							

*Median time to CRR was not calculated for Placebo, as 50% of the group never achieved CRR.

** Calculated as difference in mean change from baseline (vs. placebo)

*** P-values are from an ANCOVA model, adjusted for baseline level.

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval;; eGFR = estimated glomerular filtration rate; NR = not reported; OR = odds ratio; SELENA-SLEDAI = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index; UPCR = urine protein creatinine ratio

Table 117: The results from the BLISS-LN study (Primary and Major Secondary Efficacy outcomes)

BLISS-LN NCT01639339 (80)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference (percentage points)**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
Primary end point: primary efficacy renal response (PERR) at wk 104†	Belimumab	223	96 (43)	11	NR	NR	OR: 1.6	1.0 to 2.3	0.03	The end points of a PERR and complete renal response were analyzed with logistic regression.
	SoC	223	72 (32)							
Complete renal response at wk 104‡	Belimumab	223	67 (30)	10	NR	NR	OR: 1.7	1.1 to 2.7	0.02	
	SoC	223	44 (20)							
PERR at wk 52§	Belimumab	223	104 (47)	11	NR	NR	OR: 1.6	1.1 to 2.4	0.02	
	SoC	223	79 (35)							
Time to renal-related event or death¶	Belimumab	223	N/A	NR	NR	NR	HR: 0.5	0.3 to 0.8	0.01	The time to a renal-related event or death was analyzed with the use of a Cox proportional-hazards regression.
	SoC	223	N/A							
Ordinal renal response without urinary sediment at wk 104‖										
Complete renal response	Belimumab	223	67 (30)	10	NR	NR	NR	NR	0.01	Ordinal renal response without urinary sediment was analyzed with a rank analysis of covariance.
	SoC	223	44 (20)							
Partial renal response**	Belimumab	223	39 (18)	<1	NR	NR	NR	NR	NR	
	SoC	223	38 (17)							
No response	Belimumab	223	117 (52)	−11	NR	NR	NR	NR	NR	
	SoC	223	141 (63)							

† The PERR at week 104 (week 100, confirmed at week 104) is defined as a ratio of urinary protein to creatinine of 0.7 or less and an eGFR that is no worse than 20% below the pre-flare value or at least 60 ml per minute per 1.73 m^2 and no rescue therapy for treatment failure.

‡ The complete renal response at week 104 (week 100, confirmed at week 104) is defined as a ratio of urinary protein to creatinine of less than 0.5, an eGFR that is no worse than 10% below the pre-flare value or at least 90 ml per minute per 1.73 m^2, and no rescue therapy.

§ The PERR at week 52 was the response at week 48, confirmed at week 52.

¶ For this end point, events were defined as the first event that occurred among the following: death; progression to end-stage kidney disease; doubling of the serum creatinine level from the baseline level; increased proteinuria, impaired kidney function, or both; or kidney-related treatment failure. Data on patients who discontinued belimumab or placebo, withdrew from the trial, or were lost to follow-up were censored on the date of the event. Data on patients who completed the 104-week treatment period were censored at the week 104 visit. The time to event in days was defined as the event date minus the treatment start date plus 1. A Cox proportional-hazards model for the comparison between belimumab and placebo was used, with adjustment for induction regimen, race, baseline ratio of urinary protein to creatinine, and baseline eGFR.
‖ The P value was from a rank analysis-of-covariance model comparing belimumab with placebo, with covariates for trial group, induction regimen (cyclophosphamide vs. mycophenolate mofetil), race (Black vs. non-Black), baseline ratio of urinary protein to creatinine, and baseline eGFR. Withdrawal from the trial, treatment failure, and discontinuation of belimumab or placebo were imputed as a nonresponse.
** This end point is defined as an eGFR that is no worse than 10% below the baseline value or within normal range and at least a 50% decrease in the ratio of urinary protein to creatinine with one of the following: a ratio of urinary protein to creatinine of less than 1.0 if the baseline ratio was 3.0 or less, or a ratio of urinary protein to creatinine of <3.0 if the baseline ratio was greater 3.0; no treatment failure; and not complete renal response.
Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; NR = not reported; N/A = not applicable; OR = odds ratio; PERR = primary efficacy renal response; SoC = standard of care

Appendix E Safety data for intervention and comparator(s)

AURORA

All safety data from AURORA was presented in 7.1.1.1.1.8.

AURORA 2

All safety data from AURORA 2 was presented in 7.1.1.2.1.9.

AURA-LV

Commonly reported adverse events

The most common TEAEs are summarised in Table 118. The incidence of TEAEs was >10% more frequent in both voclosporin groups compared to placebo (primarily attributable to GFR decrease) and the General Disorders and Administration Site Conditions (139).Infections and gastrointestinal disorders were the most frequent AEs across the 3 groups; low-dose voclosporin, high-dose voclosporin and placebo (Table 118). The next most frequent AE across all three treatment groups was Gastrointestinal Disorders (placebo: 37.5%; low-dose voclosporin: 42.7%; and high-dose voclosporin: 52.3%). Diarrhoea, nausea, and vomiting were common occurrences in the two voclosporin groups, as were diarrhoea and vomiting in the placebo group. The incidence of Infections and Infestations and Gastrointestinal Disorders appeared to increase in a dose-dependent manner (139).

Respiratory, Thoracic and Mediastinal Disorders were reported for 31.5% of patients in the low-dose voclosporin group compared to only 9.1% and 12.5% of patients in the placebo and high-dose voclosporin groups, respectively. Renal and Urinary Disorders occurred at a slightly higher frequency in the placebo group (13.6%) compared to both the low-dose (10.1%) and high-dose voclosporin groups (11.4%) (139).

Table 118: AURA-LV - Most common TEAEs (in ≥ 5% of patients in any group)

System organ class (Preferred term)	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)
Any TEAE, n (%)	82 (92.1)	85 (96.6)	75 (85.2)
Glomerular filtration rate decreased	27 (30.3)	27 (30.7)	12 (13.6)
Diarrhoea	16 (18.0)	14 (15.9)	14 (15.9)
Nausea	16 (18.0)	11 (12.5)	7 (8.0)
Cough	16 (18.0)	5 (5.7)	3 (3.4)
Hypertension	15 (16.9)	16 (18.2)	8 (9.1)
Vomiting	15 (16.9)	9 (10.2)	10 (11.4)
Anaemia	13 (14.6)	14 (15.9)	7 (8.0)
Upper respiratory tract infection	12 (13.5)	18 (20.5)	14 (15.9)
Hypokalaemia	12 (13.5)	12 (13.6)	9 (10.2)
Headache	10 (11.2)	15 (17.0)	11 (12.5)
Oedema peripheral	9 (10.1)	7 (8.0)	8 (9.1)
Arthralgia	9 (10.1)	7 (8.0)	7 (8.0)
Urinary tract infection	8 (9.0)	6 (6.8)	5 (5.7)
Back pain	8 (9.0)	5 (5.7)	3 (3.4)
Pneumonia	7 (7.9)	7 (8.0)	2 (2.3)
Decreased appetite	7 (7.9)	5 (5.7)	2 (2.3)
Alopecia	7 (7.9)	4 (4.5)	2 (2.3)
Pyrexia	6 (6.7)	10 (11.4)	1 (1.1)
Dyslipidaemia	6 (6.7)	7 (8.0)	6 (6.8)

Dyspepsia	6 (6.7)	6 (6.8)	4 (4.5)
Gastroenteritis	6 (6.7)	4 (4.5)	2 (2.3)
Renal failure acute	5 (5.6)	8 (9.1)	0 (0.0)
Herpes zoster	5 (5.6)	7 (8.0)	5 (5.7)
Abdominal pain upper	5 (5.6)	7 (8.0)	5 (5.7)
Nasopharyngitis	5 (5.6)	4 (4.5)	3 (3.4)
Muscle spasms	5 (5.6)	2 (2.3)	3 (3.4)
Dizziness	5 (5.6)	2 (2.3)	1 (1.1)
Iron deficiency anaemia	5 (5.6)	0 (0.0)	0 (0.0)
Insomnia	4 (4.5)	5 (5.7)	4 (4.5)
Hypertrichosis	3 (3.4)	7 (8.0)	0 (0.0)
Gingival hypertrophy	3 (3.4)	6 (6.8)	0 (0.0)
Blood pressure increased	3 (3.4)	5 (5.7)	1 (1.1)
Bronchitis	2 (2.2)	6 (6.8)	3 (3.4)
Tachycardia	2 (2.2)	5 (5.7)	1 (1.1)
Oedema	2 (2.2)	5 (5.7)	1 (1.1)
Gastritis	2 (2.2)	4 (4.5)	5 (5.7)
Oral candidiasis	2 (2.2)	5 (5.7)	0 (0.0)
Leukopenia	1 (1.1)	3 (3.4)	6 (6.8)

Note: *23.7 mg BID; †39.5 mg BID
Abbreviations: BID = twice daily; TEAE = treatment-emergent adverse event
Source: Rovin et al., 2019;[73] Otsuka 2018 [139]

Serious adverse events

Serious TEAEs were reported more frequently in patients treated with voclosporin (low-dose: 28.1%; high-dose: 25.0%) compared to placebo (15.9%), but the incidence did not increase with increasing dose of voclosporin (Table 119) (139).

When low-GDP countries were excluded, the incidence of TEAEs was reduced overall, especially in the two voclosporin groups; the incidence of serious TEAEs (including serious TEAEs were similar among all three treatment groups in the remaining population (139).

Table 119: AURA-LV - Most common serious TEAEs (in ≥2 patients in any group)

System organ class (Preferred term)	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)
Any serious TEAE	25 (28.1)	22 (25.0)	14 (15.9%)
Infections and infestations	11 (12.4)	12 (13.6)	7 (8.0)
Pneumonia	5 (5.6)	3 (3.4)	2 (2.3)
Urinary tract infection	2 (2.2)	1 (1.1)	0 (0.0)
Gastroenteritis	1 (1.1)	2 (2.3)	1 (1.1)
Sepsis	1 (1.1)	2 (2.3)	0 (0.0)
Renal and urinary disorders	5 (5.6)	1 (1.1)	1 (1.1)
Renal failure acute	4 (4.5)	1 (1.1)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	5 (5.6)	1 (1.1)	0 (0.0)
Pulmonary embolism	2 (2.2)	1 (1.1)	0 (0.0)
Acute respiratory distress syndrome	2 (2.2)	0 (0.0)	0 (0.0)
Nervous system disorders	4 (4.5)	3 (3.4)	1 (1.1)
Posterior reversible encephalopathy syndrome	2 (2.2)	2 (2.3)	0 (0.0)
Gastrointestinal disorders	2 (2.2)	2 (2.3)	1 (1.1)
Vascular disorders	2 (2.2)	2 (2.3)	0 (0.0)
Hypertension	2 (2.2)	2 (2.3)	0 (0.0)
Cardiac disorders	2 (2.2)	1 (1.1)	2 (2.3)
Musculoskeletal and connective tissue disorders	1 (1.1)	2 (2.3)	2 (2.3)
Systemic lupus erythematosus	1 (1.1)	2 (2.3)	2 (2.3)
Blood and lymphatic system disorders	1 (1.1)	0 (0.0)	2 (2.3)

Note: *23.7 mg BID; †39.5 mg BID
Abbreviations: BID = twice daily; TEAE = treatment-emergent adverse event
Source: Rovin et al., 2019;(73) Otsuka 2018 (139)

In contrast to serious TEAEs, a dose-dependent increase was observed in incidence of serious treatment-related TEAEs by the Investigator, but overall incidence was low even in the high-dose voclosporin group (i.e., placebo: 1.1%; low-dose voclosporin: 4.5%; high-dose voclosporin: 8.0%) (Table 120) (139).

Table 120: AURA-LV - Serious treatment-related TEAEs

System organ class (Preferred term)	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)
Any serious treatment-related TEAE	4 (4.5)	7 (8.0)	1 (1.1)
Hypertension	1 (1.1)	2 (2.3)	0 (0.0)
Pneumonia	1 (1.1)	0 (0.0)	0 (0.0)
Sepsis	1 (1.1)	0 (0.0)	0 (0.0)
Convulsion	1 (1.1)	0 (0.0)	0 (0.0)
Renal failure acute	1 (1.1)	0 (0.0)	0 (0.0)
Bacterial pyelonephritis	0 (0.0)	1 (1.1)	0 (0.0)
Bacterial sepsis	0 (0.0)	1 (1.1)	0 (0.0)
Body tinea	0 (0.0)	1 (1.1)	0 (0.0)
Bronchitis	0 (0.0)	1 (1.1)	0 (0.0)
Cellulitis	0 (0.0)	1 (1.1)	0 (0.0)
Hypersensitivity	0 (0.0)	1 (1.1)	0 (0.0)
Tuberculosis of genitourinary system	0 (0.0)	1 (1.1)	0 (0.0)
Bronchiolitis	0 (0.0)	0 (0.0)	1 (1.1)
Congestive cardiomyopathy	0 (0.0)	0 (0.0)	1 (1.1)

Note: *23.7 mg BID; †39.5 mg BID
Abbreviations: BID = twice daily; TEAE = treatment-emergent adverse event
Source: Rovin et al., 2019;[73] Otsuka 2018 [139]

Deaths

A higher proportion of patients in the low-dose voclosporin group (n=10, 11.2%) died during the study compared with the high-dose voclosporin (n=2, 2.3%) or placebo groups (n=1, 1.1%) (73). None of the 13 deaths was considered related to the study drug by the investigators (139). Most deaths (9 of 13) occurred in the first 2 months of study enrolment, and more than half of the deaths (7 of 13) occurred at 2 study sites. Two-fold more patients were randomised to low-dose voclosporin than placebo at these 2 sites, which may possibly be relevant to the imbalance of deaths. Analysis of the patients who died confirmed that these patients had more severe LN disease at baseline as evidenced by higher mean UPCR and lower mean eGFR compared to the rest of the patients (139).

Adverse events leading to treatment discontinuation

TEAEs leading to study drug discontinuation were more frequent in the two voclosporin groups but did not show a dose-dependent trend. TEAEs leading to study drug discontinuation were reported for 10.2%, 18.0%, and 15.9% of patients in the placebo, low-dose voclosporin, and high-dose voclosporin groups, respectively (Table 121). In both voclosporin groups, the most frequently occurring TEAEs leading to discontinuation were the GFR decrease and Infections and Infestations. Permanent discontinuations of study drug due to TEAEs of GFR decrease were reported for 7.9% and 5.7% of patients in the low-dose and high-dose voclosporin groups, respectively, compared to 1.1% in the placebo group (139). Treatment-related TEAEs leading to study drug discontinuation were reported for 2.3% of patients in the placebo group compared to 12.4% and 9.1% of patients in the low-dose and high-dose voclosporin groups, respectively (139).

When patients from low-GDP countries were excluded, the dose-response was normalized in the two voclosporin groups and the incidence of TEAEs leading to study drug discontinuation was similar between the placebo (13.3%) and low-dose voclosporin (10.6%) groups (139). Furthermore, when patients who died were excluded, a dose-dependent trend was observed for TEAEs leading to study drug discontinuation, reported for 9.2%, 13.9%, and 15.1% of patients in the placebo, low-dose voclosporin and high-dose voclosporin groups, respectively (139).

Table 121: AURA-LV - Most common TEAEs leading to treatment discontinuation (in ≥2% of patients in any group)

System organ class (Preferred term)	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)
Any TEAE leading to permanent study drug discontinuation, n (%)	16 (18.0)	14 (15.9)	9 (10.2)
Investigations	7 (7.9)	5 (5.7)	2 (2.3)
Glomerular filtration rate decreased	7 (7.9)	5 (5.7)	1 (1.1)
Infections and Infestations	3 (3.4)	4 (4.5)	1 (1.1)
Pneumonia	2 (2.2)	0 (0.0)	0 (0.0)
Nervous System Disorders	3 (3.4)	0 (0.0)	1 (1.1)
Renal and Urinary Disorders	2 (2.2)	0 (0.0)	3 (3.4)
Musculoskeletal and Connective Tissue Disorders	1 (1.1)	1 (1.1)	2 (2.3)
Gastrointestinal Disorders	0 (0.0)	2 (2.3)	2 (2.3)

Note: *23.7 mg BID; †39.5 mg BID
Abbreviations: BID = twice daily; TEAE = treatment-emergent adverse event
Source: Otsuka 2018 (139)

Adverse events leading to dose interruption or modification

TEAEs leading to dose modification were reported in 53.9% of patients in the low-dose voclosporin group, 58.0% of patients in the high-dose voclosporin group, and 31.8% of patients in the placebo group (139). As expected for a CNI, the most common TEAE leading to dose modification was GFR decrease (reported for 29.2% and 31.8% of patients in the low-dose and high-dose voclosporin groups, respectively, compared to 9.1% in the placebo group) (139). A summary of TEAEs leading to dose modification in the AURA-LV study is presented in Table 122.

Table 122: AURA-LV - TEAEs leading to dose modification

System organ class (Preferred term)	Voclosporin Low-dose* (n=89)	Voclosporin High-dose† (n=88)	Placebo (n=88)
Any TEAE leading to dose modification, n (%)	48 (53.9)	51 (58.0)	28 (31.8)
Investigations	26 (29.2)	28 (31.8)	9 (10.2)
Glomerular filtration rate decreased	26 (29.2)	25 (28.4)	8 (9.1)
Creatinine renal clearance decreased	0 (0.0)	1 (1.1)	0 (0.0)
Blood creatinine increased	0 (0.0)	1 (1.1)	0 (0.0)
Blood potassium increased	0 (0.0)	1 (1.1)	0 (0.0)
Electrocardiogram QT prolonged	0 (0.0)	1 (1.1)	0 (0.0)
Gamma-glutamyltransferase increased	0 (0.0)	1 (1.1)	0 (0.0)
Urine protein/creatinine ratio increased	0 (0.0)	0 (0.0)	1 (1.1)
Infections and infestations	15 (16.9)	15 (17.0)	9 (10.2)
Upper respiratory tract infection	2 (2.2)	3 (3.4)	0 (0.0)
Herpes zoster	3 (3.4)	4 (4.5)	2 (2.3)
Gastroenteritis	2 (2.2)	2 (2.3)	2 (2.3)
Sepsis	0 (0.0)	1 (1.1)	0 (0.0)
Pneumonia	3 (3.4)	1 (1.1)	1 (1.1)
Cellulitis	1 (1.1)	1 (1.1)	1 (1.1)
Gingivitis	1 (1.1)	1 (1.1)	0 (0.0)
Urinary tract infection	1 (1.1)	1 (1.1)	0 (0.0)
Viral infection	0 (0.0)	1 (1.1)	1 (1.1)
Bacterial pyelonephritis	0 (0.0)	1 (1.1)	0 (0.0)
Bacterial sepsis	0 (0.0)	1 (1.1)	0 (0.0)
Body tinea	0 (0.0)	1 (1.1)	0 (0.0)
Tuberculosis of genitourinary system	0 (0.0)	1 (1.1)	0 (0.0)
Pulmonary tuberculosis	3 (3.4)	0 (0.0)	0 (0.0)
Dengue fever	1 (1.1)	0 (0.0)	0 (0.0)
Furuncle	1 (1.1)	0 (0.0)	0 (0.0)
Herpes simplex	1 (1.1)	0 (0.0)	0 (0.0)
Herpes virus infection	1 (1.1)	0 (0.0)	0 (0.0)
Infectious pleural effusion	1 (1.1)	0 (0.0)	0 (0.0)
Nasopharyngitis	1 (1.1)	0 (0.0)	0 (0.0)

Subcutaneous abscess	1 (1.1)	0 (0.0)	0 (0.0)
Bronchiolitis	0 (0.0)	0 (0.0)	1 (1.1)
Carbuncle	0 (0.0)	0 (0.0)	1 (1.1)
Escherichia urinary tract infection	0 (0.0)	0 (0.0)	1 (1.1)
Varicella	0 (0.0)	0 (0.0)	1 (1.1)
Gastrointestinal disorders	5 (5.6)	9 (10.2)	4 (4.5)
Gastritis	1 (1.1)	2 (2.3)	2 (2.3)
Diarrhoea	0 (0.0)	2 (2.3)	1 (1.1)
Gingival hypertrophy	0 (0.0)	2 (2.3)	0 (0.0)
Vomiting	1 (1.1)	1 (1.1)	0 (0.0)
Gastritis erosive	0 (0.0)	1 (1.1)	0 (0.0)
Gastrooesophageal reflux disease	0 (0.0)	1 (1.1)	0 (0.0)
Gingival swelling	0 (0.0)	1 (1.1)	0 (0.0)
Abdominal pain upper	2 (2.2)	0 (0.0)	0 (0.0)
Peptic ulcer	1 (1.1)	0 (0.0)	0 (0.0)
Duodenal ulcer	1 (1.1)	0 (0.0)	0 (0.0)
Dyspepsia	1 (1.1)	0 (0.0)	0 (0.0)
Gastric disorder	1 (1.1)	0 (0.0)	0 (0.0)
Gastrointestinal haemorrhage	1 (1.1)	0 (0.0)	0 (0.0)
Nausea	1 (1.1)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	1 (1.1)
Nervous system disorders	4 (4.5)	5 (5.7)	2 (2.3)
Headache	1 (1.1)	3 (3.4)	0 (0.0)
Posterior reversible encephalopathy syndrome	1 (1.1)	1 (1.1)	0 (0.0)
Post herpetic neuralgia	0 (0.0)	1 (1.1)	1 (1.1)
Migraine	0 (0.0)	1 (1.1)	0 (0.0)
Cerebral haemorrhage	1 (1.1)	0 (0.0)	0 (0.0)
Convulsion	1 (1.1)	0 (0.0)	0 (0.0)
Hypoesthesia	1 (1.1)	0 (0.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	0 (0.0)	1 (1.1)
Vascular disorders	3 (3.4)	4 (4.5)	1 (1.1)
Hypertension	3 (3.4)	2 (2.3)	0 (0.0)
Flushing	0 (0.0)	1 (1.1)	0 (0.0)
Malignant hypertension	0 (0.0)	1 (1.1)	0 (0.0)
Hypertensive crisis	0 (0.0)	0 (0.0)	1 (1.1)
Cardiac disorders	1 (1.1)	2 (2.3)	1 (1.1)
Pericardial effusion	0 (0.0)	1 (1.1)	0 (0.0)
Palpitations	0 (0.0)	1 (1.1)	0 (0.0)
Pericarditis	0 (0.0)	1 (1.1)	0 (0.0)
Wolff-Parkinson-White syndrome	1 (1.1)	0 (0.0)	0 (0.0)
Acute coronary syndrome	0 (0.0)	0 (0.0)	1 (1.1)
Renal and urinary disorders	4 (4.5)	3 (3.4)	4 (4.5)
Renal failure acute	2 (2.2)	3 (3.4)	0 (0.0)
Renal impairment	2 (2.2)	0 (0.0)	1 (1.1)
Oliguria	1 (1.1)	0 (0.0)	0 (0.0)
Lupus nephritis	0 (0.0)	0 (0.0)	1 (1.1)
Proteinuria	0 (0.0)	0 (0.0)	1 (1.1)
Strangury	0 (0.0)	0 (0.0)	1 (1.1)
Musculoskeletal and connective tissue disorders	1 (1.1)	2 (2.3)	2 (2.3)
Systemic lupus erythematosus	0 (0.0)	1 (1.1)	1 (1.1)
Myalgia	0 (0.0)	1 (1.1)	0 (0.0)
Back pain	1 (1.1)	0 (0.0)	1 (1.1)
Metabolism and nutrition disorders	1 (1.1)	2 (2.3)	1 (1.1)
Hypokalaemia	0 (0.0)	1 (1.1)	1 (1.1)
Metabolic acidosis	0 (0.0)	1 (1.1)	0 (0.0)
Diabetes mellitus	1 (1.1)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	2 (2.2)	1 (1.1)	0 (0.0)
Pyrexia	0 (0.0)	1 (1.1)	0 (0.0)
Fatigue	1 (1.1)	0 (0.0)	0 (0.0)
Generalised oedema	1 (1.1)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (1.1)	1 (1.1)
Thrombocytopenia	0 (0.0)	1 (1.1)	0 (0.0)
Leukopenia	0 (0.0)	0 (0.0)	1 (1.1)

Skin and subcutaneous tissue disorders	0 (0.0)	1 (1.1)	1 (1.1)
Hypertrichosis	0 (0.0)	1 (1.1)	0 (0.0)
Rash generalised	0 (0.0)	0 (0.0)	1 (1.1)
Immune system disorders	0 (0.0)	1 (1.1)	0 (0.0)
Hypersensitivity	0 (0.0)	1 (1.1)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	4 (4.5)	0 (0.0)	0 (0.0)
Acute respiratory distress syndrome	1 (1.1)	0 (0.0)	0 (0.0)
Cough	1 (1.1)	0 (0.0)	0 (0.0)
Dyspnoea	1 (1.1)	0 (0.0)	0 (0.0)
Productive cough	1 (1.1)	0 (0.0)	0 (0.0)
Pulmonary alveolar haemorrhage	1 (1.1)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (1.1)	0 (0.0)	0 (0.0)
Procedural headache	1 (1.1)	0 (0.0)	0 (0.0)

Note: *23.7 mg BID; †39.5 mg BID
Abbreviations: BID = twice daily; TEAE = treatment-emergent adverse event
Source: Otsuka 2018 (139)

Adverse events of special interest

Known adverse effects of CNIs, such as diabetes, kidney dysfunction, hyperkalaemia, and increased blood pressure, were evaluated in this study (73). Diabetes was reported in 1 patient each in the low-dose voclosporin and placebo treatment groups. Eight total patients withdrew from the study due to a >30% decrease in eGFR from baseline (placebo, n=2; low-dose voclosporin, n=3; high-dose voclosporin, n=3). No patient withdrew from the study due to hyperkalaemia, and mean blood pressure decreased from baseline and remained lower than baseline for the duration of the study for all treatment groups.

The remaining safety data from AURA-LV was presented in 7.1.1.3.1.8.

BLISS-LN

Table 123: Safety data from the BLISS-LN study

Event	Belimumab (N=224) n (%)	Placebo (N=224) n (%)
All adverse events†	214 (96)	211 (94)
All treatment-related adverse events†	123 (55)	119 (53)
Upper respiratory tract infection	26 (12)	24 (11)
Urinary tract infection	15 (7)	13 (6)
Herpes zoster	13 (6)	10 (4)
Bronchitis	11 (5)	10 (4)
Nasopharyngitis	8 (4)	8 (4)
Headache	9 (4)	5 (2)
Nausea	8 (4)	5 (2)
Rash	6 (3)	5 (2)
All serious adverse events†	58 (26)	67 (30)
All treatment-related serious adverse events†	23 (10)	25 (11)
Most common treatment-related serious adverse events, according to system organ class, occurring in ≥1% of patients in either group		
Infections and infestations	15 (7)	18 (8)
Respiratory, thoracic, and mediastinal disorders	5 (2)	1 (<1)
Blood and lymphatic system disorders	3 (1)	2 (1)
Nervous system disorders	0	3 (1)
Most common treatment-related serious adverse events occurring in ≥1% of patients in either group		

Pneumonia	3 (1)	4 (2)
Herpes zoster	3 (1)	2 (1)
Adverse events resulting in discontinuation of trial drug	29 (13)	29 (13)
Adverse events of special interest‡		
Cancer		
Excluding nonmelanoma skin cancer§	2 (1)	0
Including nonmelanoma skin cancer§	3 (1)	0
Postinfusion reactions¶	26 (12)	29 (13)
All infections of special interest, including opportunistic infections, herpes zoster, tuberculosis, and sepsis	30 (13)	34 (15)
Serious infections	9 (4)	7 (3)
Depression, suicide, or self-injury	11 (5)	16 (7)
C-SSRS suicidal ideation or behavior during trial intervention	7 (3)	12 (5)
Death	6 (3)	5 (2)
Fatal serious adverse events that began during trial intervention	4 (2)	3 (1)
Fatal serious adverse events that did not begin during trial intervention	2 (1)	2 (1)

Note: Only adverse events that occurred during the intervention period (from the first infusion to the first missed infusion or the last infusion, whichever was later, plus 28 days) are listed. Patients were counted once in each row and column for any adverse event that met the criterion. Adverse events were coded with the use of the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0. † This category includes all patients who had at least one event. Relatedness of the intervention to the event was determined by the site investigators. ‡ These events were determined according to a custom MedDRA query. § This category includes tumors of unspecified cancer that were adjudicated as cancer. ¶ These events were determined according to a custom MedDRA query or sponsor adjudication.

Abbreviations: C-SSRS = Columbia Suicide Severity Rating Scale; MedDRA = Medical Dictionary for Regulatory Activities

Appendix F Comparative analysis of efficacy and safety

The comparative efficacy and safety of voclosporin+MMF vs. MMF was described directly in the AURORA trials. The comparative analysis of efficacy and safety of voclosporin+MMF vs. belimumab+MMF/CYC is presented in Table 124.

Table 124: Bayesian meta-analysis comparing voclosporin+MMF vs. belimumab+MMF/CYC

Meta-analysis of studies comparing voclosporin + MMF to belimumab+MMF/CYC for patients with active LN											
				Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis*	Result used in the health economic analysis?
	Studies included in the analysis	Treatment	Relative to	Difference	CI	*P* value	Difference	CI	*P* value*		
Complete renal response	AURORA 1	VCS+MMF	MMF	N/A	N/A	N/A	OR: 2.66	1.84- 3.88	N/A	The ORs for the included studies were synthesized using fixed effects meta-analysis.	*Yes*
		BEL+MMF/CYC	MMF	N/A	N/A	N/A	OR: 1.75	1.14- 2.75	N/A		
		VCS+MMF	BEL+MMF/CYC	N/A	N/A	N/A	[redacted]	[redacted]			
Partial renal response	BLISS	VCS+MMF	MMF	N/A	N/A	N/A	OR: 1.25	0.80-1.96	N/A		
		BEL+MMF/CYC	MMF	N/A	N/A	N/A	OR: 1.03	0.62-1.7	N/A		
		VCS+MMF	BEL+MMF/CYC	N/A	N/A	N/A	[redacted]	[redacted]			

* p-Values are not calculated for Bayesian analyses as frequentist p-values are different from Bayesian p-values (216)

Abbreviations: BEL = belimumab; CI = confidence interval; CYC = cyclophosphamide; LN = lupus nephritis; MMF = mycophenolate mofetil; N/A = not applicable; OR = odds ratio; VCS = voclosporin

Appendix G Extrapolation

Transitions beyond the three-year study period of AURORA and AURORA 2, were applied from external literature and KOL experts. This is described in section 8.3. Below are described further details on the extrapolation of TTD.

For TTD, the model specifications for all five parametric models fitted to the data are presented in Table 125; with requested plots presented below in Figure 29 (graphing the parametric fits for MMF) and

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Figure 30 (graphing the parametric fits for voclosporin + MMF). It must be noted that parametric models are only used over the time period for which TTD data is available, so the fits are only compared to the KM period as there is no extrapolation of TTD used in the model.

Figure 29: TTD curves for all parametric models, MMF

Abbreviations: KM = Kaplan-Meier; MMF = mycophenolate mofetil; TTD = time to treatment discontinuation

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Figure 30: TTD curves for all parametric models, VCS+MMF

Abbreviations: KM = Kaplan-Meier; MMF = mycophenolate mofetil; TTD = time to treatment discontinuation; VCS = voclosporin

Justification of the choice of the log-logistic curve has been done systematically, as suggested in TSD 14[6].(217) Based on the log-cumulative hazard plots, Schoenfeld residuals and two PHs tests detailed in the CS, the hypothesis of PHs is not rejected, so dependent models are fit. Based on visual inspection, the exponential and Weibull models seem to have the worst fit and are therefore excluded from the further comparison. Additionally, when considering the MMF KM data, the log-normal curve seems to be underestimating the treatment discontinuation at 36 months and is therefore excluded from consideration. This leaves the log-logistic and generalised gamma parameterisations, which are difficult to distinguish from one another visually since they are primarily overlapping in both figures. Both the AIC and BIC for the log-logistic were more than 2 points below the respective AIC and BIC values for the generalised gamma, which indicates that the former is the best fitting model. Therefore, the log-logistic was used in the base case.

[6] TSD14: "The fit of alternative models should be assessed systematically. Log-cumulative hazard plots (or suitable residuals plots), AIC/BIC tests (or other suitable tests of internal validity), and clinical plausibility based upon expert judgement, external data, or biological reasoning should be presented and assessed. Visual inspection should not be relied upon, but where it is used it is important to include numbers at risk data in diagrams of Kaplan Meier curves, as this aids the review of model fit via visual inspection."

Table 125: Parameters and Covariance Matrices for each model

Modelled distribution	Results		Intercept	Treatment (Placebo)	MMF@Screening (No)	Scale	Shape	
Exponential	Fitted Model	Model Parameters	[redacted]					
	Covariance Matrix	Intercept						
		Treatment (Placebo)						
		MMF@Sceening (No)						
		Scale						
Weibull	Fitted Model	Model Parameters						
	Covariance Matrix	Intercept						
		Treatment (Placebo)						
		MMF@Sceening (No)						
		Scale						
Log-Logistic	Fitted Model	Model Parameters						
	Covariance Matrix	Intercept						
		Treatment (Placebo)						
		MMF@Sceening (No)						
		Scale						
Log-Normal	Fitted Model	Model Parameters						
	Covariance Matrix	Intercept						
		Treatment (Placebo)						
		MMF@Sceening (No)						
		Scale						
Generalised Gamma	Fitted Model	Model Parameters						
	Covariance Matrix	Intercept						
		Treatment (Placebo)						
		MMF@Sceening (No)						
		Scale						
		Shape						

Abbreviations: MMF = mycophenolate mofetil

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Appendix H - Literature search for HRQoL data

The literature search for HRQoL data was conducted as a part of an economic SLR, which was carried out to identify all relevant evidence regarding cost-effectiveness, budget impact, HRQoL and utilities for the treatment of LN. The review was conducted in line with the requirements set out by the DMC. The results of this SLR were used to develop cost-effectiveness and budget-impact models.

The eligibility of studies identified and included in the review was defined by the PICOS criteria outlined in Table 126. For a publication to be included, it must match criteria from each of the PICOS components. Studies that did not match the criteria in at least one component were excluded.

Table 126: PICOS for the economic SLR

PICOS	Inclusion criteria	Exclusion criteria
Patient population	Patients with lupus nephritis	Patients with systemic lupus erythematosus alone
Interventions	Any medical intervention Best supportive care	Complementary and alternative medicine
Comparators	Any medical intervention Best supportive care	No restrictions
Outcomes	Economic evaluations: (Incremental) costs (Incremental) (quality-adjusted) life years Incremental cost-effectiveness ratio Resource use and costs: Direct and indirect medical costs Direct and indirect non-medical costs Productivity losses Healthcare resource use e.g., hospitalization, number of ER visits Utilities/ HRQoL Generic measures, including but not limited to: Visual Analogue Scale (VAS), TTO, Standard gamble (SG), EQ-5D, SF-6D, SF-36, Health Utilities Index (HUI) Disease specific measures, including but not limited to: LupusPRO, SLE Symptom Checklist (SCC), Kidney Disease Quality of Life (KDQoL), and Kidney Symptom Questionnaire (KSQ)	
Study design	Cost-effectiveness studies Budget-impact analysis Prospective studies (interviews, questionnaires, cohort studies) Retrospective studies (hospital records, database studies, claims analyses)	Narrative reviews Systematic reviews* Preclinical studies Prognostic studies Case reports Commentaries and letters Consensus reports
Countries	No restriction	N/A

Language	All languages	N/A
PD date	No restrictions	N/A

*Up to 5 SLR publications were used for citation review

Abbreviations: ER = emergency room; EQ-5D = EuroQol Five Dimension; HRQoL = health-related quality of life; HUI = health utilities index; KDQoL = kidney disease quality of life; KSQ = kidney symptom questionnaire; N/A = not applicable; PD = publication date; PICO = patient intervention comparator outcome; PRO = patient reported outcome; SCC = SLE symptom checklist; SF-36 = 36-Item Short Form Survey; SF-6D = Short-Form Six-Dimension; SG = standard gamble; SLE = systemic lupus erythematosus; SLR = systematic literature review; TTO = time trade-off; VAS = visual analogue scale

Searches were carried out in Embase, Medline (In-Process), APA PsychINFO and EconLit using ProQuest. Additionally, NHSEED, HTAD and DARE databases were searched through the CRD database. Search hits are displayed in Table 127.

Table 127: Search hits for the economic SLR

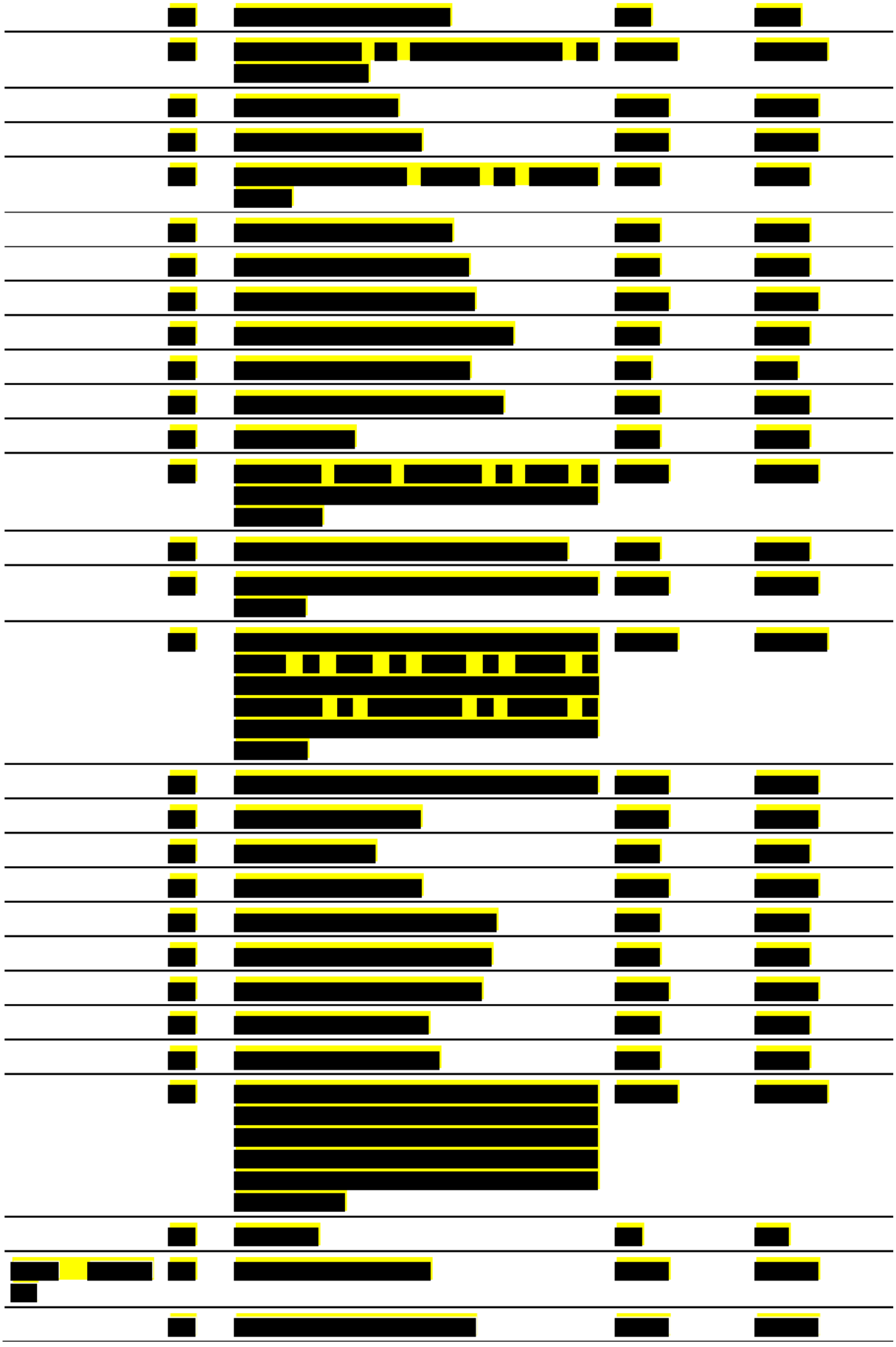
Search engine	Database	Parent SLR (01.06.2021)	First SLR update (04.02.2022)
ProQuest	Embase	1487	123
ProQuest	Medline (in-Process)		
ProQuest	APA PsycINFO		
ProQuest	EconLit		
CRD	Other reviews (DARE) Technology assessments (HTAD) Economic Evaluations (NHSEED)	30	0
Total		1517	123

Abbreviations: CRD = Centre for Review and Dissemination; DARE = Database of Abstracts of Reviews of Effects; HTAD = Health Technology Assessments Database; NHSEED =National Health Service Economic Evaluations Database; SLR = systematic literature review

The full search strategy of economic SLR including the filters for the cost-effectiveness, cost and resource use, and utilities are presented in Table 128. Records obtained at S127 and S131 levels were combined for a total of 123 unique records.

Table 128: Economic SLR search terms used in Embase, Medline (In-Process), APA Psychinfo, and EconLit (using ProQuest)

Topic	#	Terms	# Results	
			1 June 2021	4 February 2022
[redacted]				



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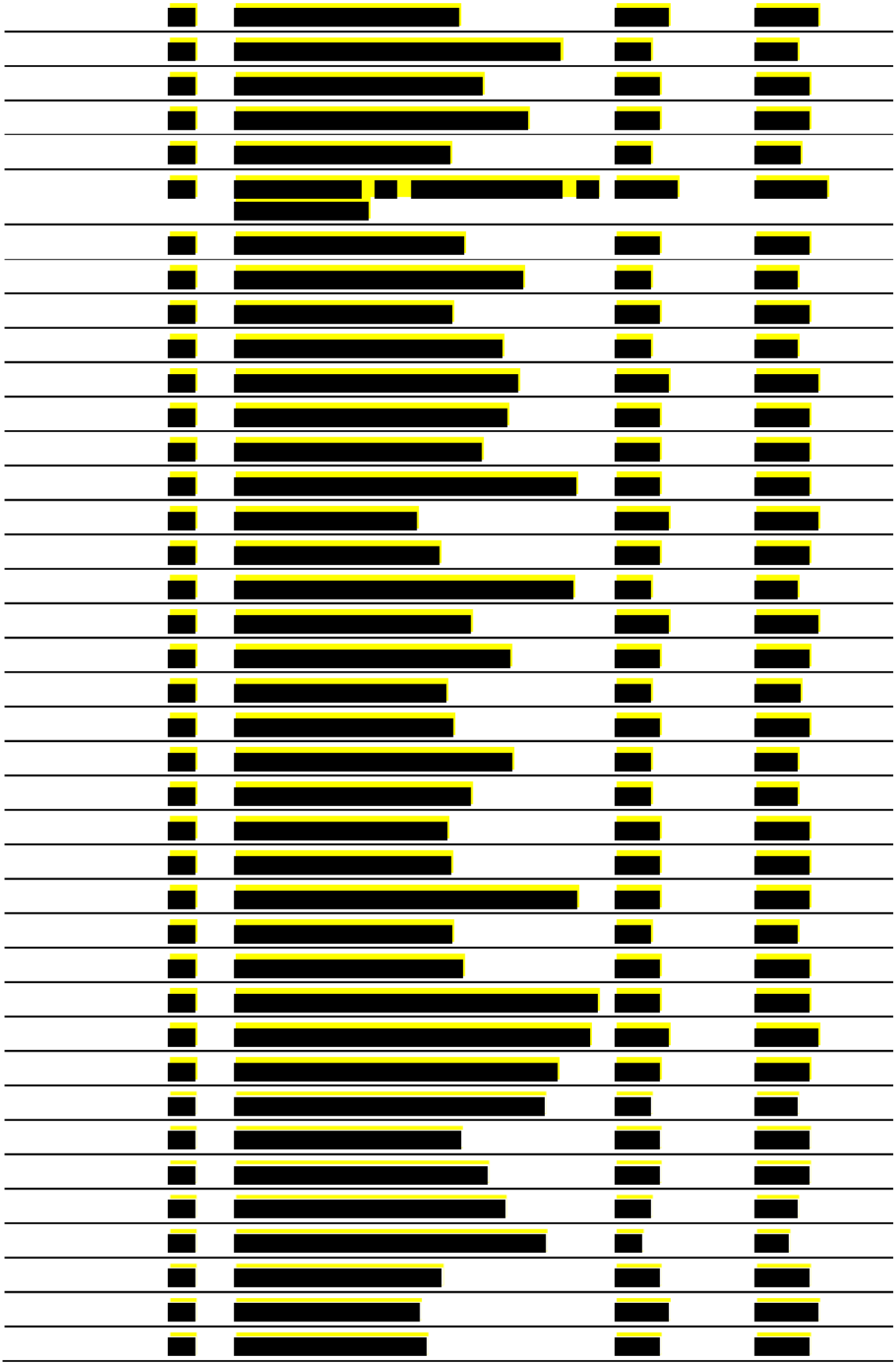

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Parent search date: 1 June 2021
First update search date: 4 February 2022
*Duplicates are removed from the search but included in the result count.
° Duplicates are removed from the search and the result count.
Note: records obtained at S127 and S131 levels were combined in EndNote. Duplicates were removed using EndNote and DistillerSR tools. A total of 123 unique records were identified.

Abbreviations: SLR = systematic literature review

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Searches for conference proceedings were independent of searches for peer-reviewed publications. Conference proceedings that were indexed in Embase were searched electronically, whereas those that were not indexed in Embase were hand-searched using "Lupus nephritis" search terms in whichever format is provided by the conference. Conference searches are outlined in Table 129.

Table 129: Conference searches for the economic SLR

Conference	2019	2020	2021	2022
International Congress on Systemic Lupus Erythematosus (LUPUS)	Embase	Embase	Embase	N/A
European Lupus Congress/Meeting (SLEuro)	Embase	Embase	Embase	N/A – meeting in Oct 2022
European Congress of Rheumatology (EULAR)	Embase	Embase	Embase	N/A – meeting in June 2022
World Congress of Nephrology (WCN)	Embase	Embase	Embase	Hand search
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	Embase	Embase	Embase	N/A – meeting in May 2022
European renal association - European dialysis and transplant association (Annual congress)	Hand search	Hand search	Hand search	N/A – meeting in June 2022

Abbreviations: EULAR = European Congress of Rheumatology; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; LUPUS = International Congress on Systemic Lupus Erythematosus; N/A = not applicable; SLEuro = European Lupus Congress/Meeting; SLR = systematic literature review; WCN = World Congress of Nephrology

The searches for full HTA review documents and submission dossiers were independent of that conducted for peer-reviewed publications. The NICE website was hand-searched using Lupus nephritis search terms in whichever format is provided by the website.

Study selection

Abstract/title review of all references was performed in double and independently by two reviewers. Any discrepancies were resolved by a third reviewer. The same process was applied for articles that are selected for full-text review. A PRISMA diagram provided in Figure 31 below illustrates how studies were included/excluded through both the parent and update searches.

Searches of conference proceedings were performed by a single reviewer and checked by a second reviewer. Conference abstracts which met the eligibility criteria were collated in a database and were matched up to include peer-reviewed publications where relevant to determine if any additional information was provided. If the data presented in a conference abstract was available from a peer-reviewed publication the conference abstract was excluded. If duplicate data was presented in multiple conference abstracts, only the most recent abstract was included.

Data extraction

After all relevant publications were identified and received, the relevant data were extracted from the articles. One researcher extracted the data, and the second researcher independently reviewed all data extracted for each endpoint. The second reviewer checked the data extraction file for accuracy and completeness, by checking if all data presented in the database corresponded directly with what was presented in the selected articles.

Quality assessment

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QA was performed for all publications except for conference proceedings, as there was insufficient methodological data to assess the study quality. Cost-effectiveness studies identified went through a QA using the Drummond checklist (218). The QA was conducted in conjunction with the data extraction and delivered in the same extraction sheet.

Published cost-effectiveness studies

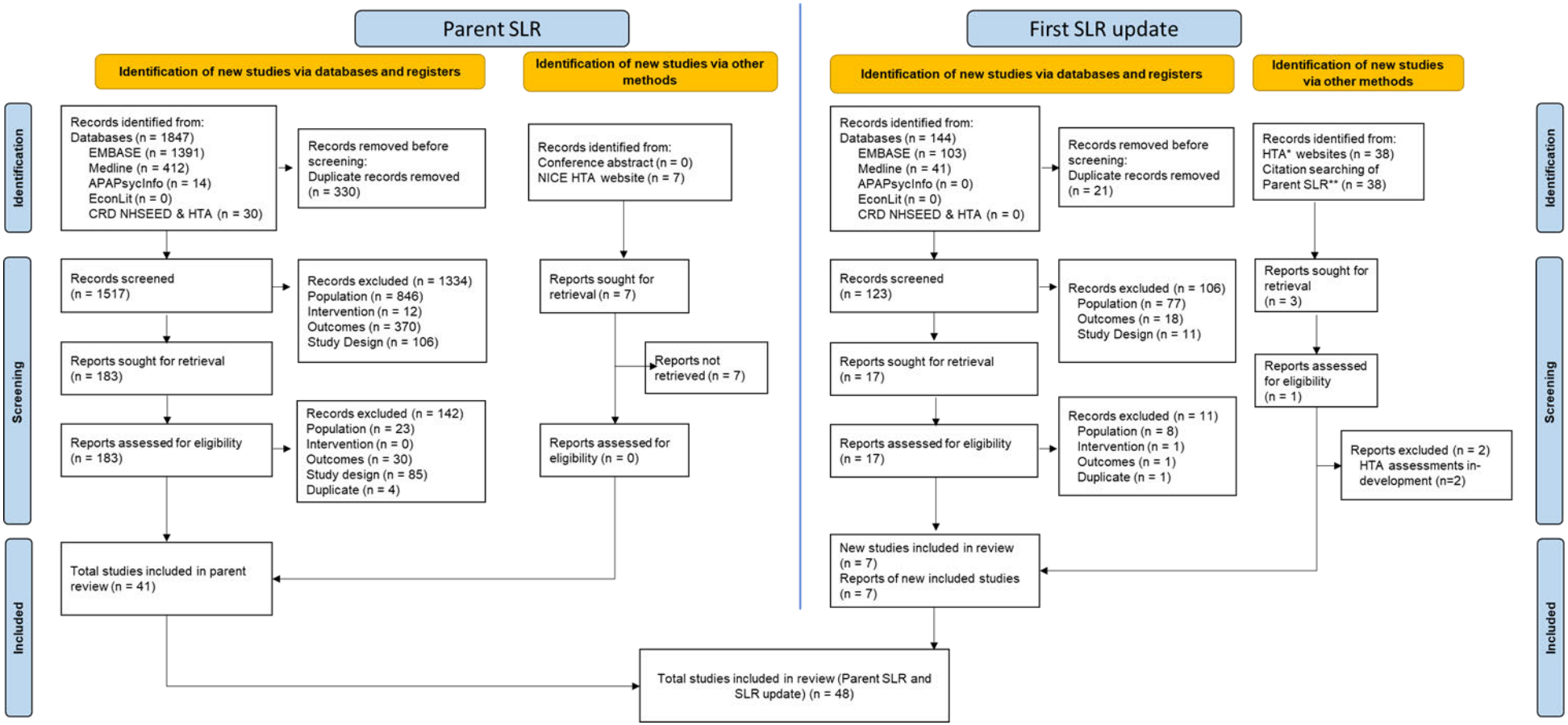
Search results

The initial parent SLR search was conducted on 01 June 2021. A total of 1,517 titles/abstracts were screened for eligibility. Subsequently, 1,334 records were excluded based on titles and abstracts. The remaining 183 publications were assessed for inclusion. Among the excluded publications (n=142), 23 exclusions were based on population (11 of which referred to publications looking at SLE population in general), 30 on outcomes, 85 on study design, and four were duplicates. In total, 41 publications were identified and extracted. Five publications reported on economic evaluations, 21 on healthcare cost and resource use and 15 on HRQoL/utilities. One publication reported both HRQoL and cost and resource use together with cost-effectiveness analysis.(143) One presented cost and resource use data together with a cost-effectiveness analysis.(219) The review did not identify any relevant health technology assessment.

An update search to the SLR was conducted on 04 February 2022. In total, 123 titles/abstracts were screened for eligibility. Subsequently, 106 records were excluded based on titles and abstracts. The remaining 17 publications were assessed for inclusion. Among the excluded publications (n=11), eight exclusions were based on population, one each on intervention and outcomes, and one was a duplicate. In total, seven publications were identified and extracted: six publications from the SLR update(220-225) and one after crosschecking the list of exclusions from the parent SLR (226). Of the seven publications, two reported on economic evaluations, four on healthcare cost and resource utilization and one on HRQoL.

After the parent and update SLRs, a total of 48 studies were included and extracted for this economic SLR. The overview of the aggregated search results can be found in Figure 31.

Figure 31: Economic SLR PRISMA for parent and updated SLR searches



*The search strategy was updated for considering the SLE patients with 'renal damage' or 'renal activity', therefore citations excluded in parent SLR were searched again for additional studies

**Included European HTA agencies such as The National Institute for Health and Care Excellence (NICE), Agenzia Italiana del Farmaco (AIFA) Gemainsamer Bun-desausschuss (G-BA), Haute Autorie de Sante (HAS), Norwegian Medicines Agency (NoMA), Scottish Medicines Consortium (SMC), Tandvårds-och Läkemedelsförmånsverket (TLV) and Zorginstituut Nederland (ZiNL)

Abbreviations: HTA = health technology assessment; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLE = systemic lupus erythematosus; SLR = systematic literature review

Published health-related quality of life and utility studies

Among the 48 verified studies, 17 reported QoL data, which can be found in Table 130. Overall, interventions and comparators varied between studies or were not reported due to the nature of the study design. In Daleboudt et al. (2011) (227), two distinct treatment protocols were evaluated. Cyclophosphamide together with prednisone was compared to AZA methylprednisolone/prednisone or MMF in two studies (228, 229). Furthermore, patients in Arends et al. (2014) received cyclophosphamide and prednisone followed by MMF and prednisone and subsequently AZA and prednisone. Patients in Kim et al. (2018) were on various treatments, i.e., hydrocortisone, corticosteroids, methotrexate, AZA, MMF and tacrolimus. Hydroxychloroquine or prednisone were also given in Rogers et al. (2019). Bandhan et al. (2021) compared low-dose oral prednisolone to high-dose oral prednisolone. Lastly, one study reported treatments as “Standard of Care” (19).

Most publications were prospective studies (n=7), including two RCTs and a single-armed trial. Furthermore, seven observational studies and three retrospective studies were identified.

Around a quarter of the studies were conducted in the Netherlands (n=4) and two in Egypt. Other countries included the US, Colombia, Canada, Hong Kong, India, Korea, and Bangladesh. Three studies included populations from various continents. It was unclear where the study of Rogers et al. (2019) was conducted, though it should be noted that it was a conference abstract.

Two of the studies with an international LN stud population also had the largest sample size: 1,078 and 566, respectively (19, 230). Aside from these and one RCT (221), all LN sample sizes were below 100. The smallest LN population size was reported in Tse et al. (2006) with 12 patients (228).

Although inclusion criteria varied across studies, a total of eleven studies required the fulfilment of the Criteria of Classification of the ACR. Some of these studies specified further that at least four out of the 11 criteria must have been met. Moreover, two studies demanded the satisfaction of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (231, 232). For LN specifically, few studies reported criteria. Three studies required biopsy-proven LN (19, 229, 233) or alternatively a diagnosis of LN identified by the renal disorder variable of the American College Of Rheumatology (ACR) classification criteria in Hanly et al. (2016). In one RCT, patients were eligible if they had proteinuria ≥500 mg/24 h and either had high titer of anti-dsDNA and low complements levels (C3 [<0.9 g/L] and/or C4 [<0.1 g/L]) or histology suggestive of class III or IV by renal biopsy (221). In Vu et al. (1999), patients were considered to have nephritis if they had ever manifested the features listed in the 7th criterion for the diagnosis of SLE: persistent proteinuria of at least 0.5g/24h or >3+ by dipstick, or cellular casts in the urine. Only four studies mentioned exclusion criteria, which comprised e.g., disease flares, active infections, previous malignancies, pregnancy, refusal of reliable contraceptives, known allergies for study medications, failure to complete questionnaires, impaired liver function, or patients requiring dialysis (221, 228, 233, 234).

Table 130: Overview of studies reporting HRQoL

First Author, Year	Intervention	Comparator	Study Design	Country	Sample Size (N)	Inclusion Criteria	Exclusion Criteria
Sliem, 2010	N/A	N/A	Observational study	Egypt	59	All patients who fulfilled the Criteria of Classification of the ACR for diagnosis of SLE	NR
Aroca Martínez, 2017	NR	NR	Retrospective study	Colombia	NR	Patients with LN	NR
Jolly, 2018	N/A	N/A	Retrospective study	USA, Canada, Mexico, Argentina, Turkey, The Philippines, China	1078	SLE patients meeting 4 out of 11 ACR classification criteria	NR
Daleboudt, 201	NIH treatment protocol	Euro-Lupus treatment protocol	Prospective study	The Netherlands	32	Diagnosis of proliferative LN and a received treatment according to either the NIH or the Euro-Lupus protocol	NR
Grootscholten, 2003	N/A	N/A	Observational study	Netherlands	17	Consecutive lupus patients with stable disease, not involved in the initial development of the SLE Symptom Checklist (SSC) treated in five university outpatient clinics for nephrology or rheumatology; all patients fulfilled at least four ACR criteria for SLE	NR

Grootscholten, 2007	CYC/ prednisone	AZA/ methylprednisolone/ prednisone	RCT, Open-label	Netherlands	47	Presence of ≥4 ACR criteria for SLE, age 18 to 60 years, creatinine clearance (Cockcroft-Gault) >25 ml/min, and biopsy-proven proliferative LN. Patients with WHO class IV LN were eligible when they had signs of active nephritis or a deterioration of renal function; patients with WHO class III LN had to meet both criteria	NR
Hanly, 2004	N/A	N/A	Observational study	Canada	36	All patients fulfilled the ACR criteria for SLE. Nephropathy was defined as the presence of any of the following indicators: proteinuria >500mg/day, cellular casts, glomerular filtration <50%, abnormalities on renal biopsy, or ESRD treated by transplant or dialysis.	NR
Tse, 2006	Prednisolone and oral CYC	MMF	Prospective study	Hong Kong, China	12	The main inclusion criterion was a history of not fewer than two episodes of diffuse proliferative LN, amongst which one episode was treated with CYC-based induction immunosuppression and the other treated with MMF-based immunosuppression. In addition, the two studied episodes must be separated by no less than nine months	Patients currently experiencing a disease flare, as indicated by clinical manifestations and/or a dose of prednisolone above 10mg daily
Arends, 2014	IV CYC + oral prednisone followed by MMF + oral prednisone followed by AZA + oral prednisone	N/A	Single-arm trial	Netherlands	71	All patients were aged between 18 and 70 years, fulfilled ≥4 ACR criteria for SLE and had active proliferative LN, defined as biopsy-proven LN (WHO class III or IV, in combination with class V in seven patients; renal biopsy had to be performed less than one year before inclusion), active urinary sediment (>5	Patients with active infection, malignancy <5 years before inclusion (except basal cell carcinoma), pregnancy or refusal to use reliable contraceptives during the first 2.5 years of treatment, or known allergy for the study medication

						dysmorphic erythrocytes per high-power field and/or presence of cellular casts) and proteinuria > 0.5 g/day	
Hanly, 2016	Standard of care	NR	Prospective study	USA, Europe, Canada, Mexico, Asia	566	Patients fulfilled the ACR classification criteria for SLE; Nephritis was identified by the renal disorder variable of the ACR classification criteria and/or biopsy evidence of nephritis as per the ISN/RPS criteria	NR
Muhammed, 2018	NR	NR	Prospective study	India	42	Patients satisfied the SLICC Classification 2012 criteria and were 18 years of age or older	NR
Kim, 2018	Hydroxychloroquine, Corticosteroid, Methotrexate, AZA, MMF, Tacrolismus	NR	Retrospective study	Korea	93	Patients with SLE who met the 1982 revised and 1997 updated ACR classification criteria for SLE	Failure to complete the questionnaire on self-reported measured physical activity
Rogers, 2019	Hydroxychloroquine or Prednisone	NR	Observational study	NR	67	SLE patients	NR
Gaballah, 2019	NR	NR	Observational study	Egypt	42	Patients who met the SLICC SLE classification criteria were included	NR
Vu, 1999	Hydroxychloroquine, Prednisone	NR	Observational study	USA	104	All patients fulfilled the 1982 revised criteria of the ACR for the diagnosis of SLE. Two groups of patients were studied: (l) patients with ESRD due to lupus nephritis who were receiving longterm hemodialysis or peritoneal dialysis, and patients who did not require any form of renal replacement therapy. Patients were considered to have nephritis if they had ever	NR

						manifested the features listed in the 7th criterion for the diagnosis of SLE: (a) persistent proteinuria of at least 0.5 g/24 h or> 3+ by dipstick, or (b) cellular casts in the urine.	
Clarke, 2008	NR	NR	Observational study	Canada, USA, UK	81	Patients fulfilling the ACR revised criteria for SLE.	NR
Bandhan, 2021	Methylprednisolone + **low-dose oral prednisolone** + CYC + hydroxychloroquine + angiotensin receptor blocker	Methylprednisolone + **high-dose oral prednisolone** + CYC + hydroxychloroquine + angiotensin receptor blocker	RCT	Bangladesh	170	Patients who fulfilled the ACR criteria for SLE. The LN cases were diagnosed if proteinuria ≥500 mg/24 h and either had high titer of anti-dsDNA (>75 U/mL) and low complements level (C3 [<0.9 g/L] and/or C4 [<0.1 g/L]) or on renal biopsy: histology suggestive of class III or IV LN (ISN/RPS 2003 classification of LN).19 Adults (≥18 years) of both genders and female patients of childbearing potential who were in a reliable method of contraception (preferably a barrier method) signed the informed written consent and were enrolled.	Pregnant or lactating women, patients willing to have treatment with MMF rather than CYC, took CYC within the prior 4 weeks at screening, took ≥15 mg of prednisolone (or equivalent) per day for a period of ≥10 days during the previous month, renal thrombotic microangiopathy, eGFR ≤45 mL/min/1.73 m^2, dialysis-dependent patients, requiring renal dialysis, a previous/ planned kidney transplant, altered liver function, malignancy, lymphoproliferative disease or previous total lymphoid irradiation, active bleeding disorders, active tuberculosis, diabetes mellitus, hypersensitivity or contraindications to CYC, corticosteroids or any components of these drug products, any overlap autoimmune conditions which may affect the study assessments or outcomes.

Abbreviations: AZA = azathioprine; ACR = American College of Rheumatology; CYC = cyclophosphamide; ESRD = end-stage renal disease; HRQoL = Health-related Quality of life; ISN/RPS = International Society of Nephrology and Renal Pathology Society; IV = intravenous; LN = lupus nephritis; MMF = mycophenolate mofetil; N/A = not applicable; NIH = National Institutes of Health; NR = not reported; RCT = randomised controlled trial; SLE = systemic lupus erythematosus; SLICC = Systemic Lupus International Collaborating Clinics; SSC = SLE symptom checklist; WHO = World Health Organization

Population characteristics

Population characteristics per study and study arm are shown in Table 131.

No patient characteristics have been disclosed in Aroca Martínez et al. 2017 (235), or characteristics contained data of non-LN patients as in Grootscholten et al. 2003 (236), Hanly et al. 2004 (237) and Gaballah et al. 2019 (232). These studies are therefore not in Table 131.

The average patient age was between 28 and 41 years. The median age was given by two studies, which were 31 to 35 years.

The majority of the patients were female in all studies with available data. The highest proportion of women with 100% was reported in Clarke et al. 2008 (226) in the SLICC renal damage 2 and 3 arms, the lowest proportion with 62.5% was reported in the NIH treatment protocol arm in Daleboudt et al. 2011 (227).

Patient ethnicity was disclosed in five studies. Most patients in Grootscholten et al. 2007 (229) and Arends et al. 2014 (233), were of Caucasian ethnicity (87% and 75%, respectively). In Tse et al. 2006 (228), all patients were Asian. The greatest diversity was reported in Hanly et al. 2016 (19) with a third of the population being Caucasian, a fifth Asian and a quarter Black. In addition, 17.7% of the patients were Hispanic and 4.2% of another, not further specified ethnicity. In Vu et al. 1999 (238), approximately three-quarters of the patients were Hispanic, 10-23% Black, 0-12% Caucasian, and 1-2% were of another ethnicity.

The SLEDAI or SLEDAI-2K Index was reported in seven studies. The indices showed differences in the individual treatment arms. Two studies assessing active or non-active LN patients showed similar results with a mean of 9.4 and 9.1 for active LN patients and 2.2 and 3.2 for non-active LN patients or LN in remission. The highest mean SLEDAI Index was 17 (233), and the highest median was 22 in the cyclophosphamide/prednisone arm in Grootscholten et al. 2007 (229). Furthermore, SLEDAI-2K indices were reported in Hanly et al. 2016 with a mean of 8.5 or 3.6 without the renal variable (19) and in Kim et al. 2018 with a median of 47 (234).

In the five studies reporting average disease duration values varied greatly, ranging from 0.5 to 12.6 years. Likewise, median disease duration in three other studies ranged from 1.9 months until eight years.

Although data extraction variables included previous therapy lines and comorbidity index values, no data could be identified for HRQoL studies.

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Table 131: Population characteristics

First author, Year	Treatment arm/ group	Sample size (n)	Age	Female (%)	Ethnicity (%)	SLEDAI Index	Disease duration (years)
Sliem, 2010	SLE patients with nephritis	59	28.6 (NR); range: 16-42	94.9	NR	SLEDAI: mild: 51%; moderate to severe: 27.2%	5.6 (3.4)
Jolly, 2018	LN patients	539	40.3 (13.1)	NR	NR	SLEDAI: 4.0 (4.9)	NR
	Non-Active LN patients	410	41.1 (13.1)	NR	NR	SLEDAI: 2.2 (2.7)	NR
	Active LN patients	129	37.9 (12.9)	NR	NR	SLEDAI: 9.4 (5.9)	NR
Daleboudt, 2011	LN patients NIH treatment protocol	16	36.8 (10.3)	62.5	NR	NR	12.4 (4.9)
	LN patients Euro-Lupus treatment protocol	16	33.8 (10.7)	87.5	NR	NR	9.8 (4.8)
	LN patients overall	32	35.5 (10.4)	75	NR	NR	11.1 (5)
Grootscholten, 2007	Overall LN patients	47	Median (IQR): 31 (25-40)	89	Caucasian: 87	SLEDAI: median (IQR): 21 (17-26)	Median (IQR): 8 (range: 1-66)
	LN patients on CYC/prednisone	27	Median (IQR): 28 (23-35)	NR	Caucasian: 85	SLEDAI: median (IQR): 22 (17-27)	NR
	LN patients on AZA/methylprednisolone/ prednisone	20	Median (IQR): 33 (29-43)	NR	Caucasian: 90	SLEDAI: median (IQR): 20 (16-22)	NR
Tse, 2006	LN patients	12	NR	83.3	Asian: 100	NR	NR
Arends, 2014	IV CYC + oral prednisone followed by MMF + oral prednisone followed by AZA + oral prednisone	71	36.6 (11.7)	77	Caucasian: 75; Black: 9.86; Asian: 15.49	SLEDAI: 17 (6)	Median (Range): 0.2 (0-16)
Hanly, 2016	LN patients	566	31.3 (11.9)	84.3	Caucasian: 32.2; Black: 21.4; Asian: 17.7; Hispanic: 24.4; Non-Hispanic: NR; Other: 4.2	SLEDAI-2K: 8.5 (6.7); SLEDAI-2K without renal variable: 3.6 (3.8)	0.5 (0.3)

Muhammed, 2018	LN patients (No Neuropsychiatric SLE (NPSLE))	42	NR	NR	NR	NR	NR
Kim, 2018	LN patients	93	Median (IQR): 35 (28-44)	91.4	NR	SLEDAI-2K: median (IQR): 4.0 (0.0–6.0)	Median (IQR) in months: 1.9 (0.2–6.1)
Rogers, 2019	Active nephritis	34	NR	NR	NR	SLEDAI: 9.1 (4.3)	NR
	Nephritis in Remission	33	NR	NR	NR	SLEDAI: 3.2 (2.2)	NR
Vu, 1999	ESRD	22	36.1 (10)	95.5	Caucasian: 0; Black: 22.7; Hispanic: 72.2; Other: 1.6	SLEDAI: 3.5 (4.7)	11.5 (6)
	Preserved Renal Function	82	38.7 (10.2)	86.6	Caucasian: 12.2; Black: 10.1; Hispanic: 75.6; Other: 1.2	SLEDAI: 5.2 (4.7)	6.6 (6.2)
Clarke, 2008	SLICC renal damage = 1	54	39.1 (12.8)	88.7	NR	NR	10.6 (5.8)
	SLICC renal damage = 2	15	37.8 (8.9)	100	NR	NR	12.6 (7.3)
	SLICC renal damage = 3	12	37.8 (7.8)	100	NR	NR	15.8 (4.7)
Bandhan, 2021	Low-dose group	85	26.56 (6.41)	87.5	NR	NR	1.81 (2.04)
	High-dose group	85	30.25 (8.63)	81.2	NR	NR	3.5 (4.47)

Values is mean (SD) unless otherwise specified.
Abbreviations: AZA = azathioprine; ESRD = end-stage renal disease; CYC = cyclophosphamide; IV = intravenous; IQR = interquartile range; LN = lupus nephritis; MMF = mycophenolate mofetil; NIH = National Institutes of Health; NPSLE = neuropsychiatric SLE; NR = not reported; SD = standard deviation; SLE = systemic lupus erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SLICC = Systemic Lupus International Collaborating Clinics

Appendix I Mapping of HRQoL data

As the AURORA 1 and 2 studies did not collect EQ-5D data, the SF-36 data were mapped into EQ-5D-3L data. However, this excluded the possibility of applying Danish-specific preference weights, and therefore UK weights are used. The mapping of SF-36 data to EQ-5D-3L data was presented in section 8.4.1.2. Below is summarised the SF-36 domains and the mapping into EQ-5D-3L.

Summary of SF-36 domains

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Summary of SF-36 mapped to EQ-5D scores

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Summary of MMRM Analysis for AURORA 1

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SF-36 results from the integrated studies: AURORA 1 and AURORA 2 and mapped EQ-5D

Appendix J Probabilistic sensitivity analyses

The table below has been copied directly from the model, in line with the guidelines. The inputs sheet in the model lists all of the assumptions for the probabilistic analysis.

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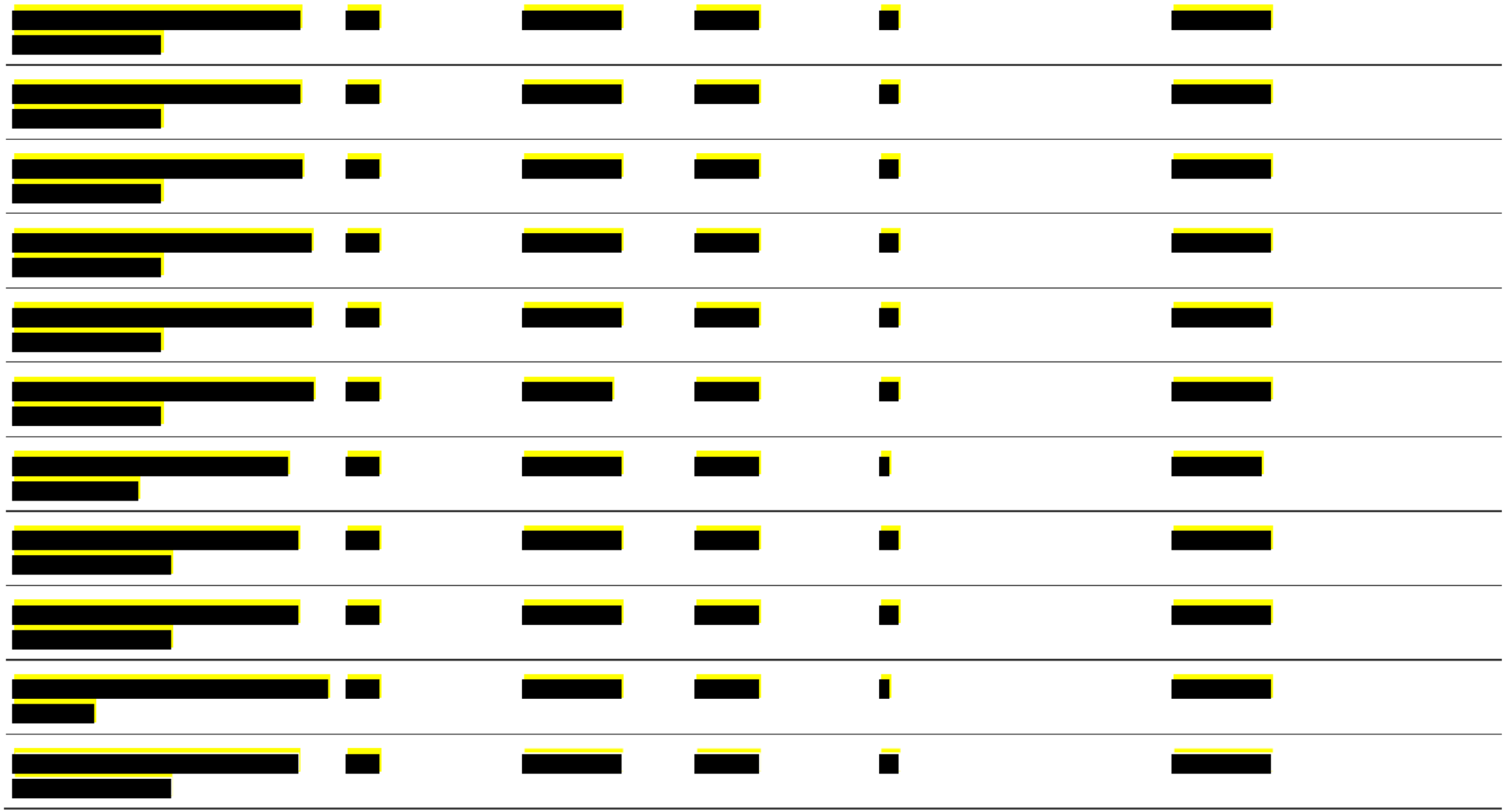

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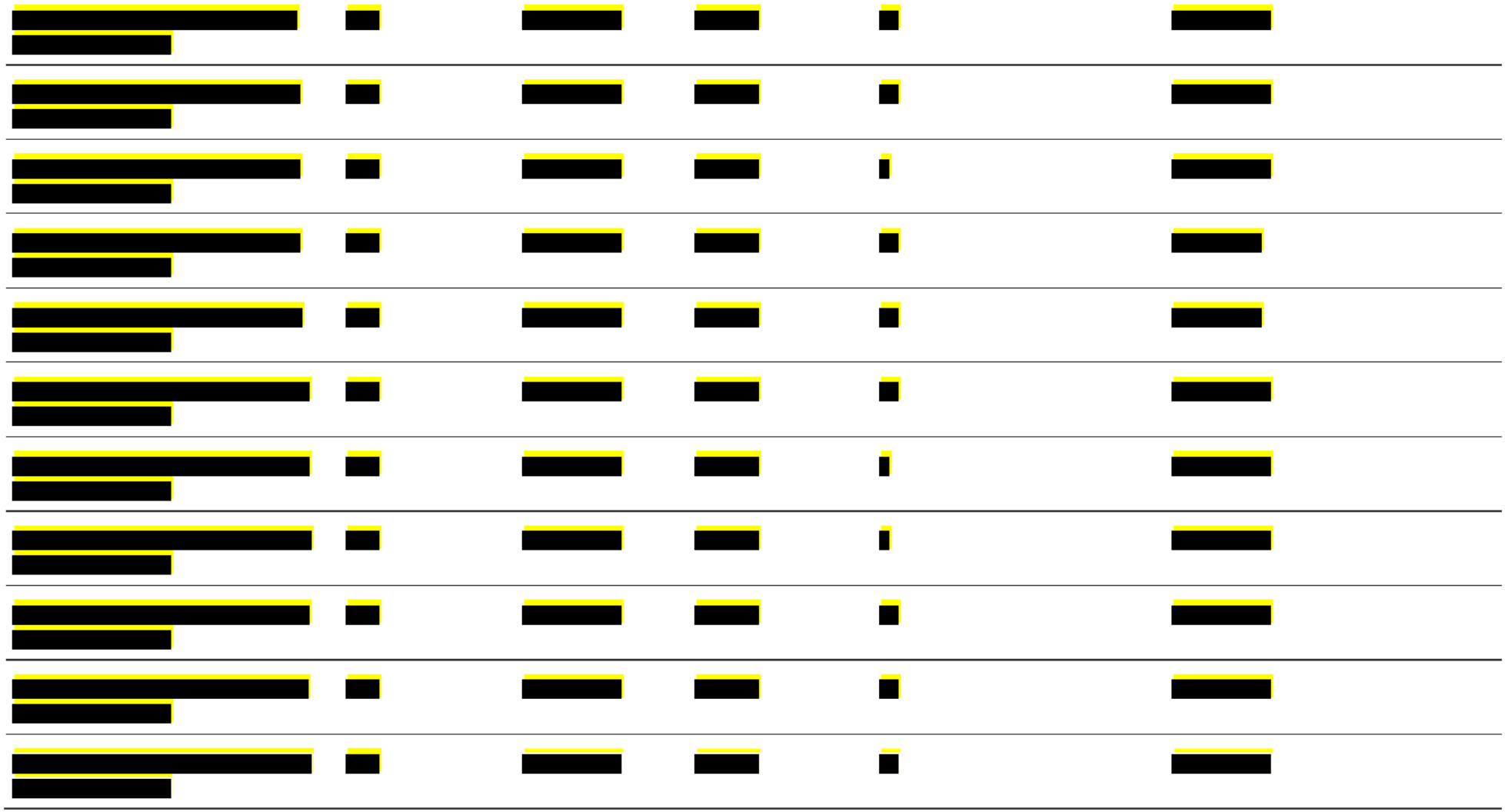

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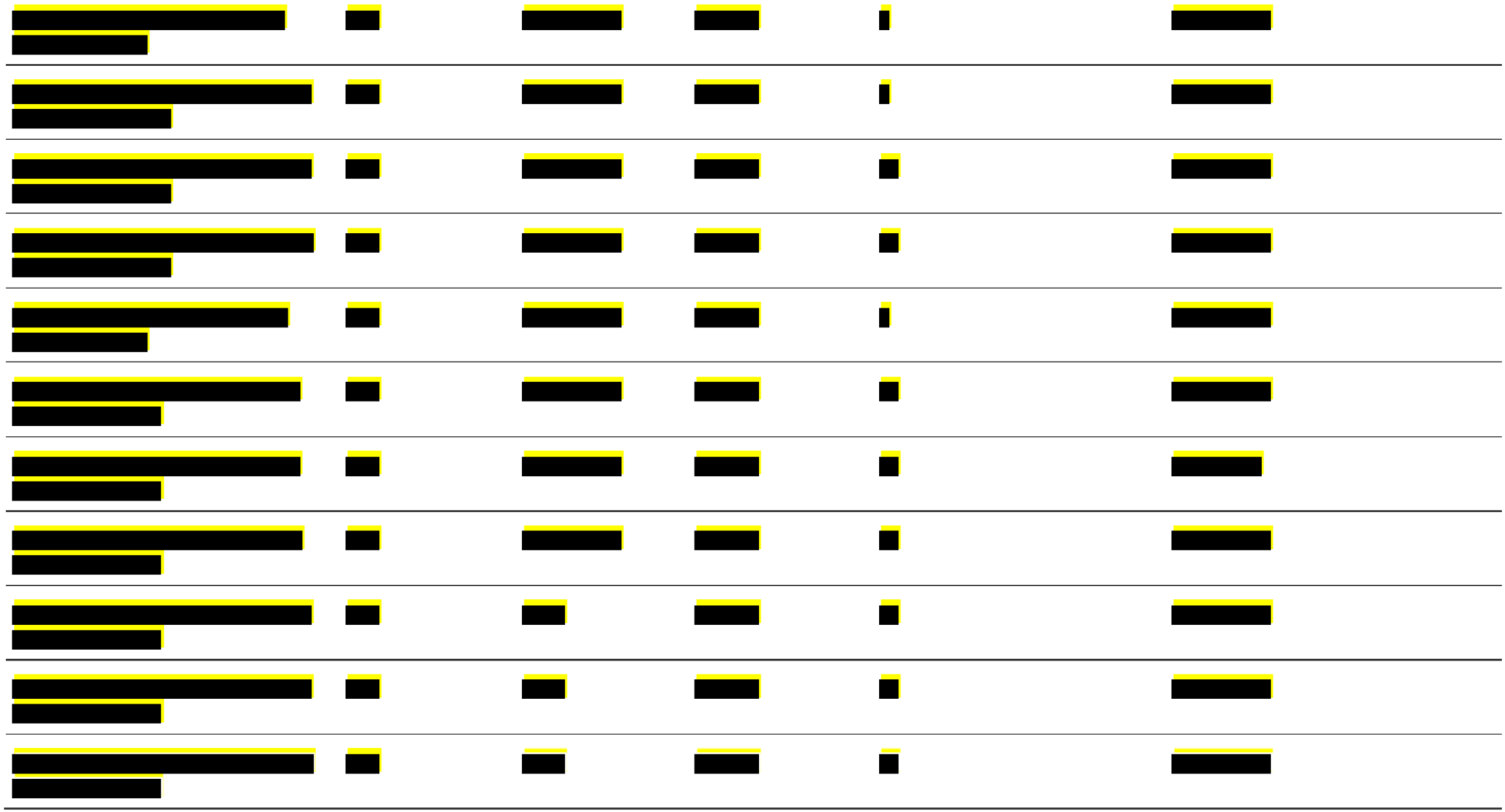

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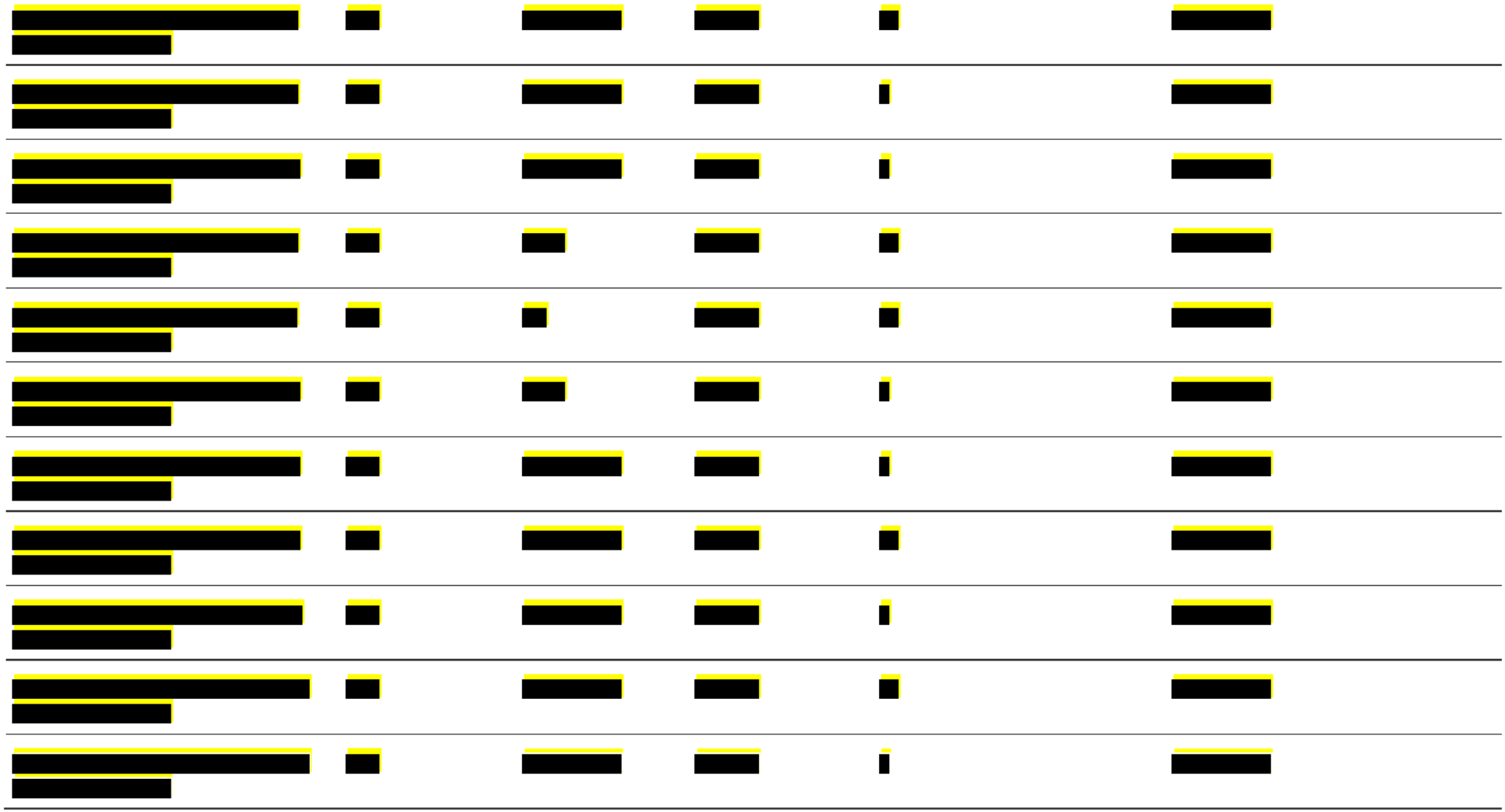

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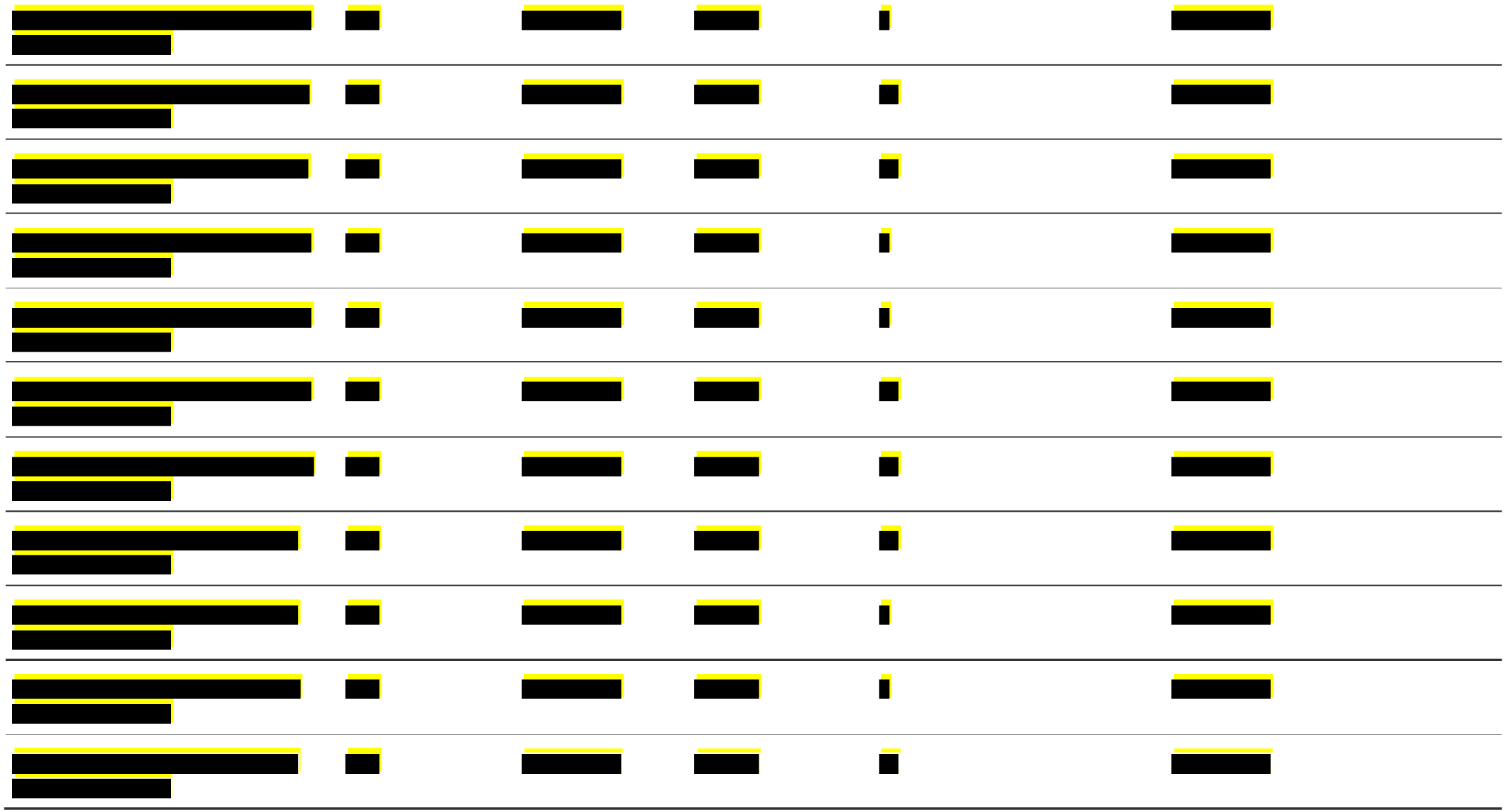

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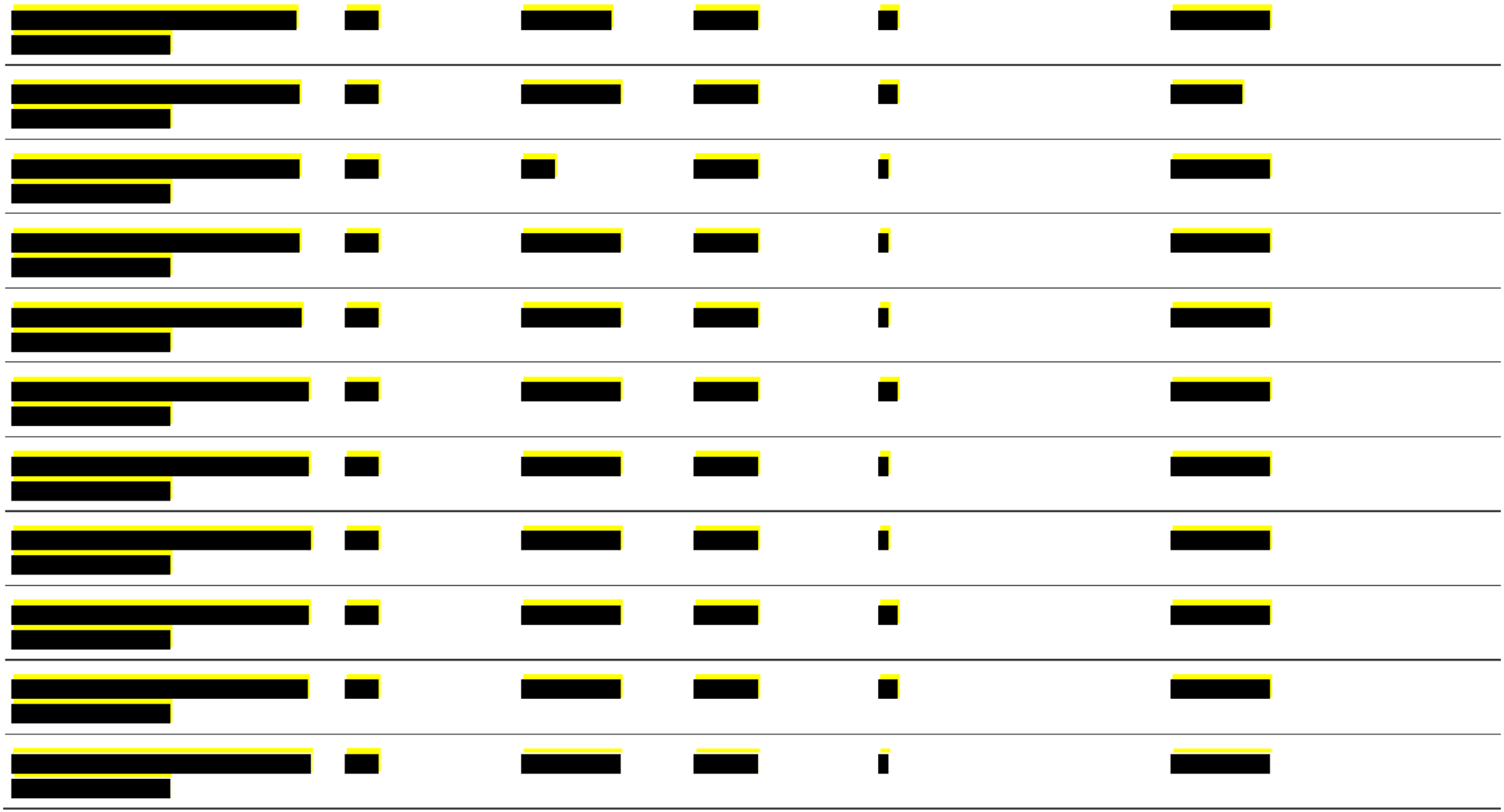

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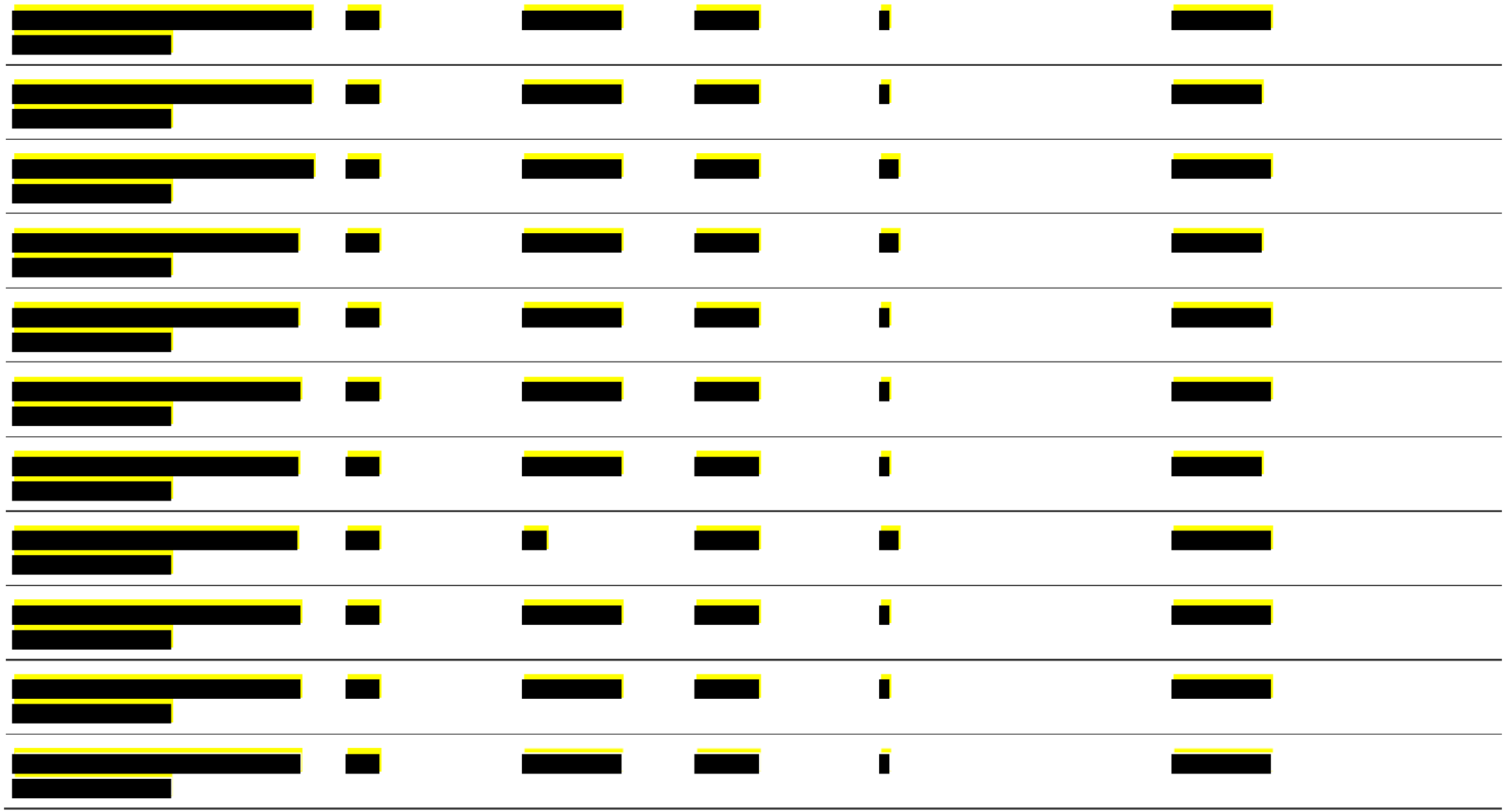

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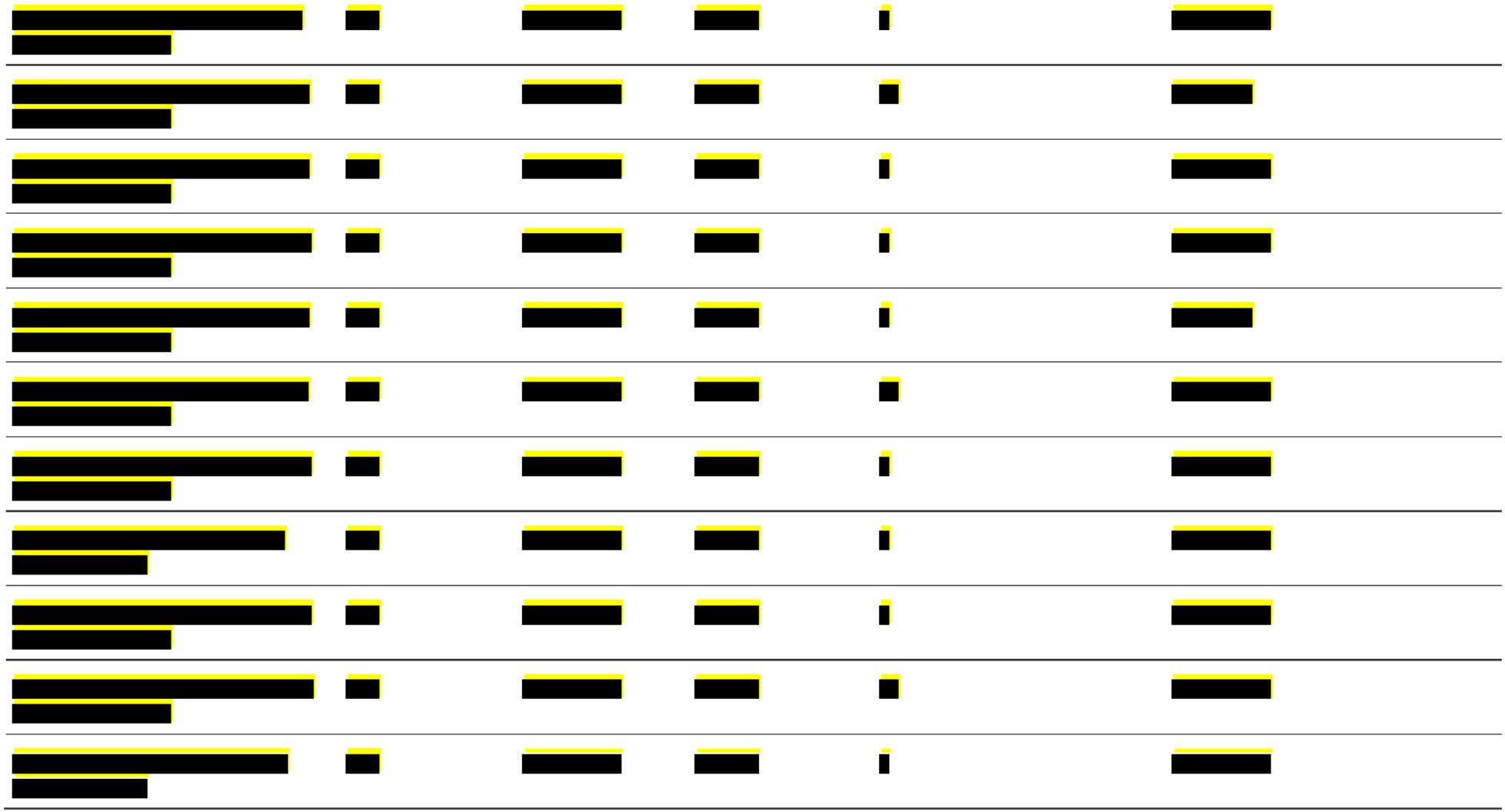

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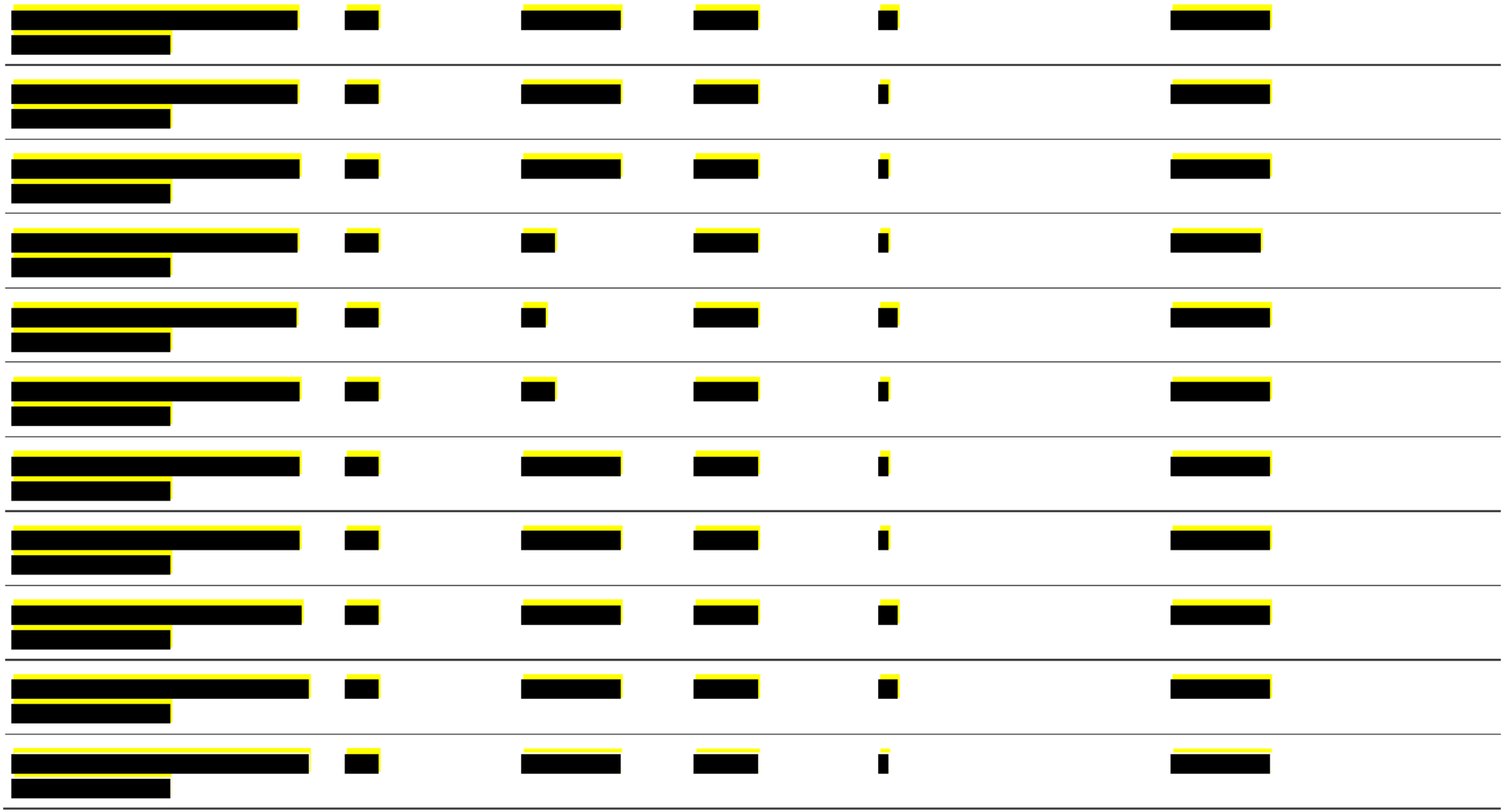

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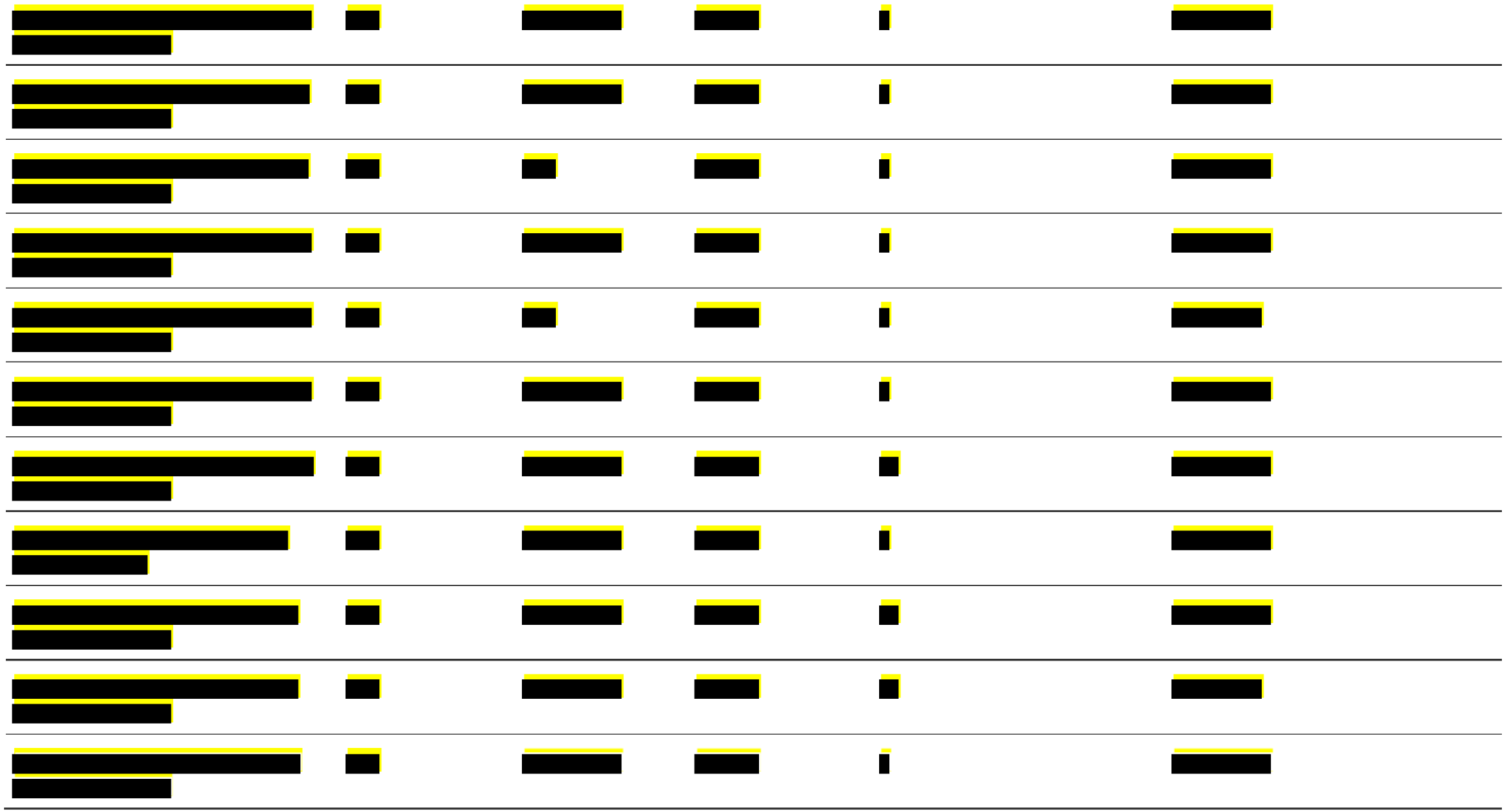

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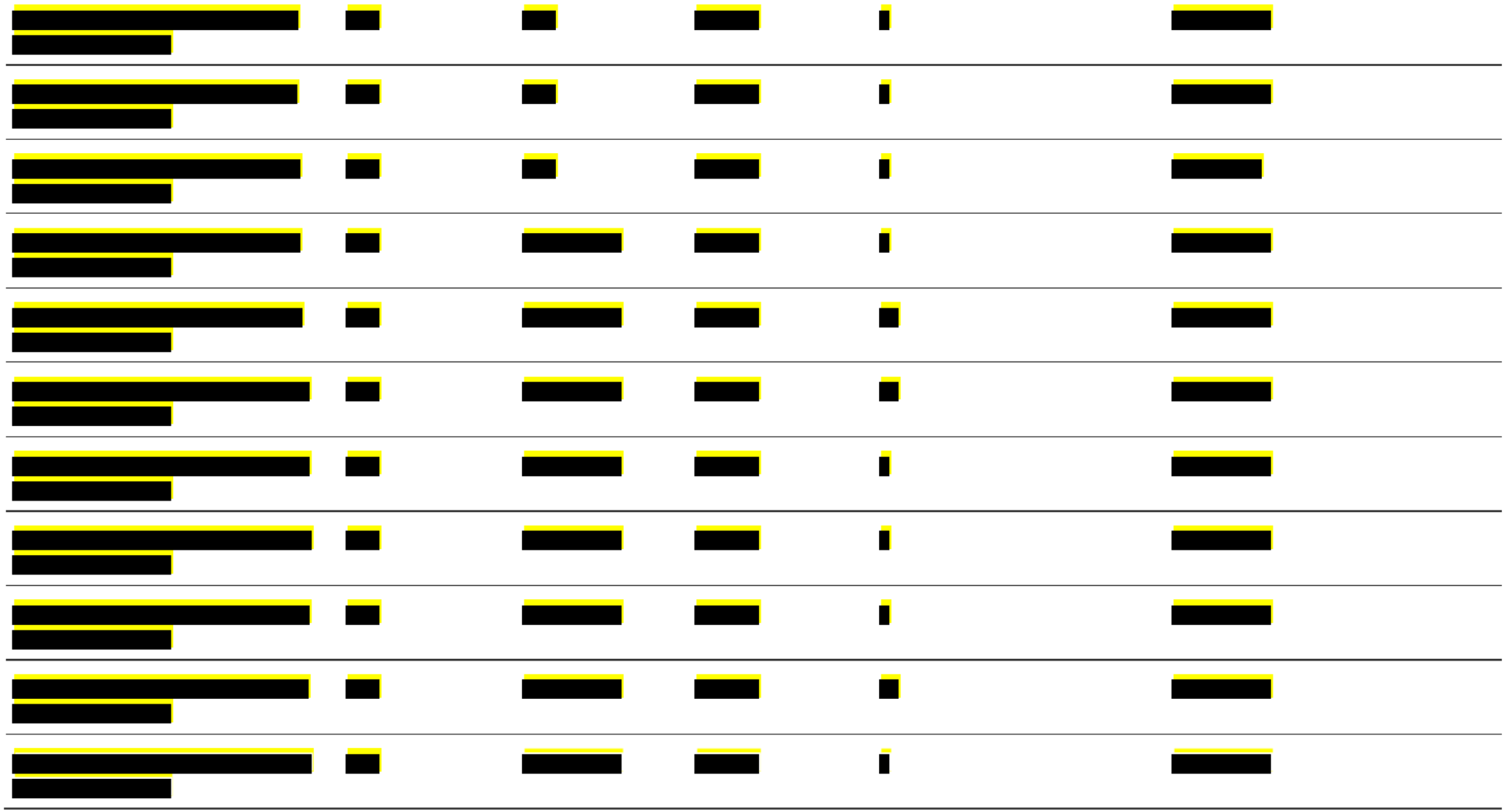

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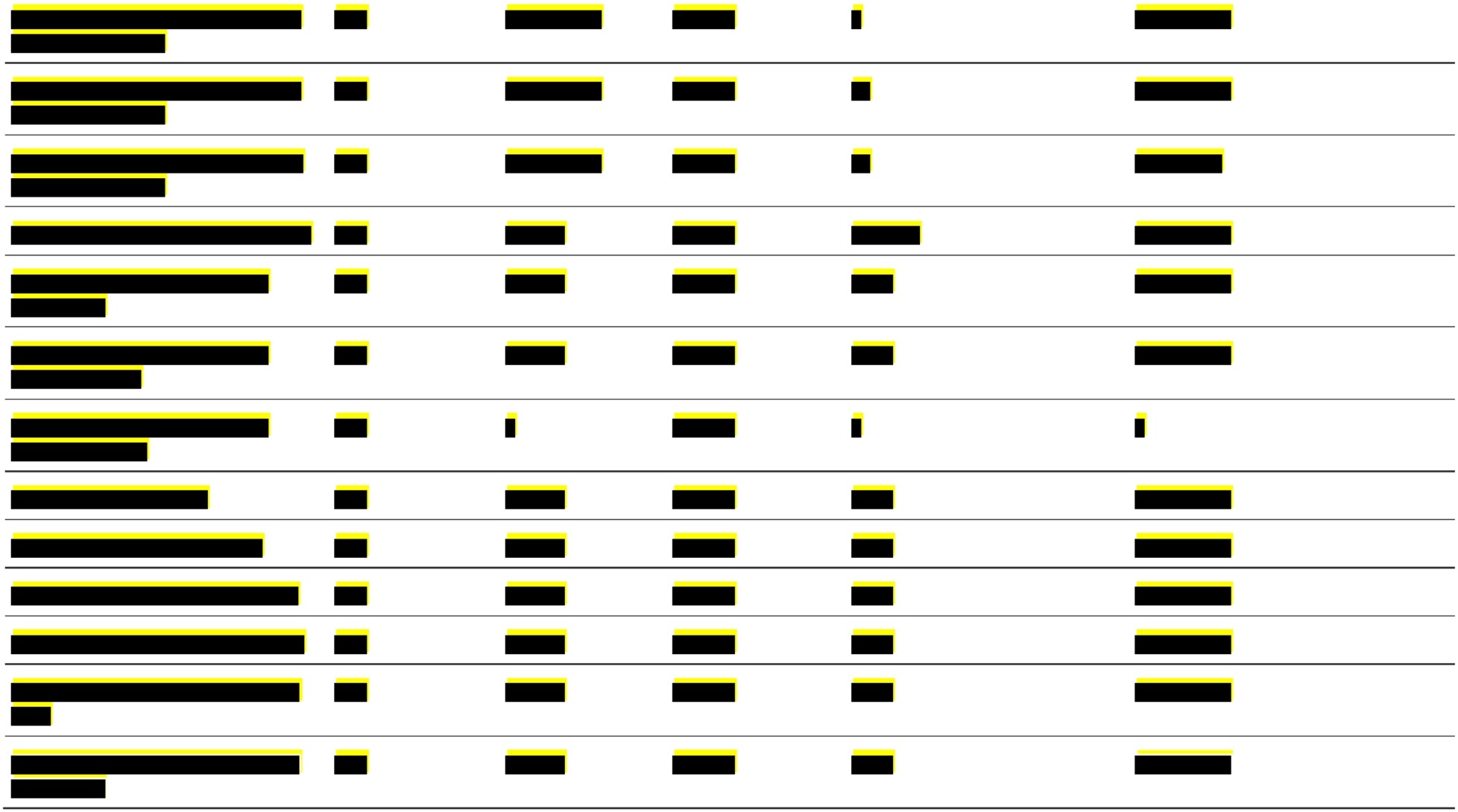

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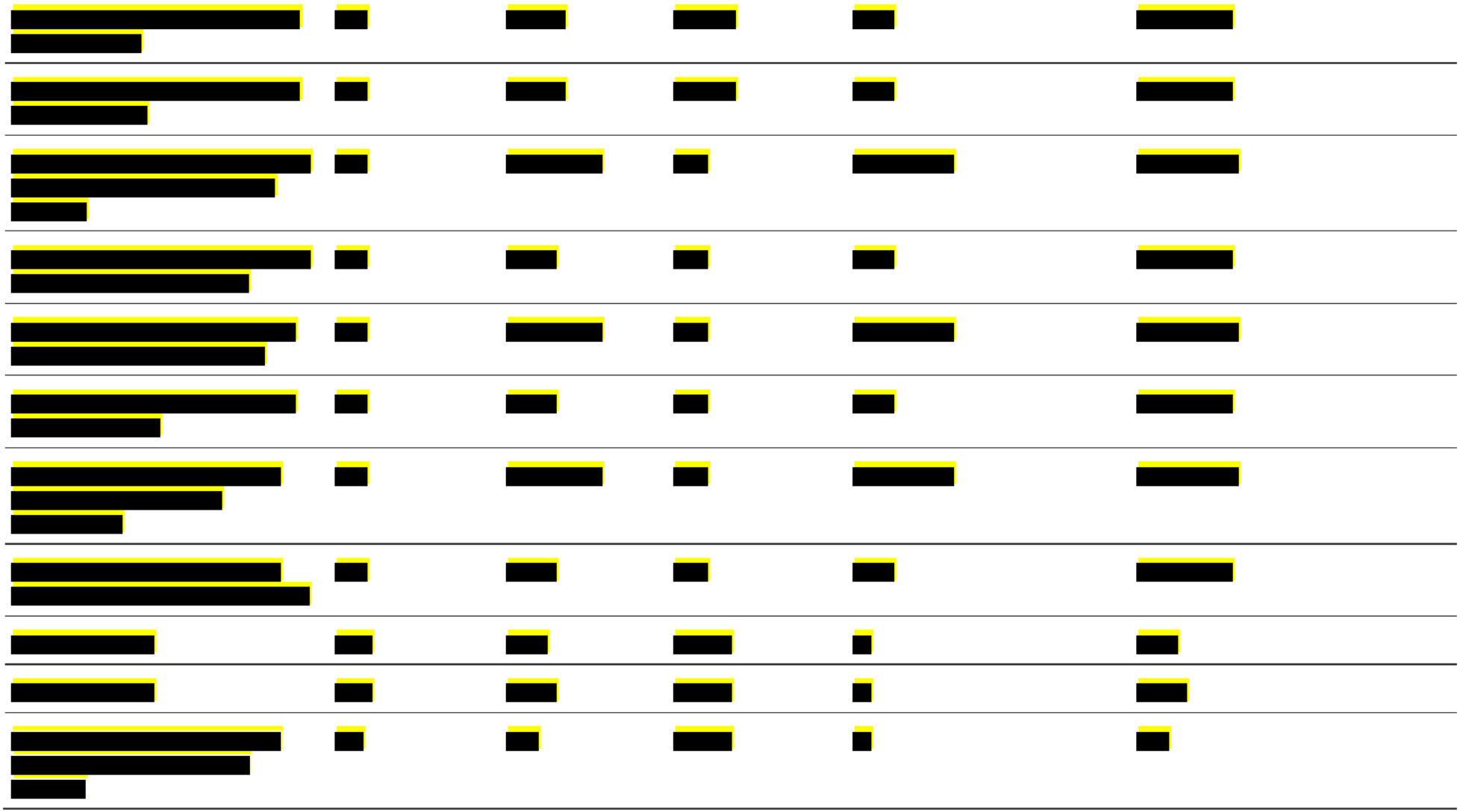

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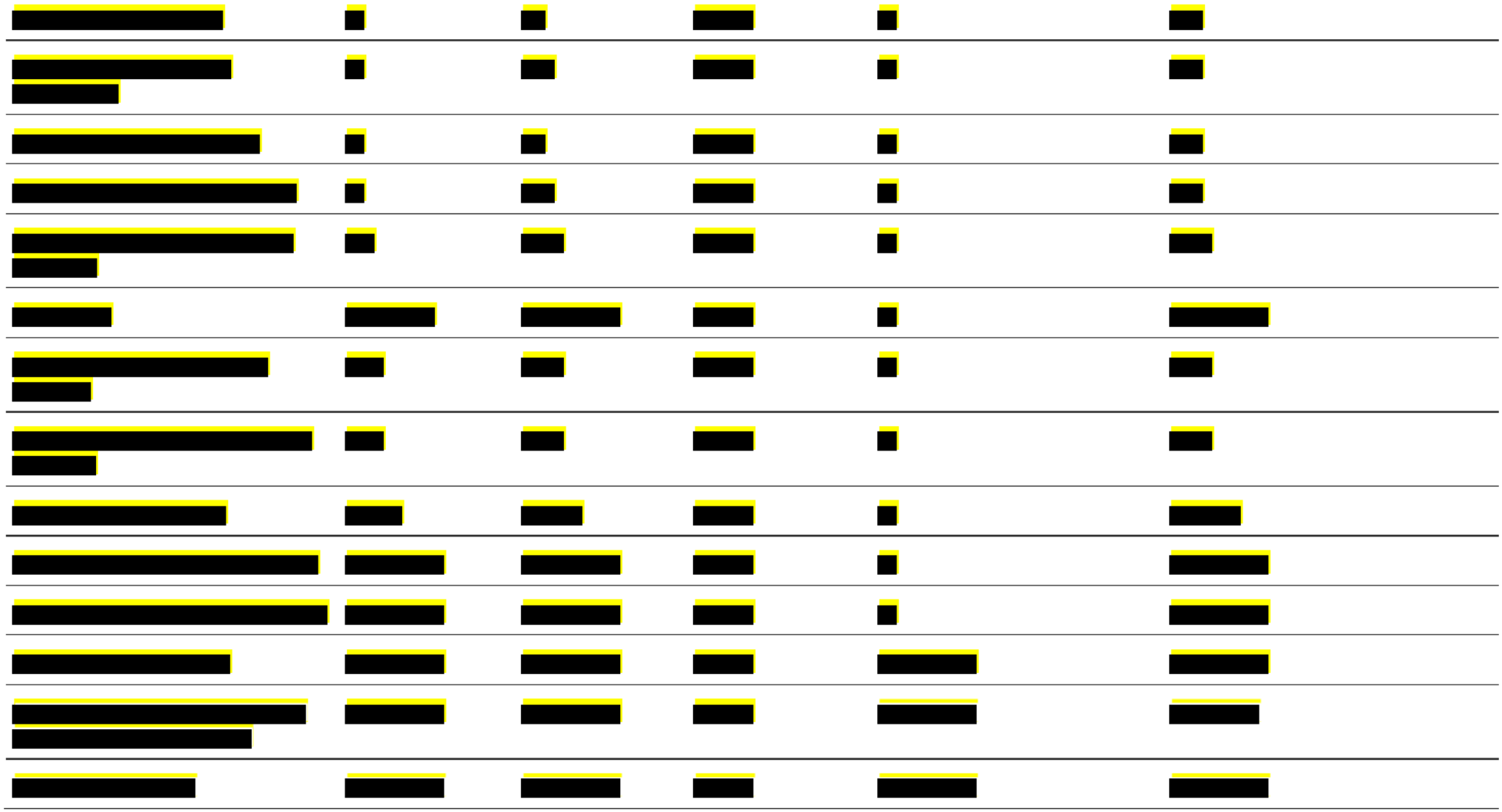

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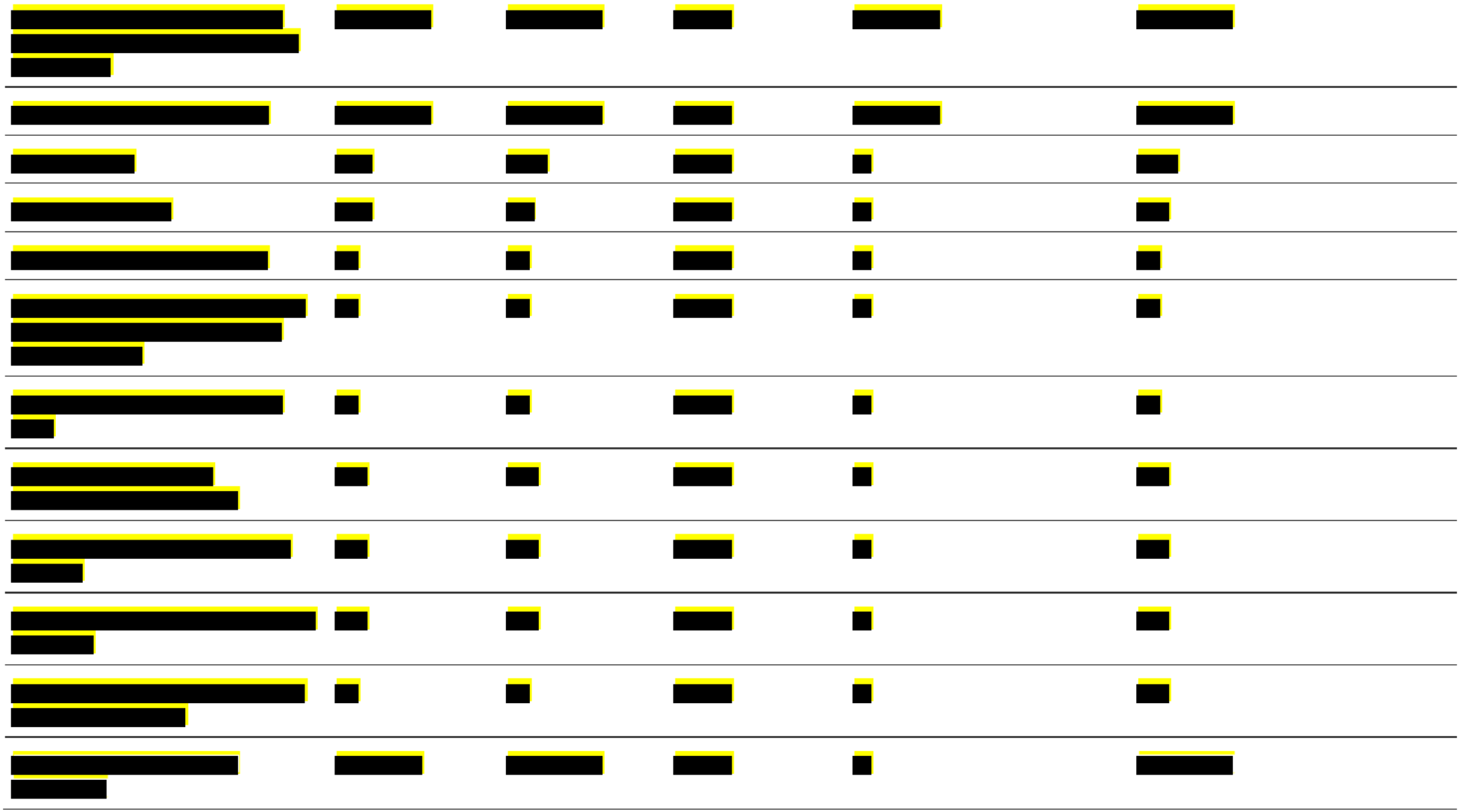

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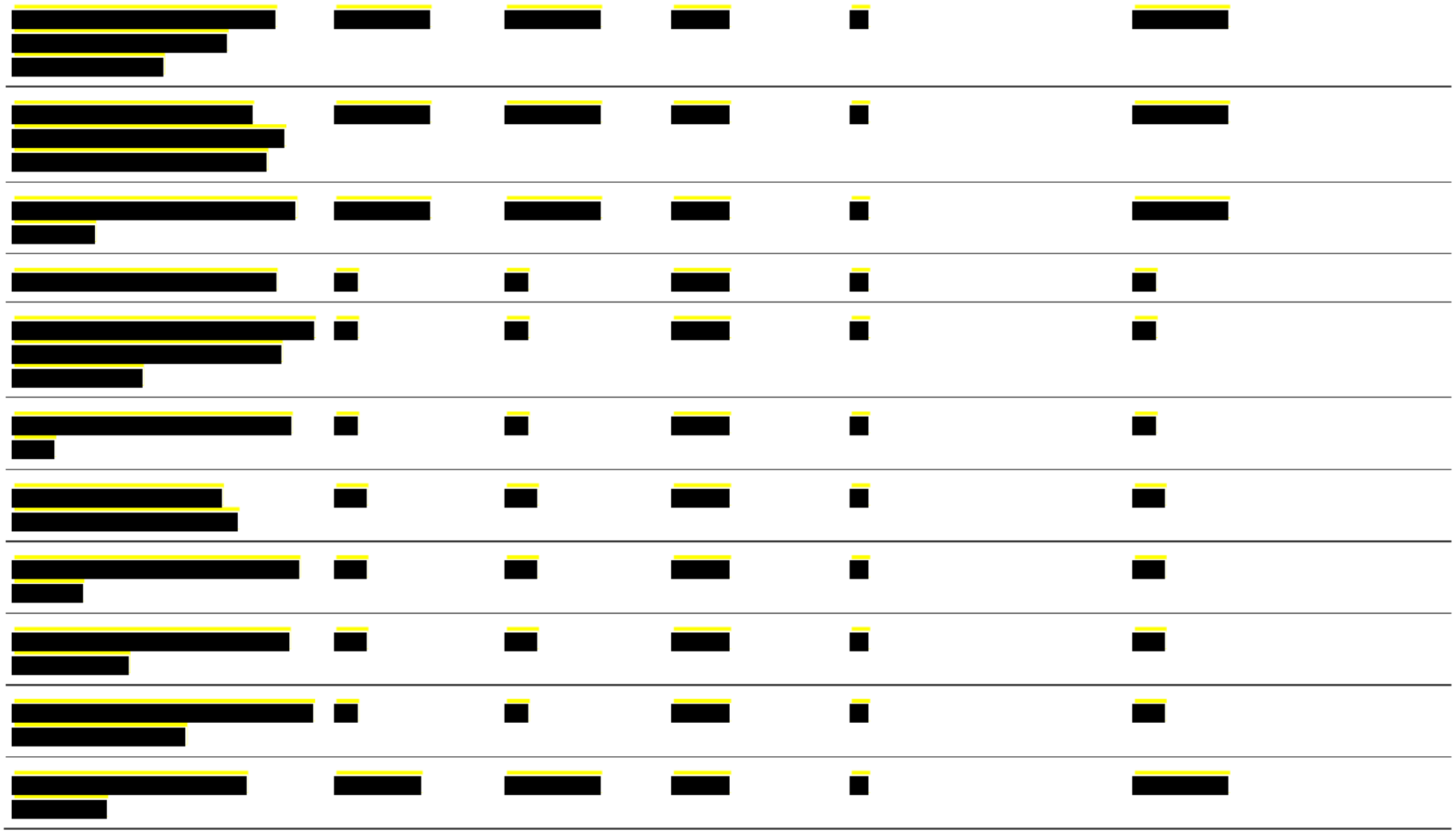

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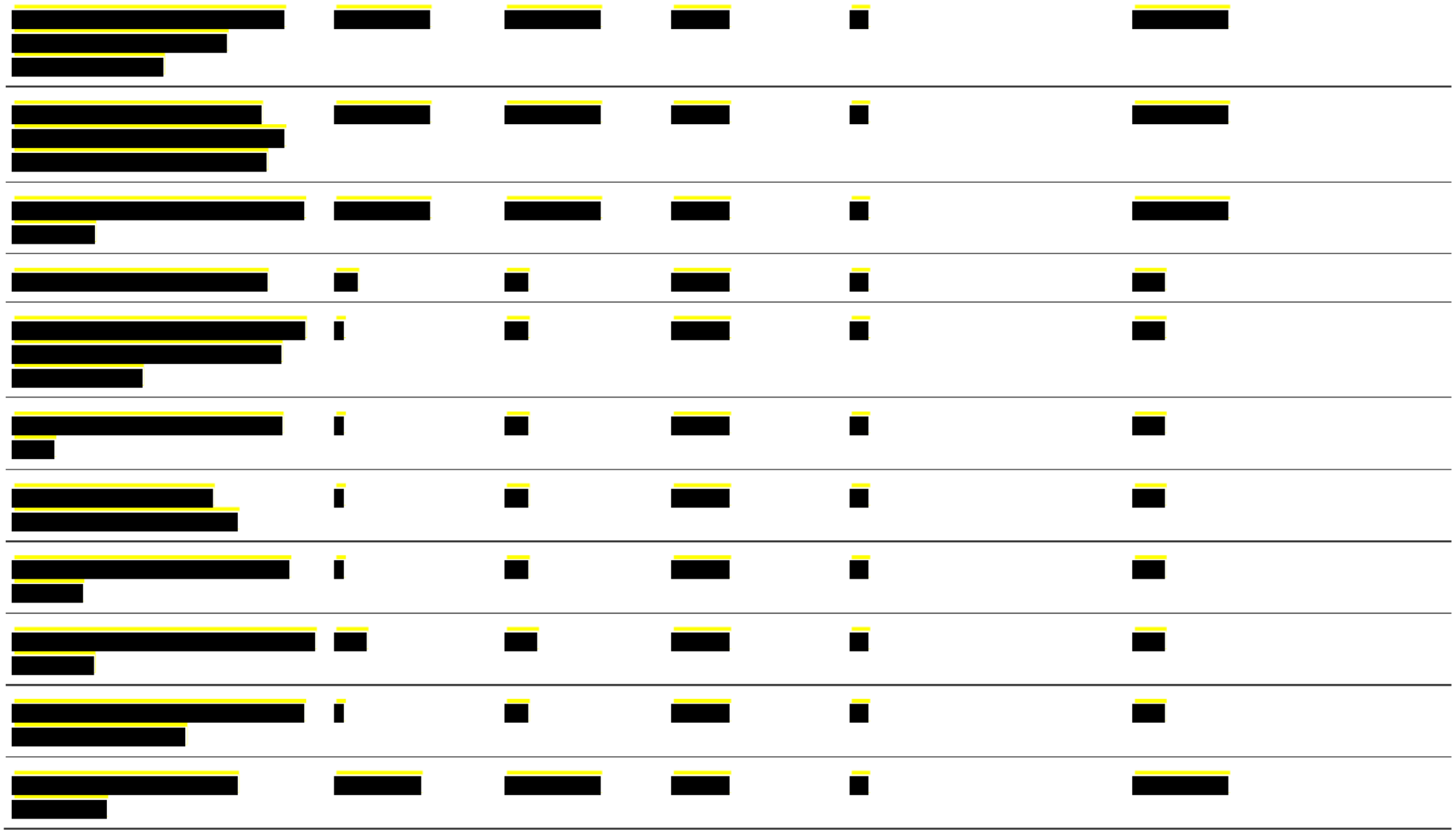

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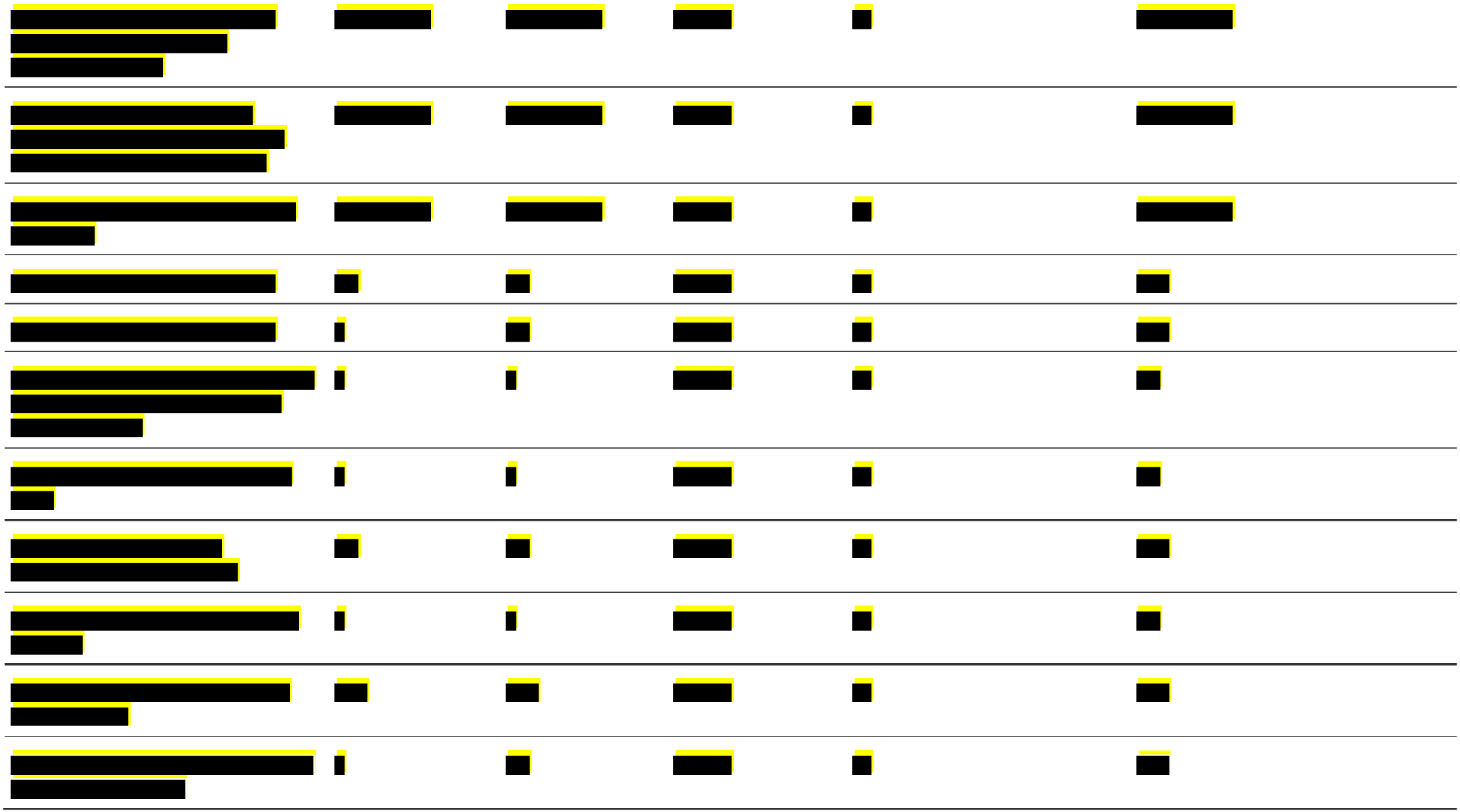

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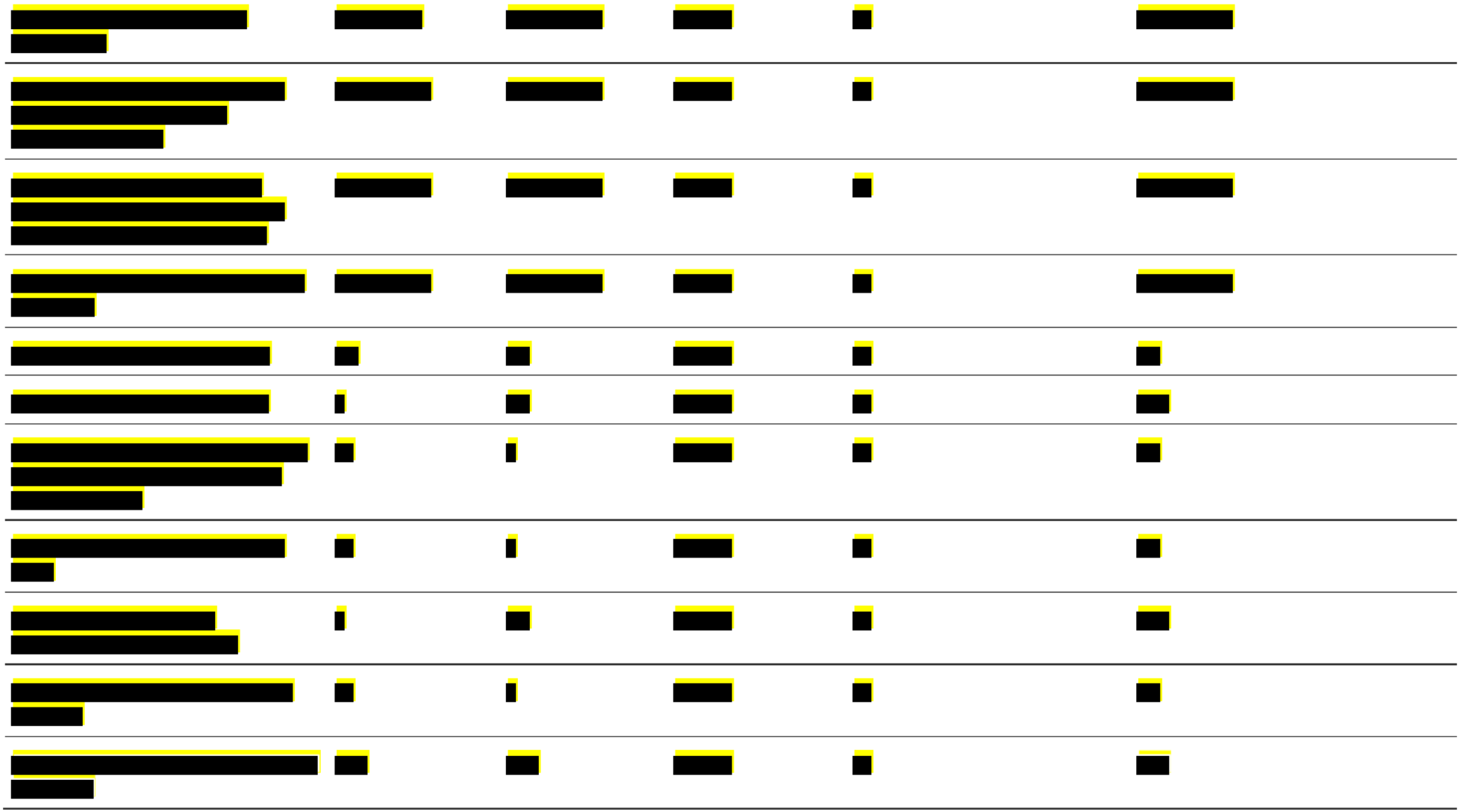

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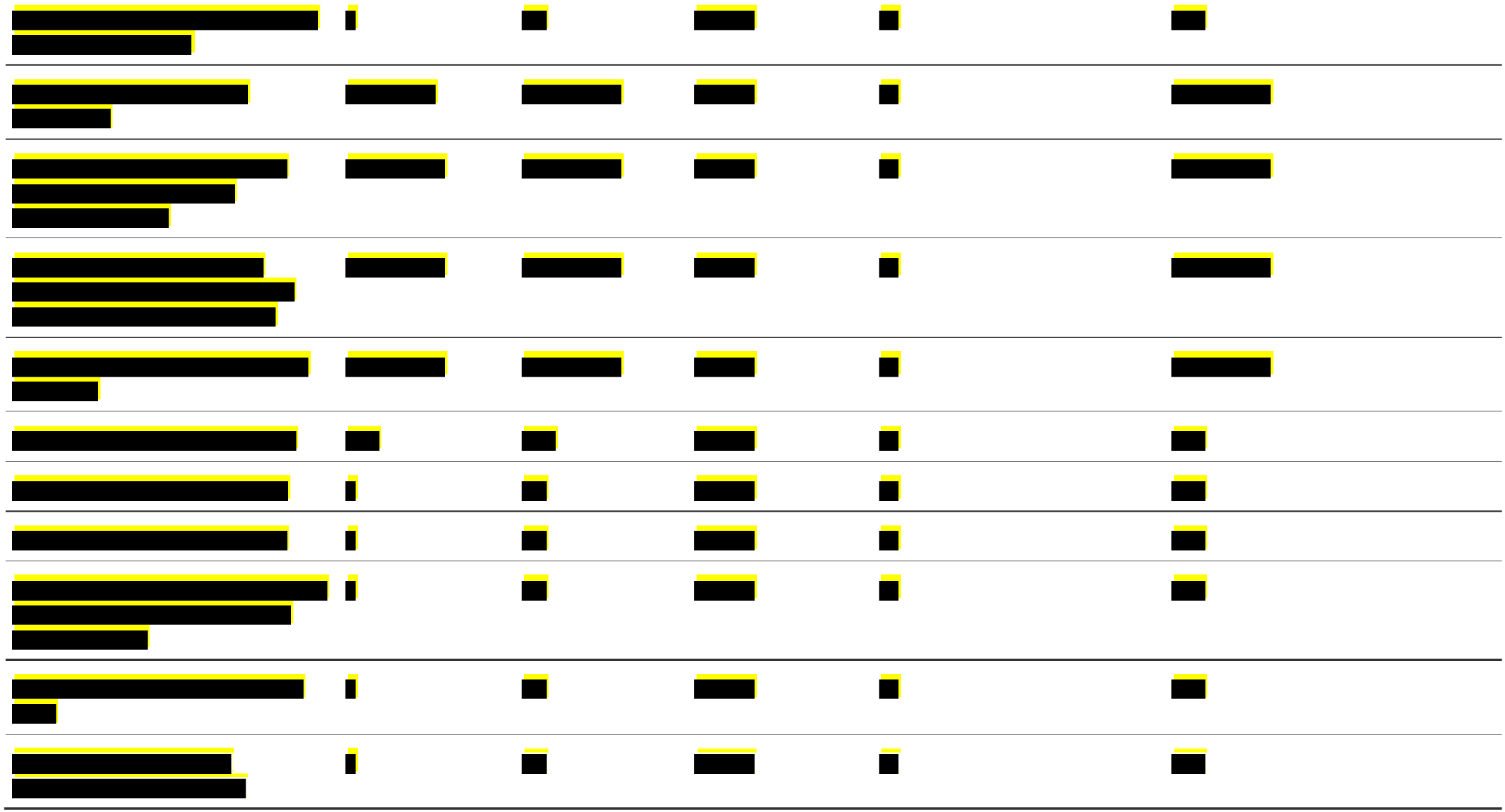

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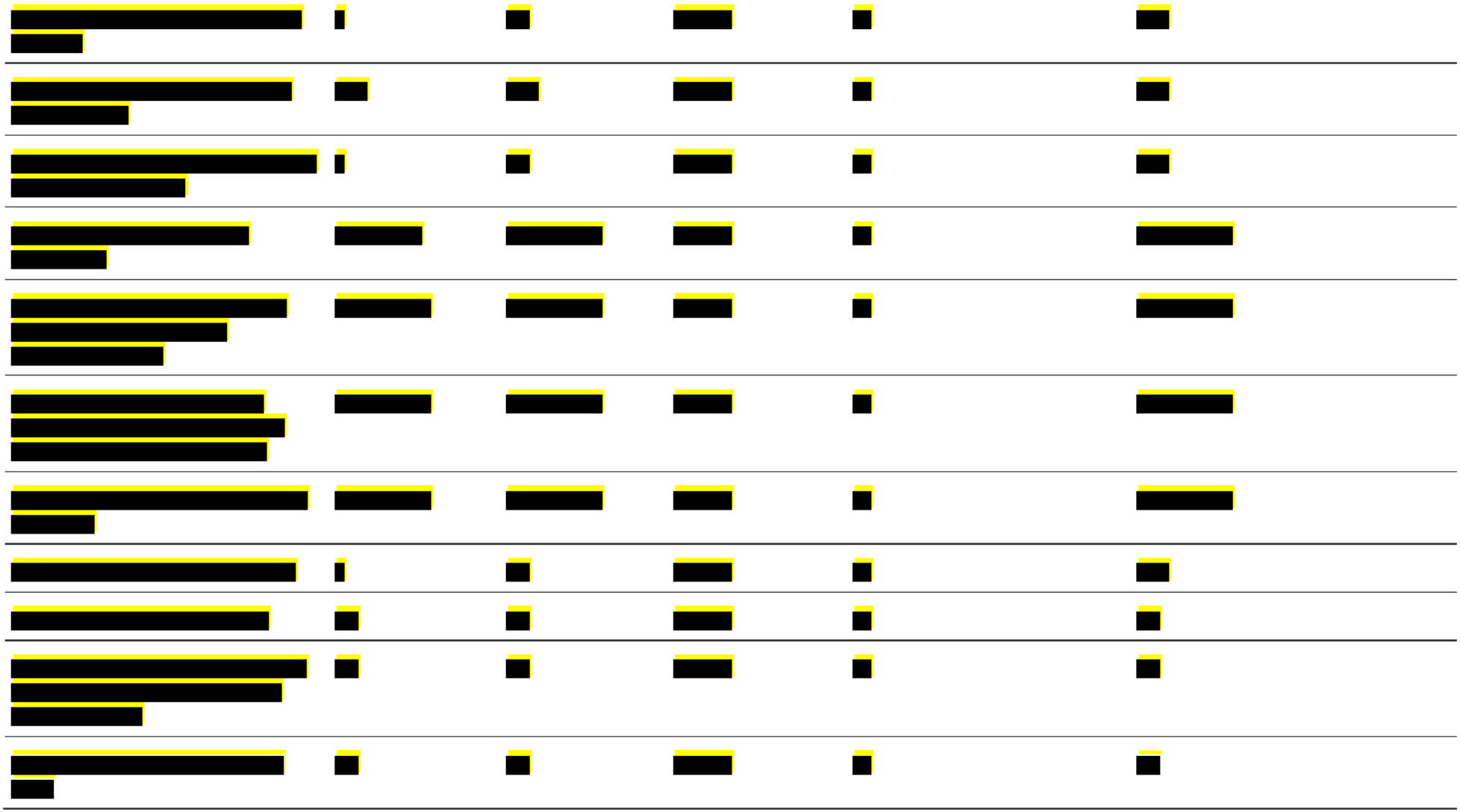

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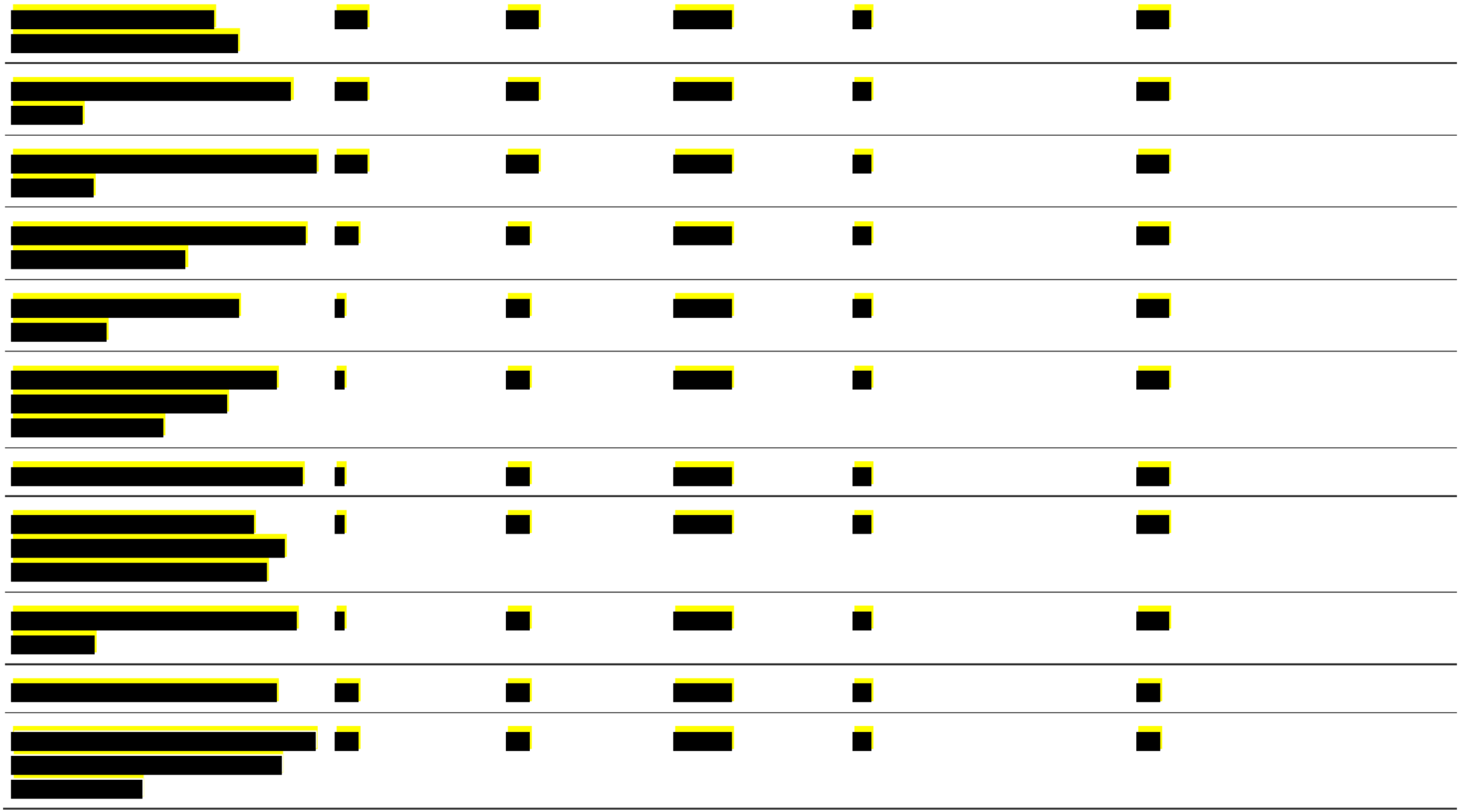

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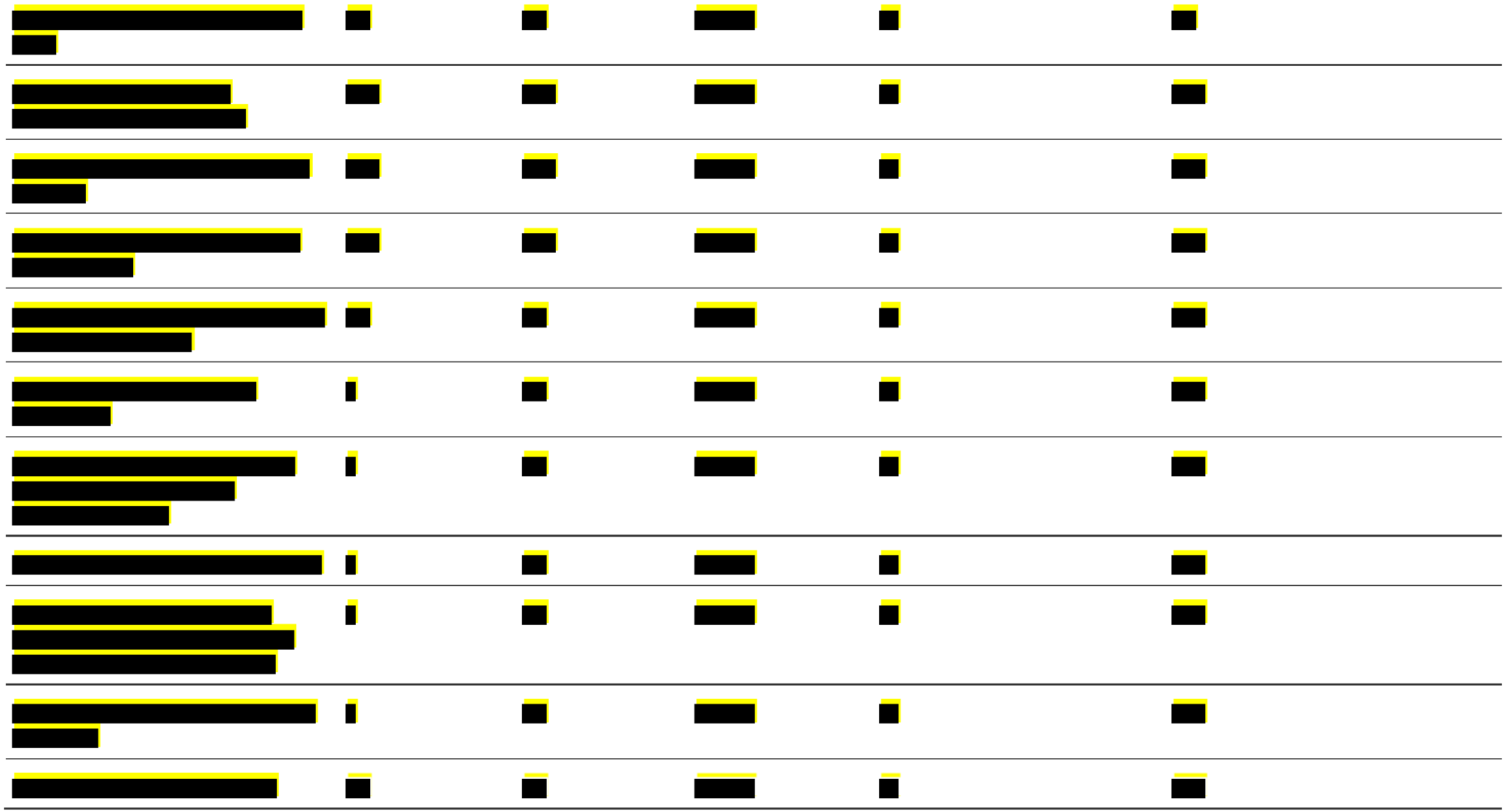

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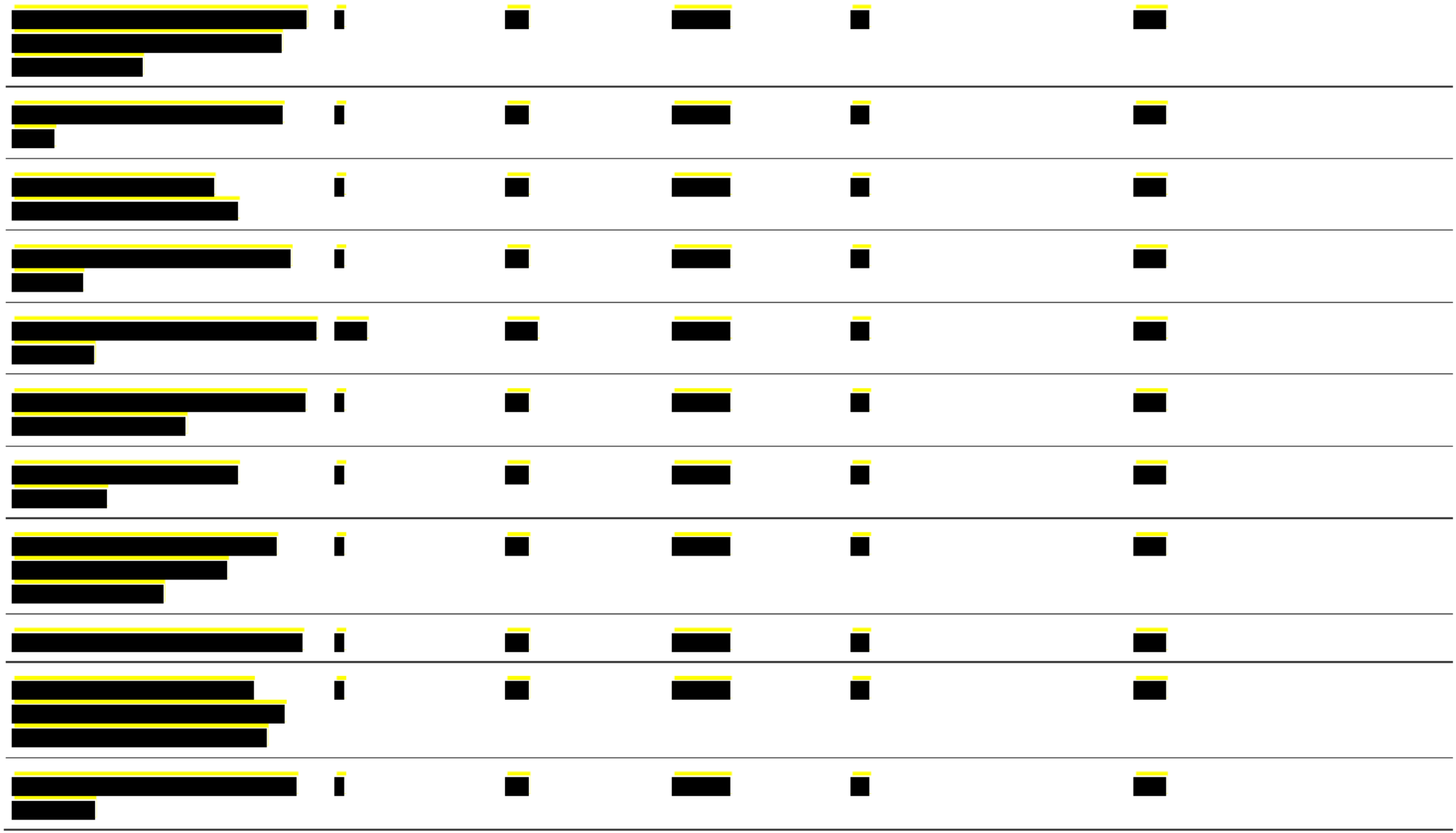

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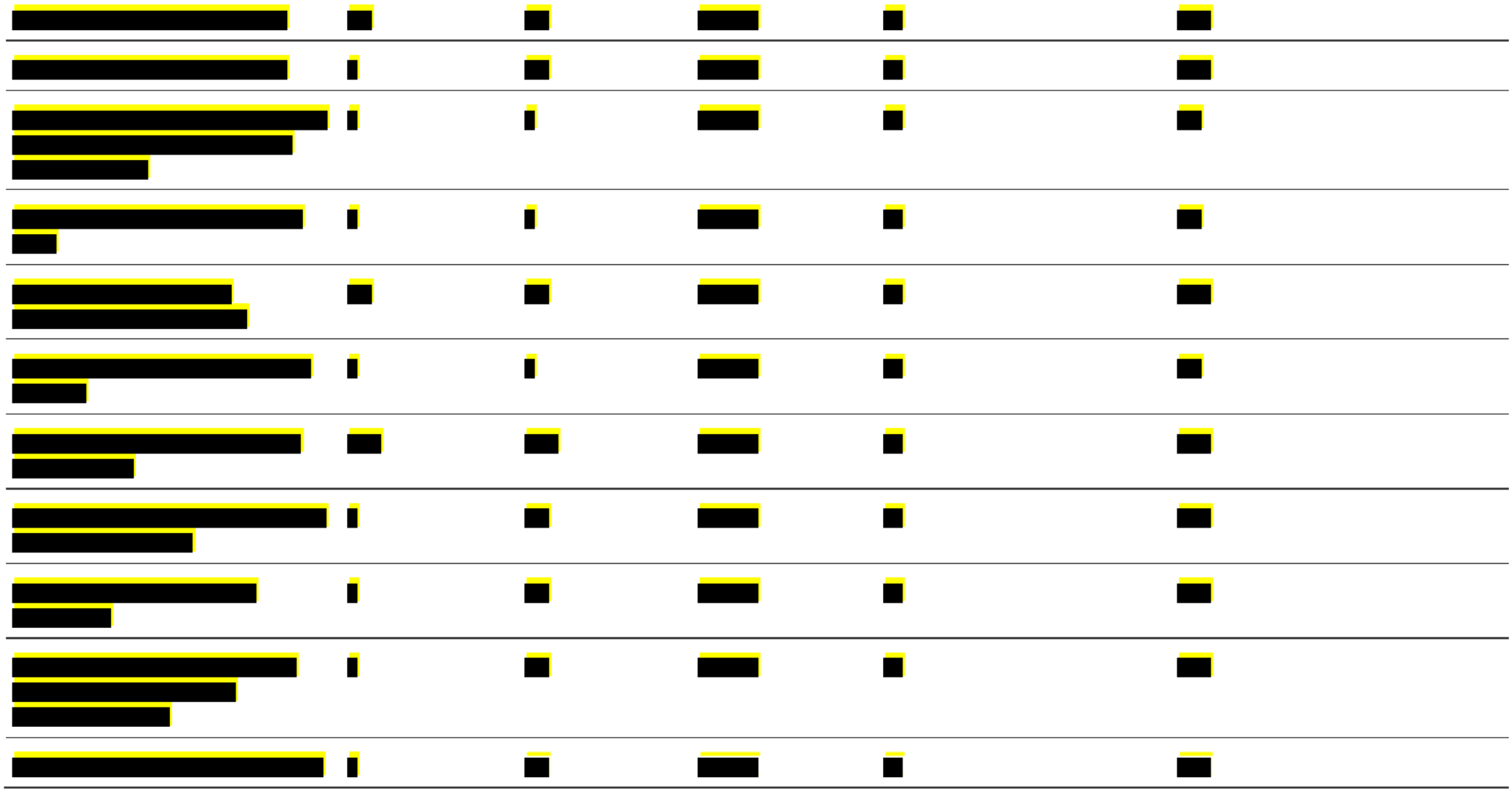

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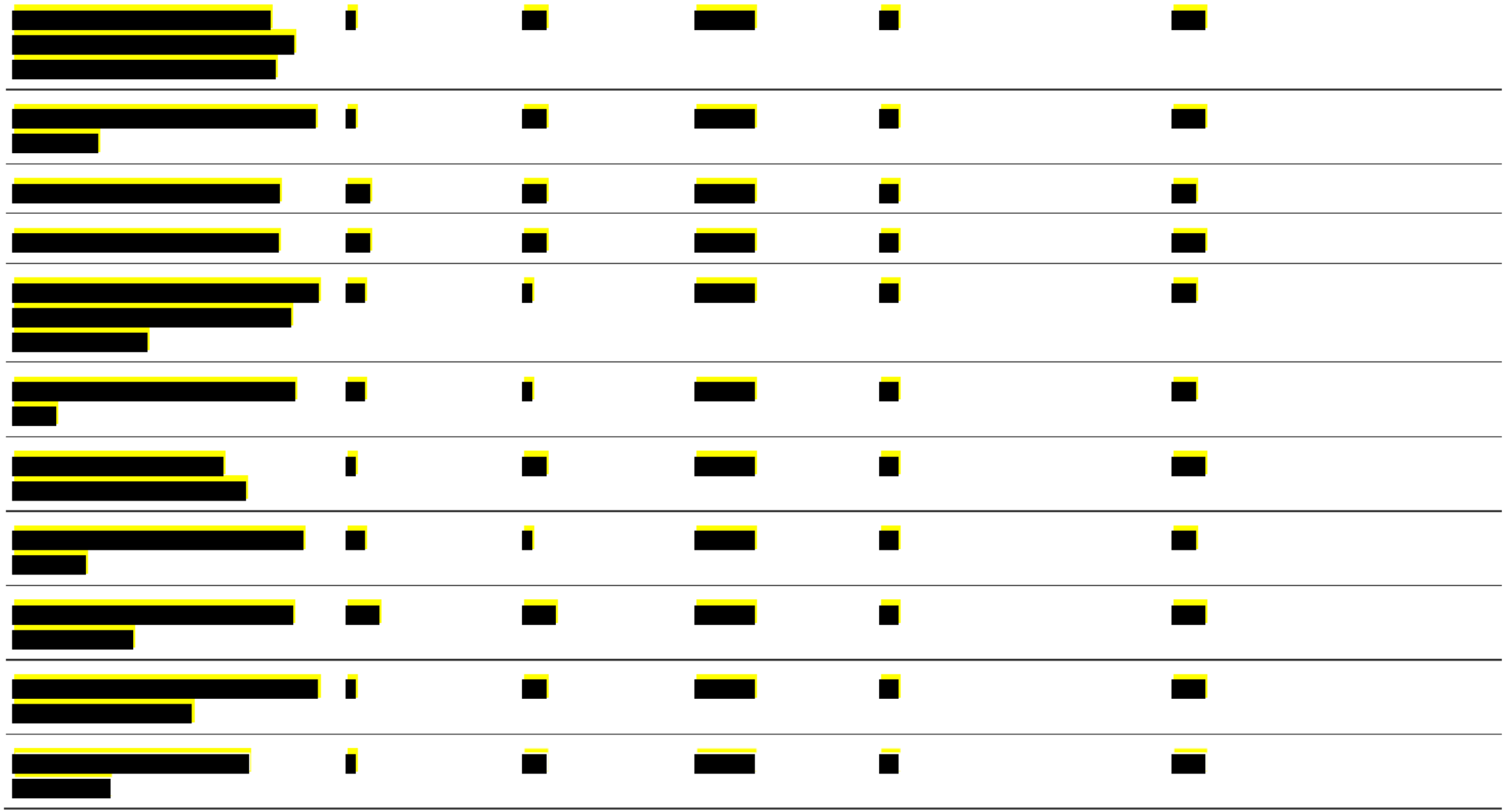

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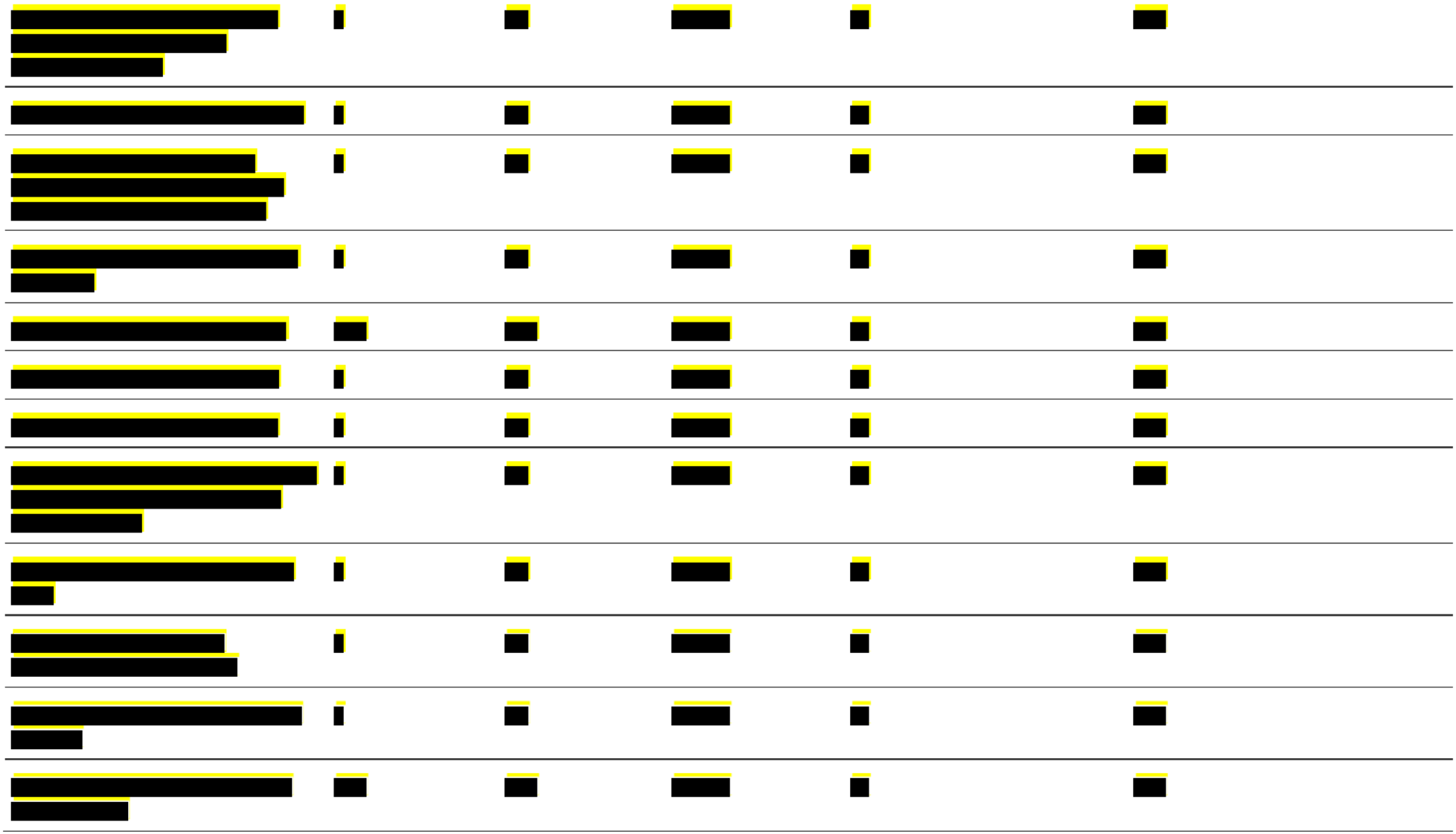

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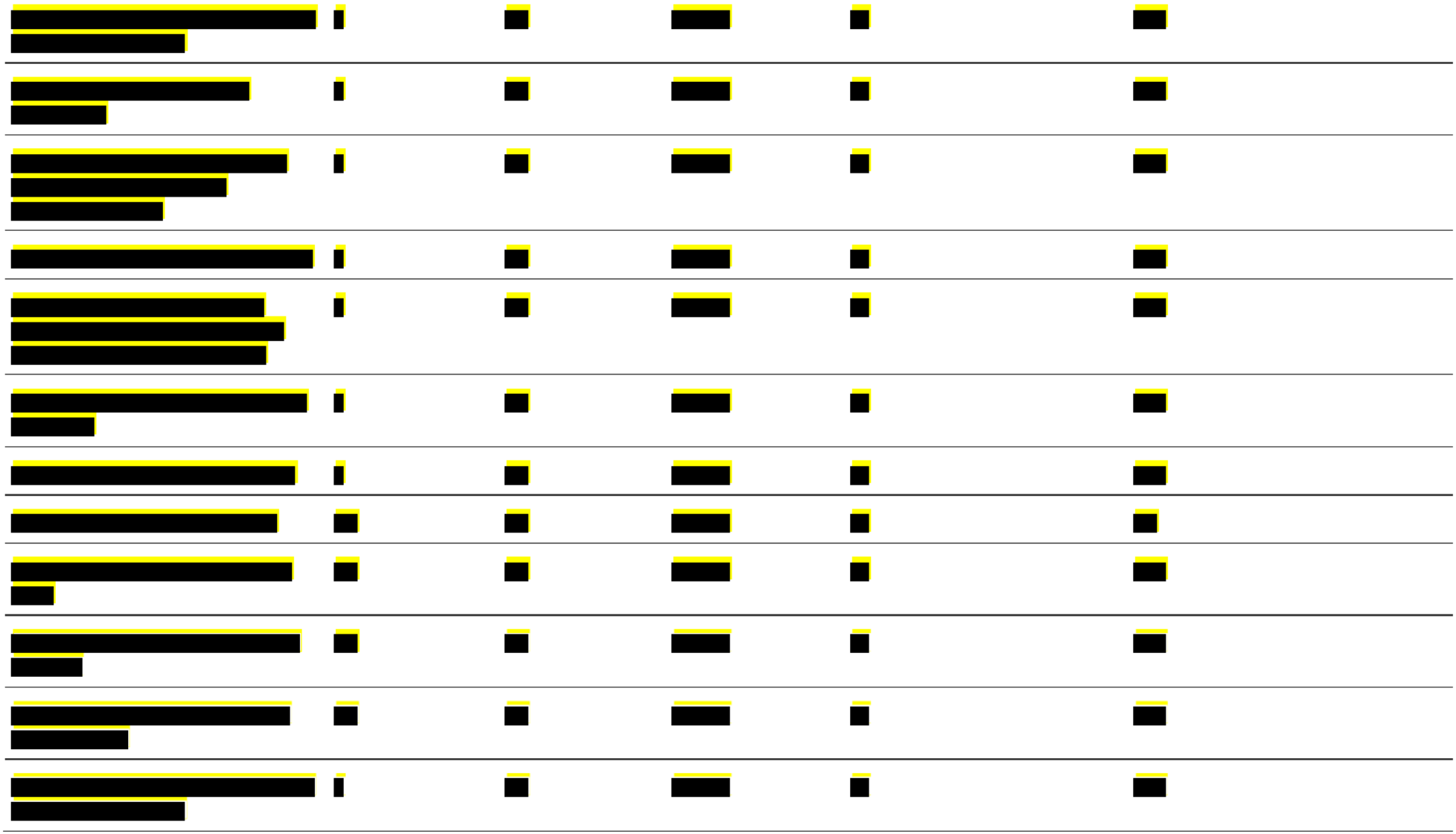

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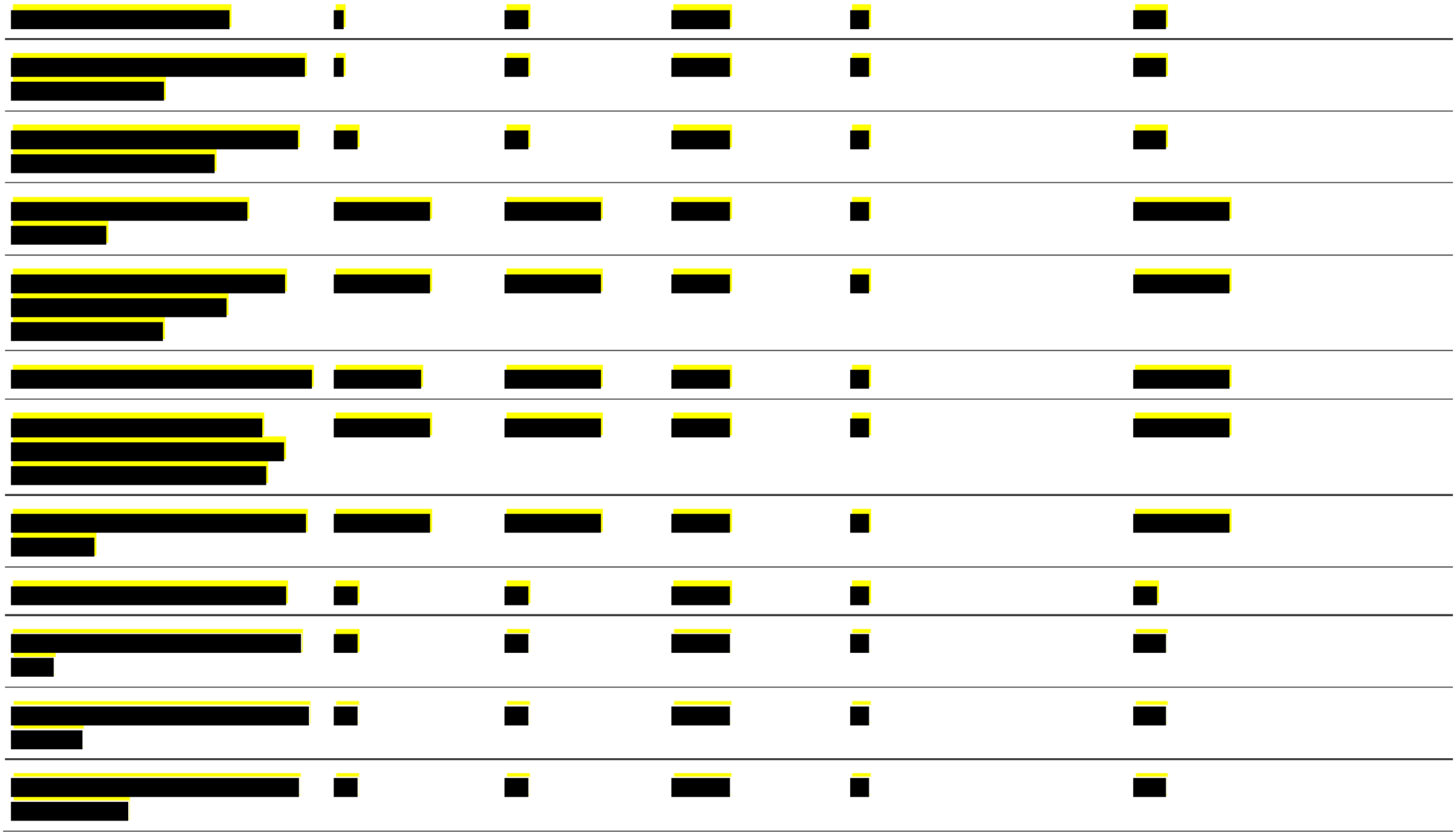

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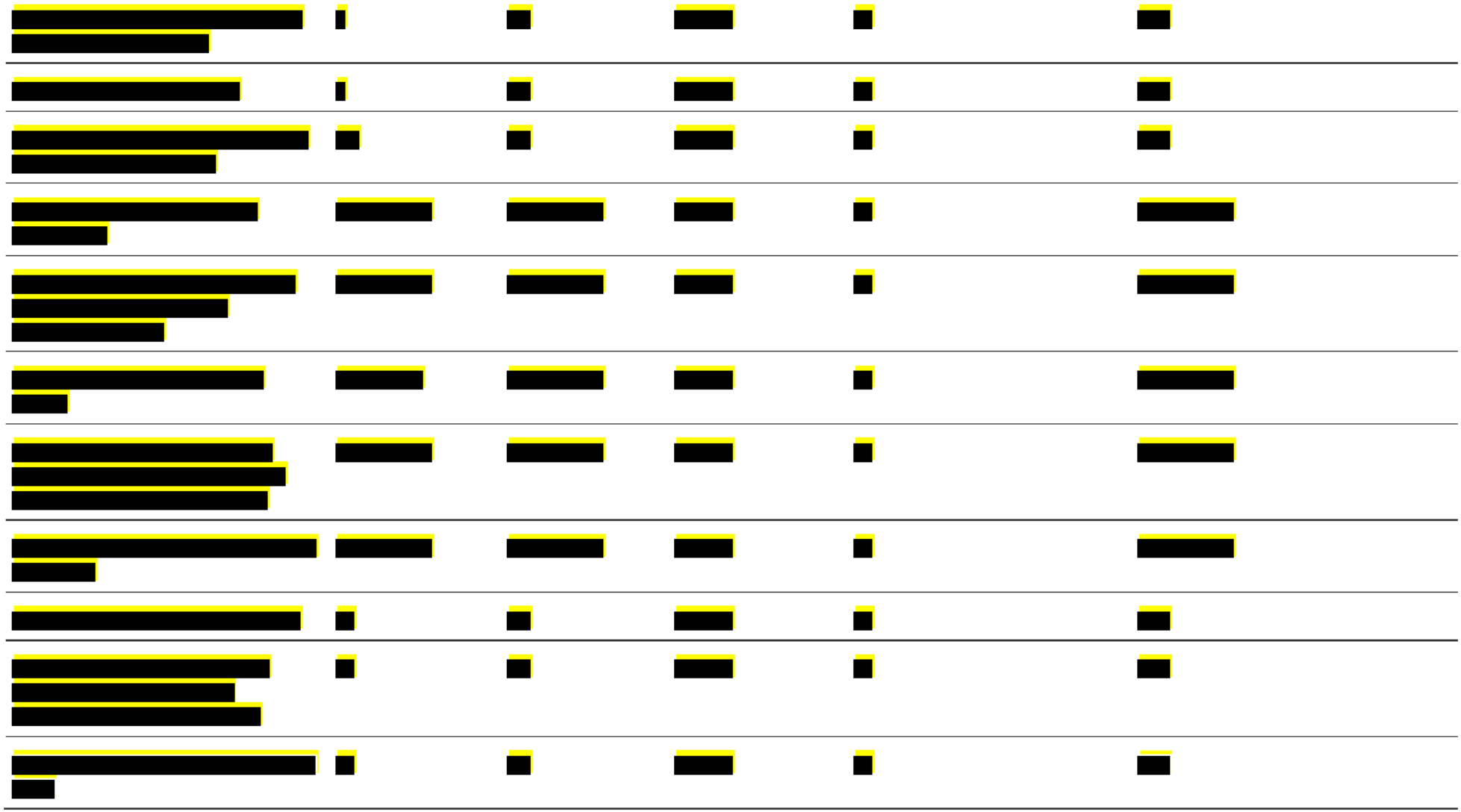

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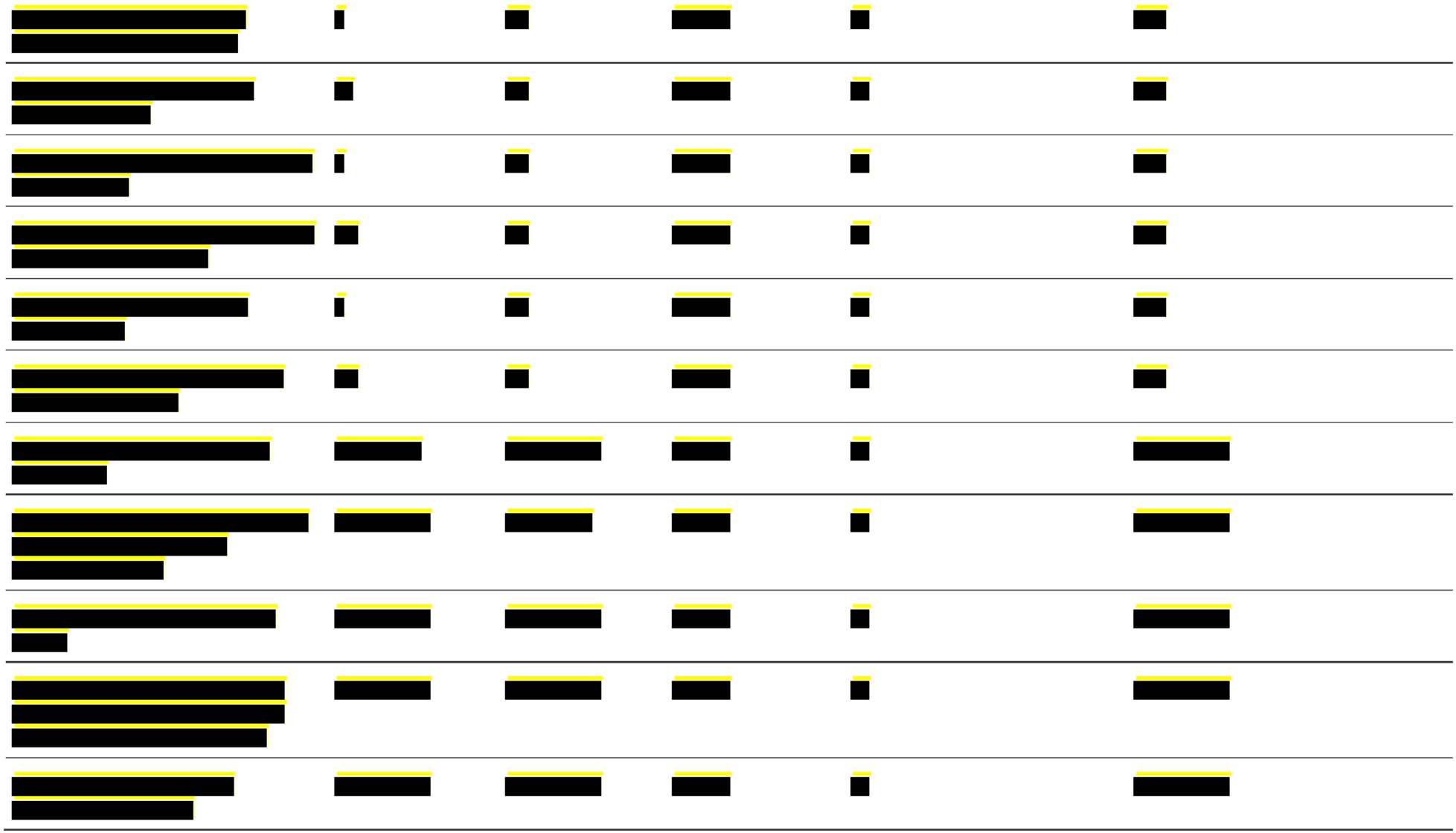

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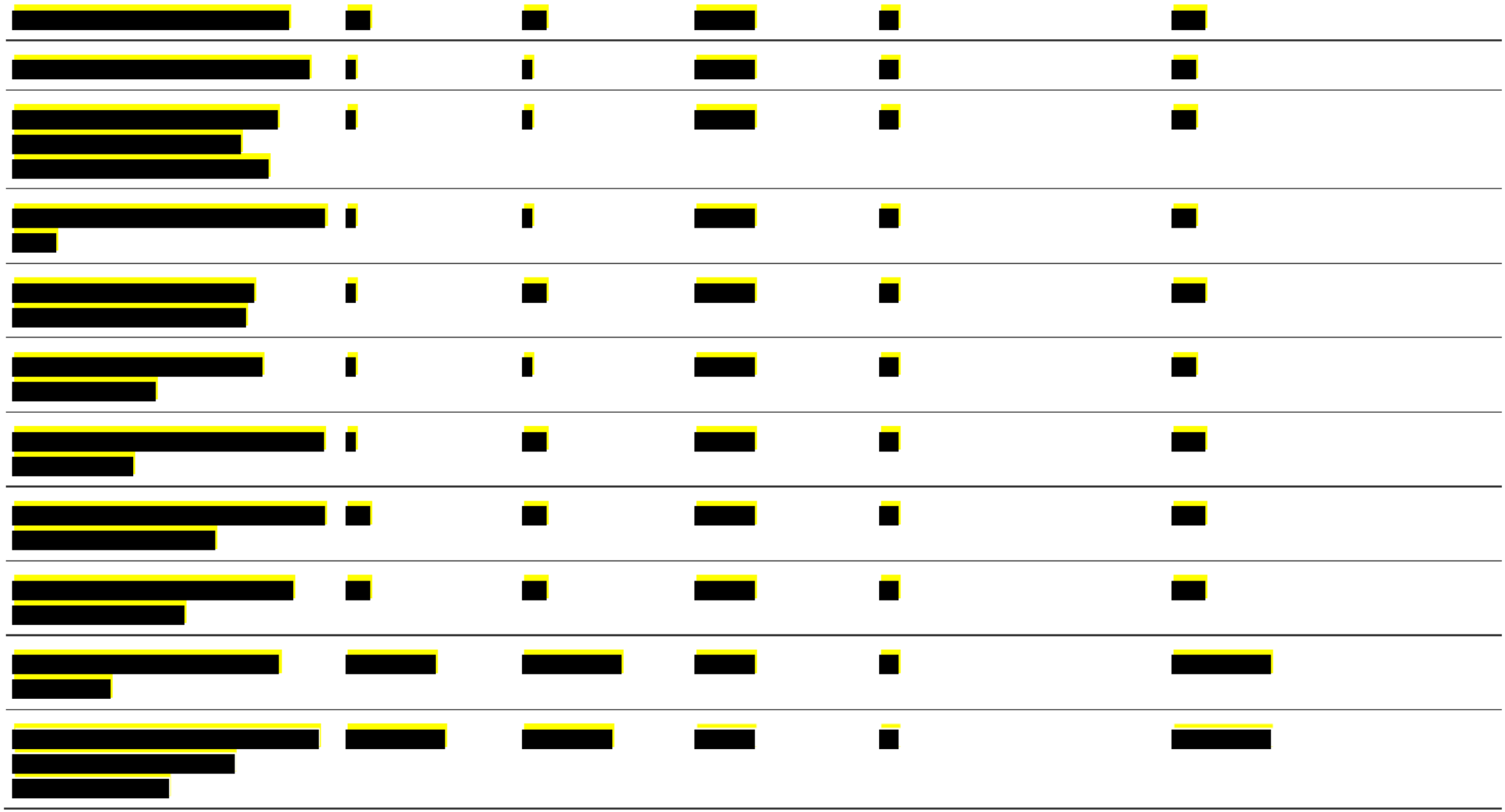

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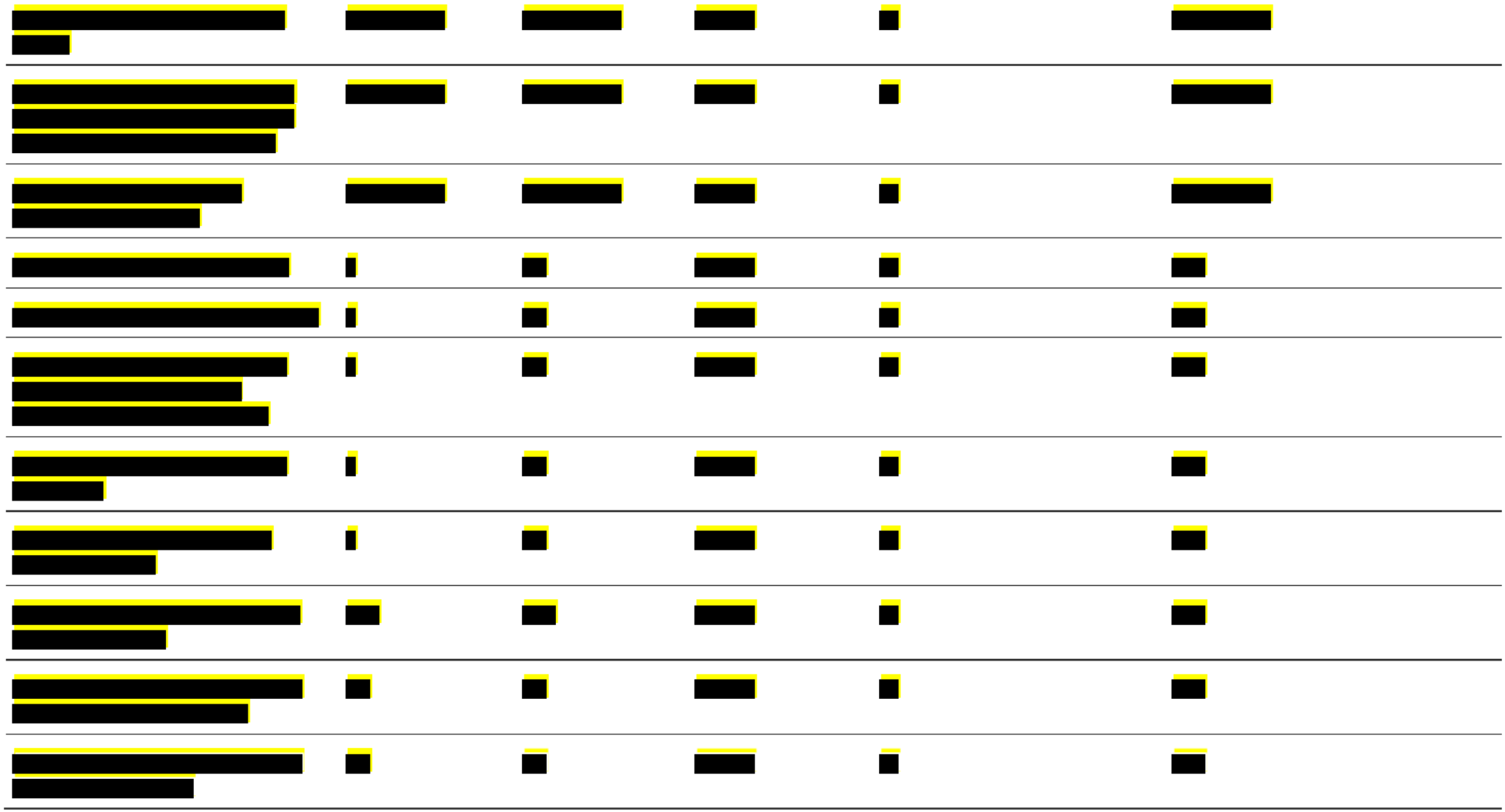

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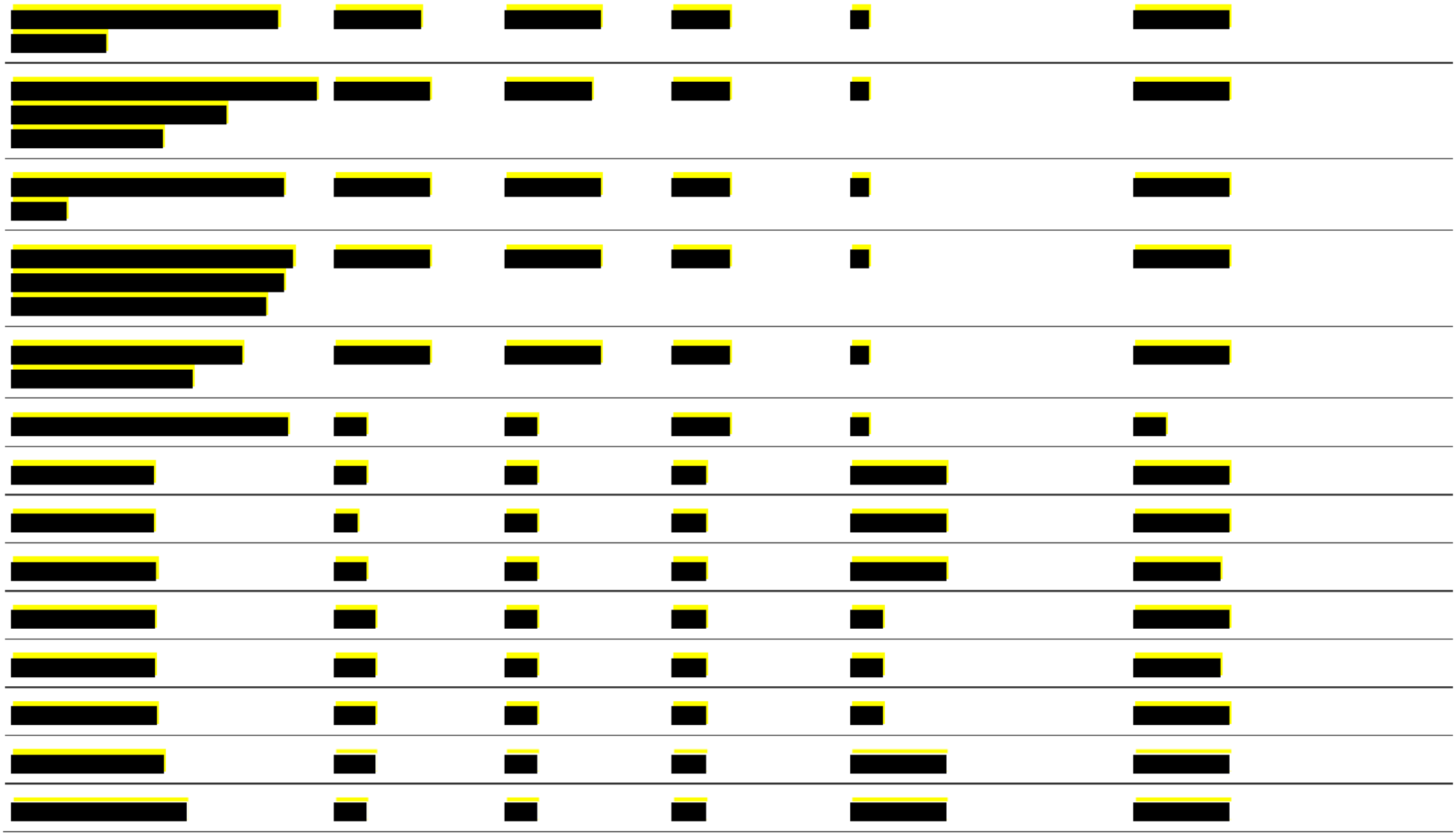

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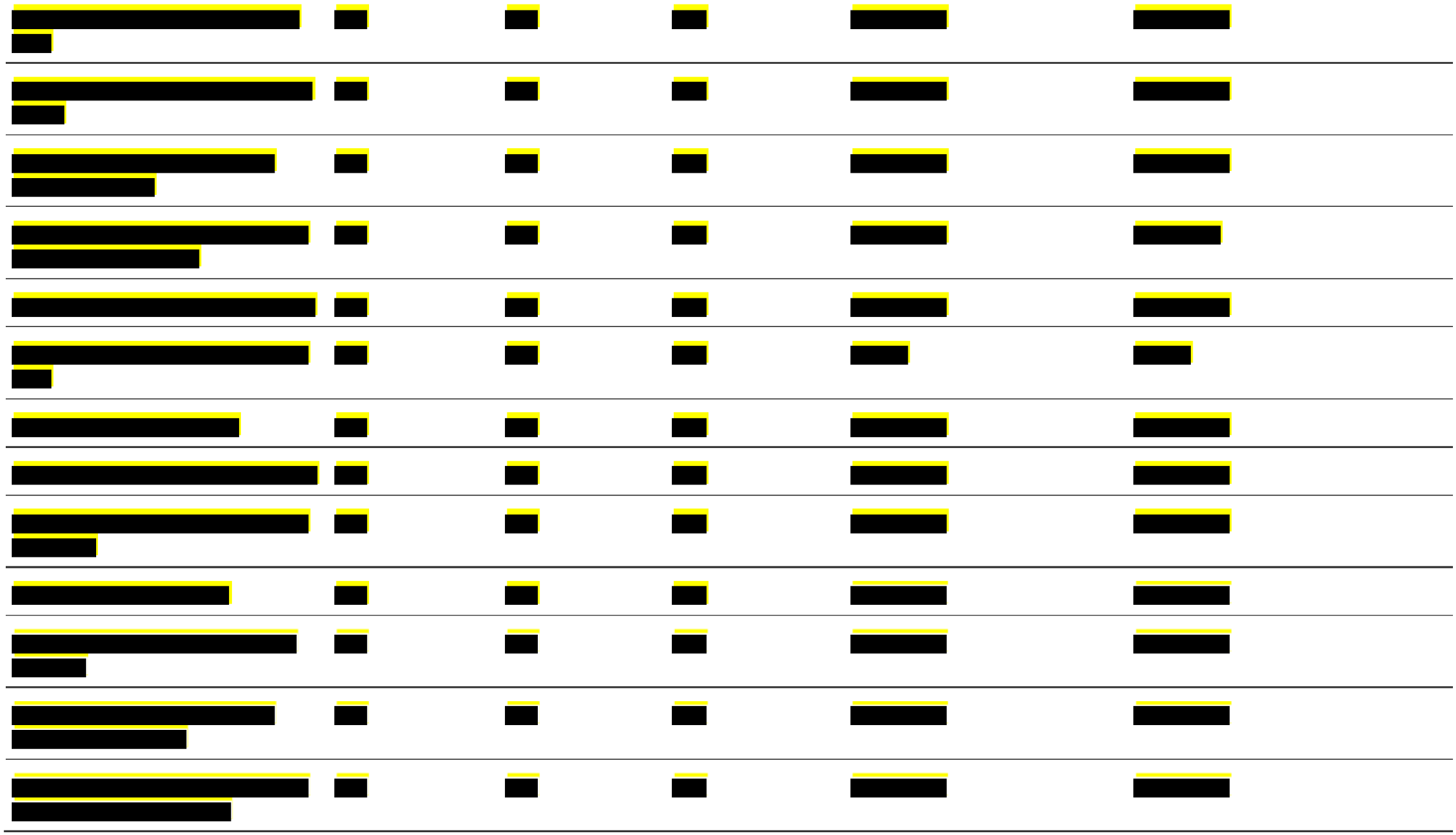

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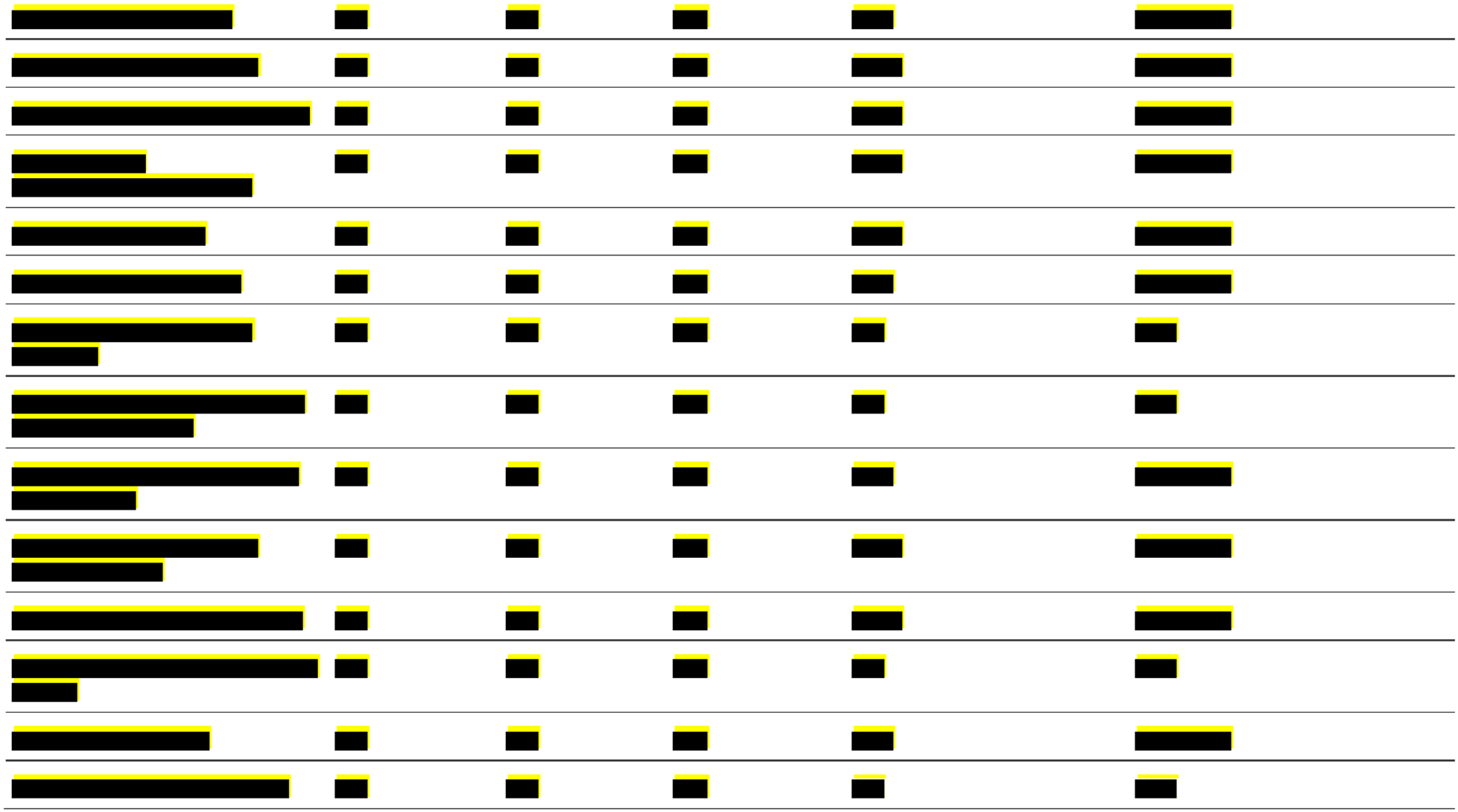

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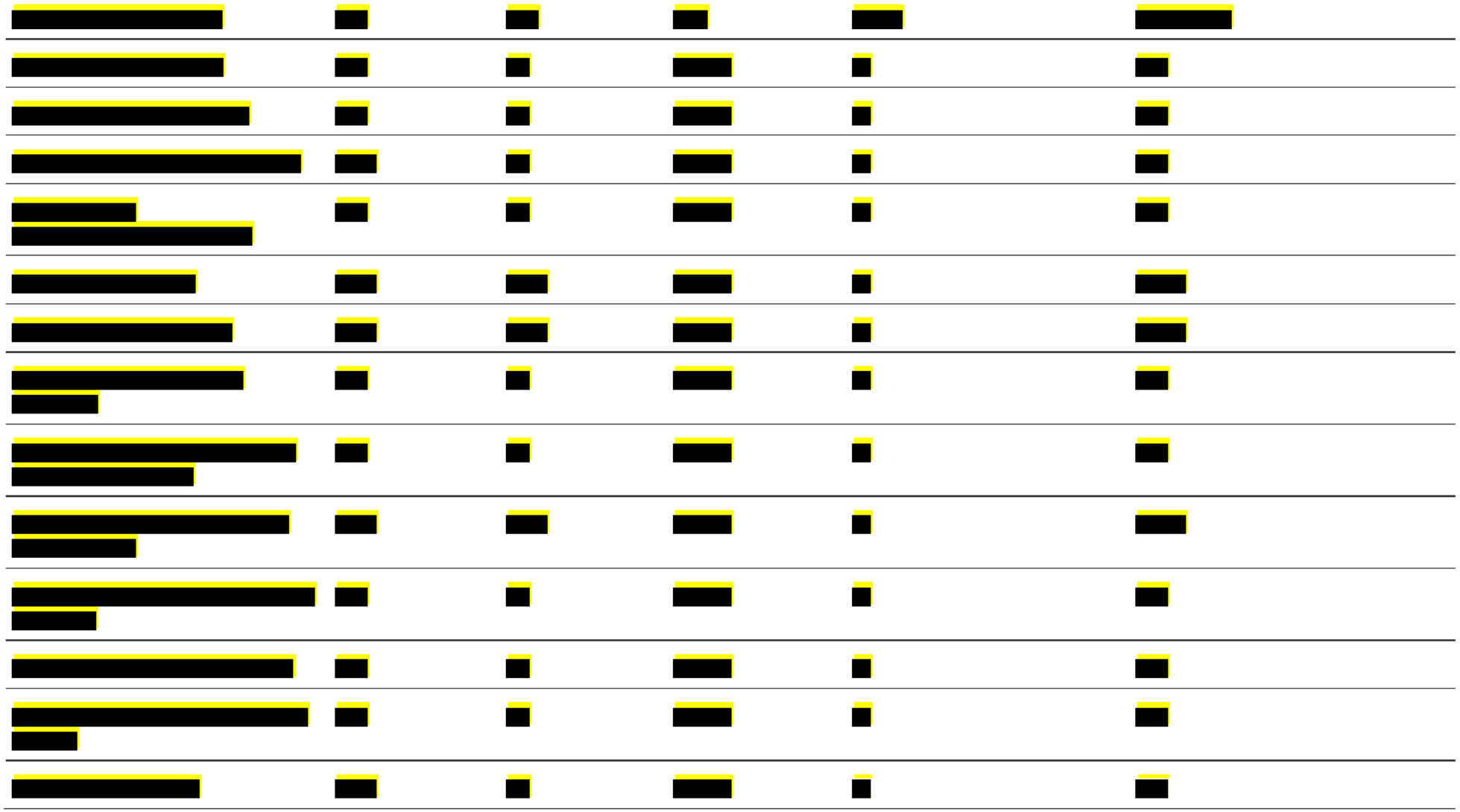

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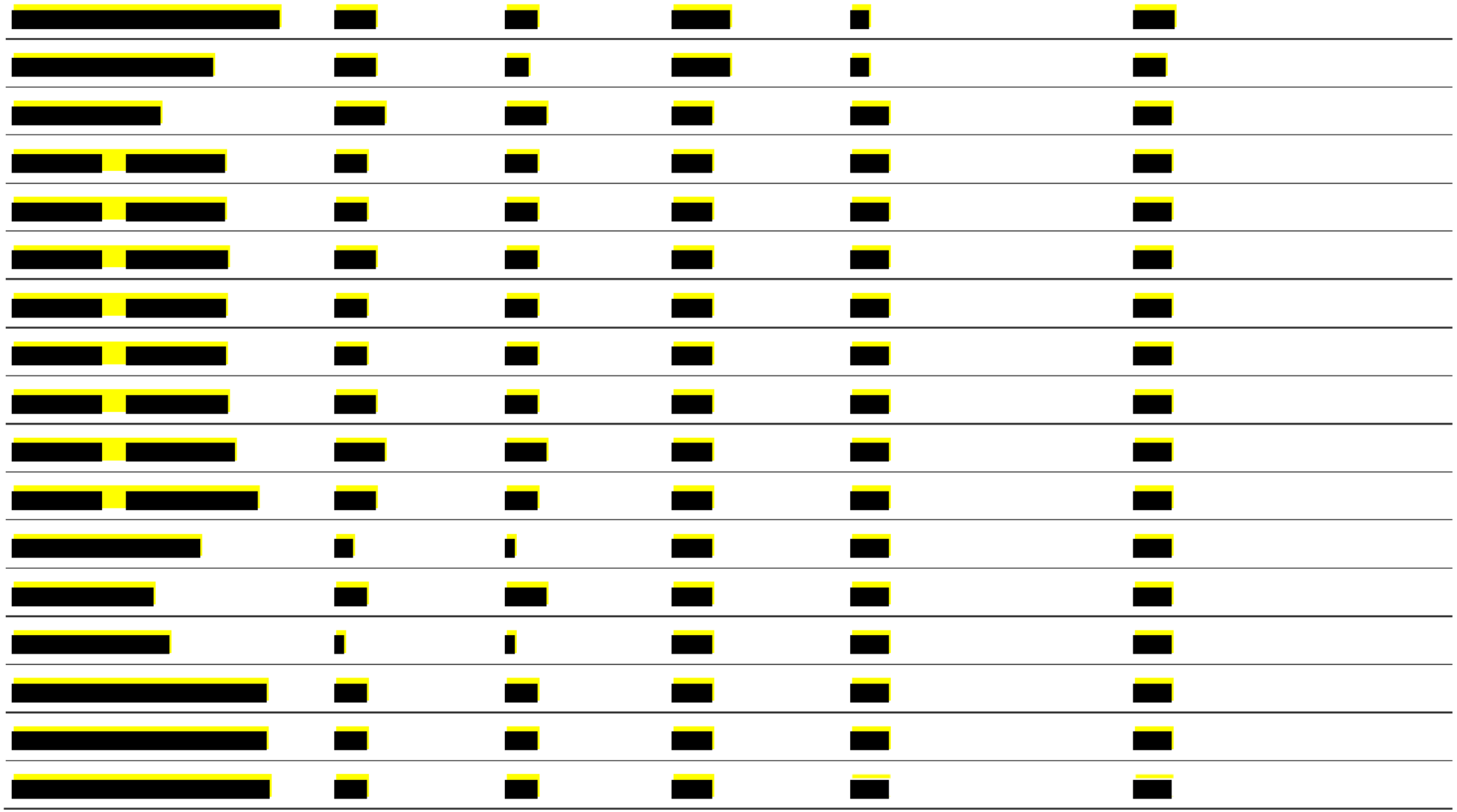

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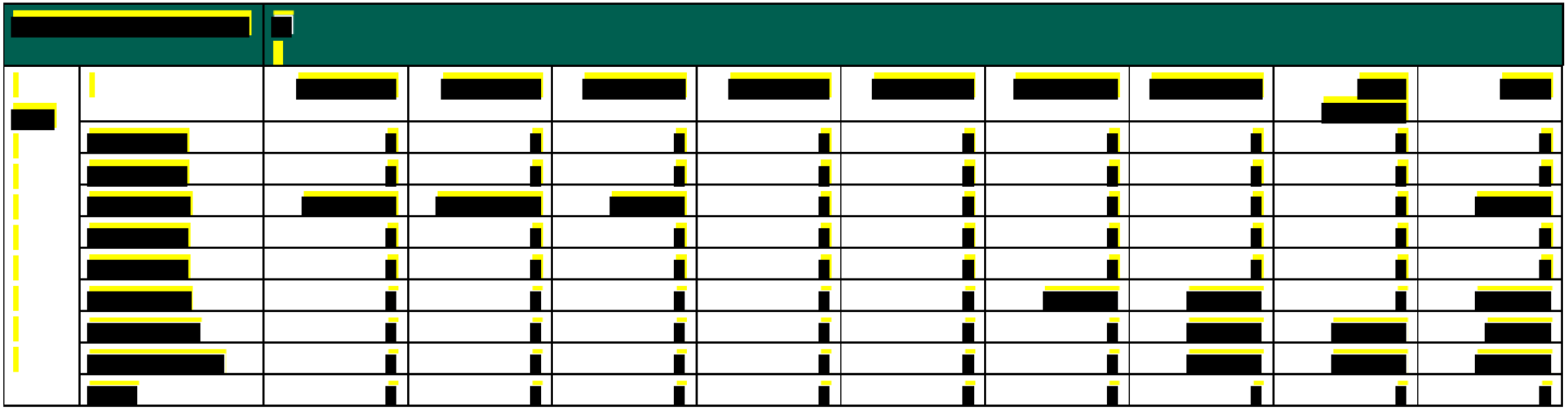
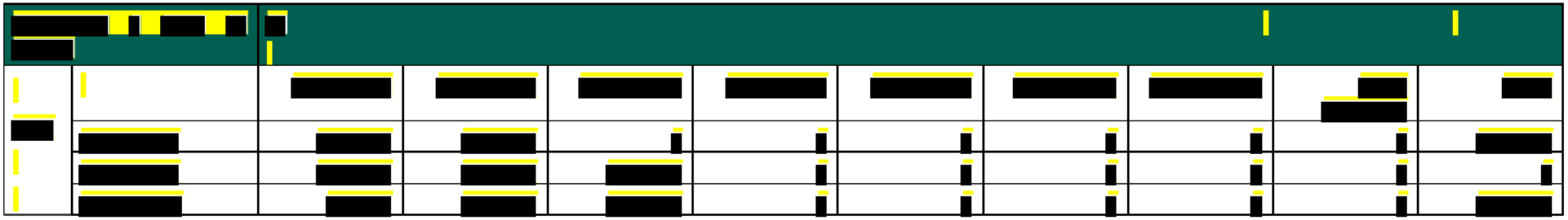
Appendix K Transition probabilities

Below are presented the transition probabilities calculated using the count method for voclosporin+MMF and MMF for each model cycle for the first 36 months and the long term transition probabilities.

Voclosporin+MMF transition probabilities:



Abbreviations: AD = active disease; CKD = chronic kidney disease; CR = complete response; MMF = mycophenolate mofetil; PR = partial response



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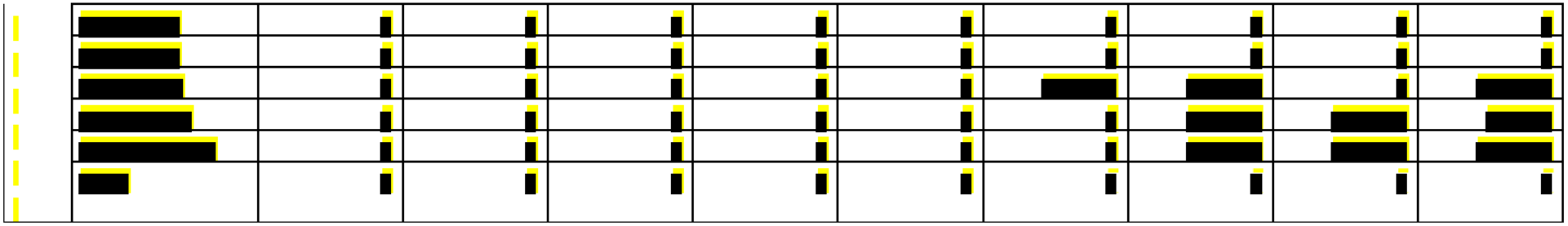
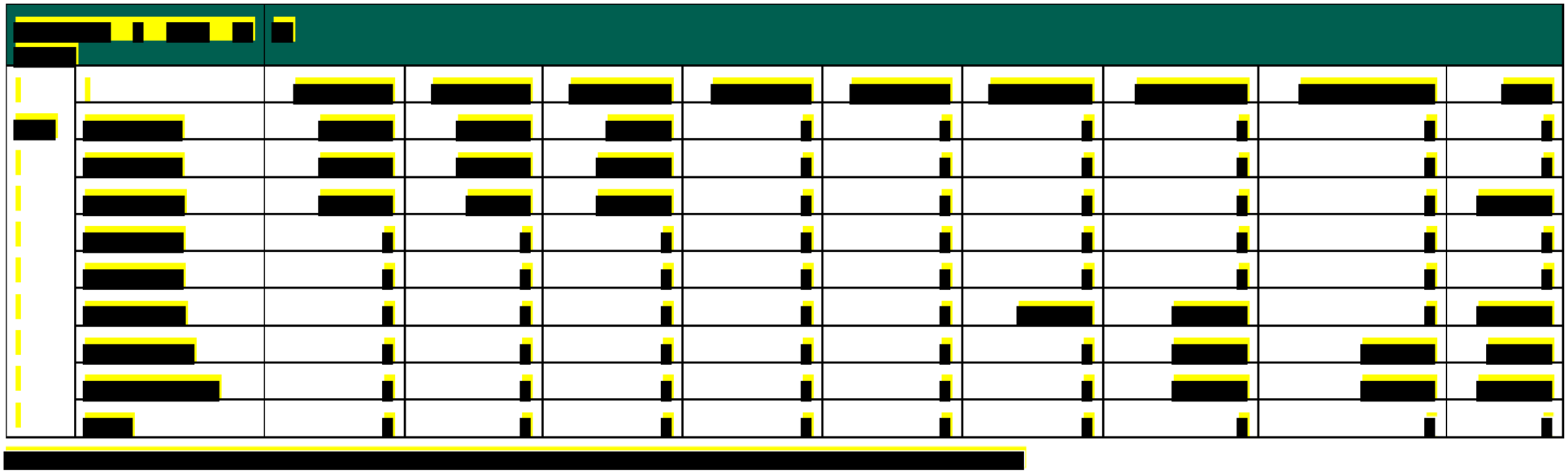


Abbreviations: AD = active disease; CKD = chronic kidney disease; CR = complete response; MMF = mycophenolate mofetil; PR = partial response



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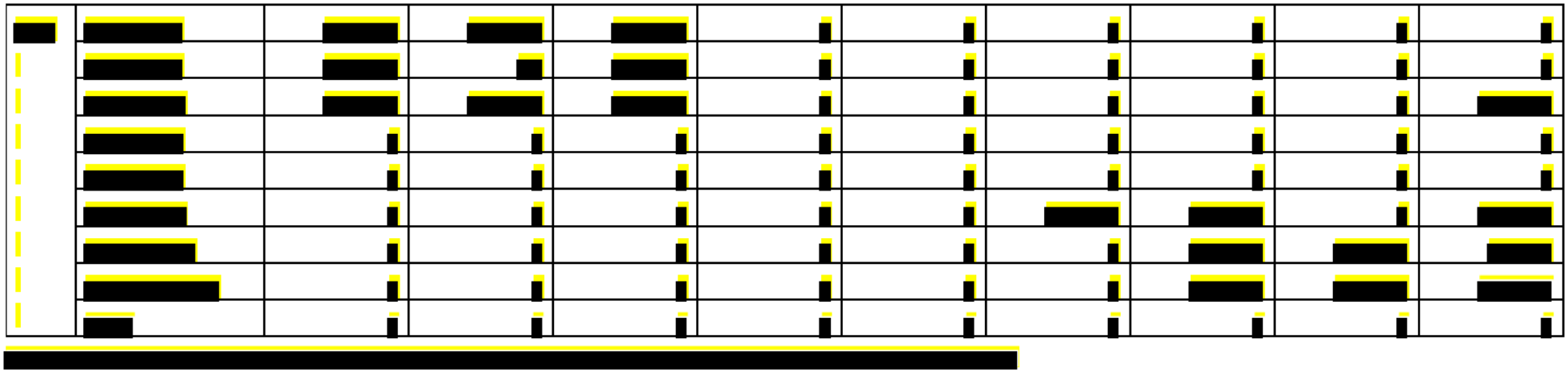

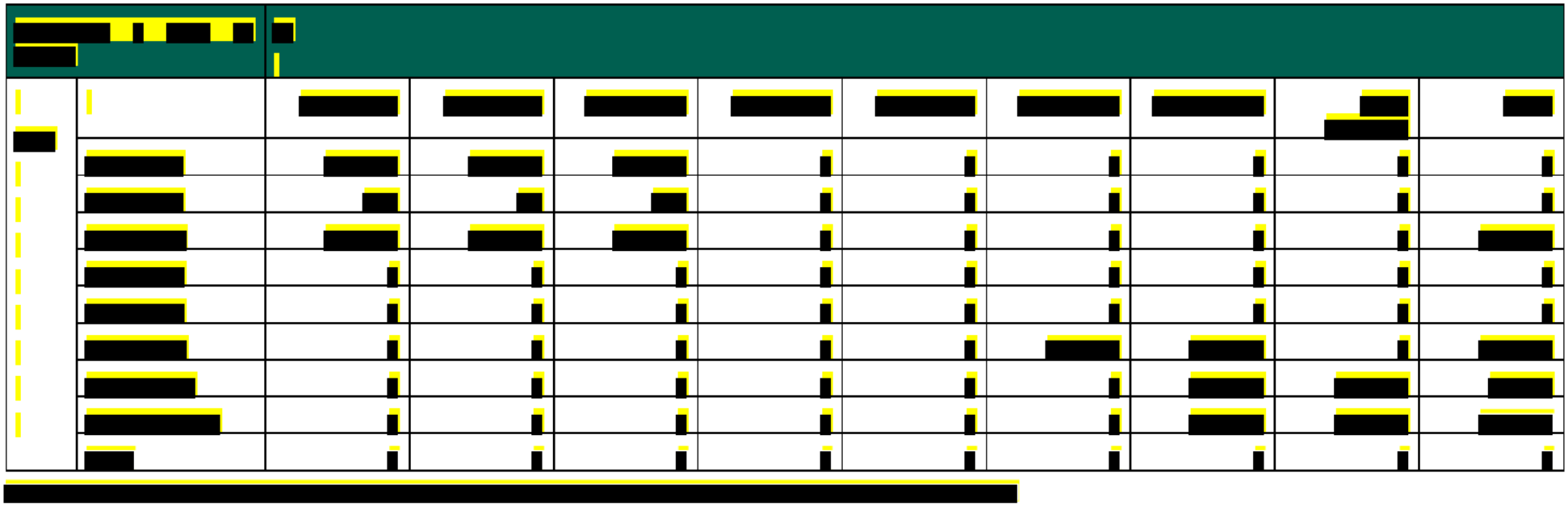

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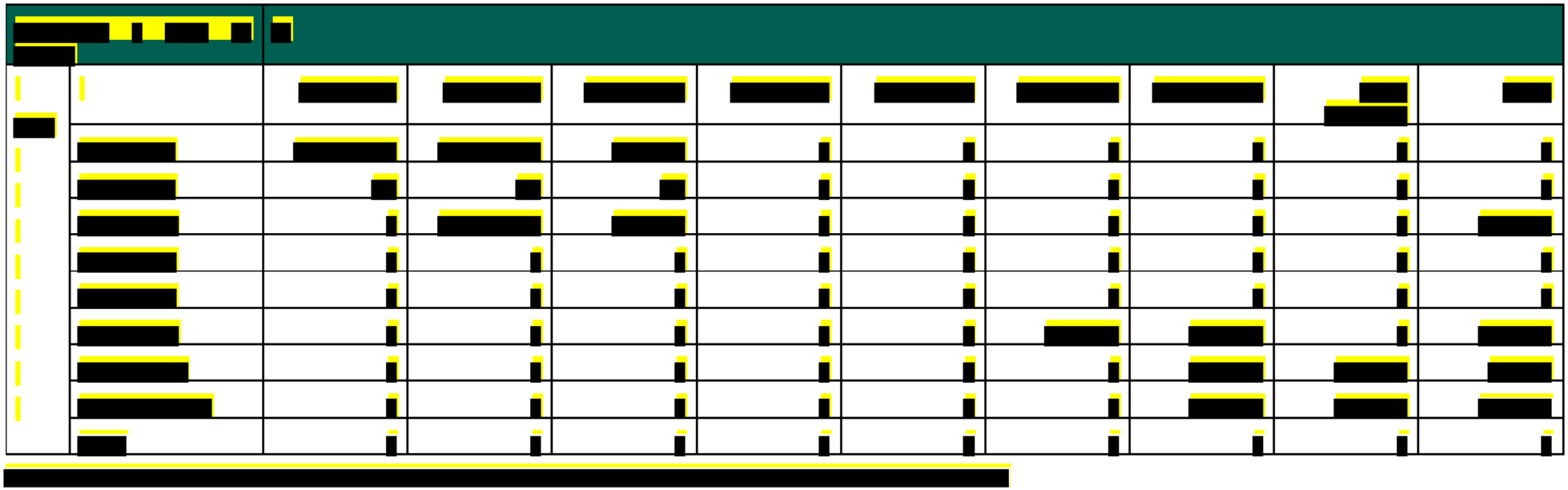

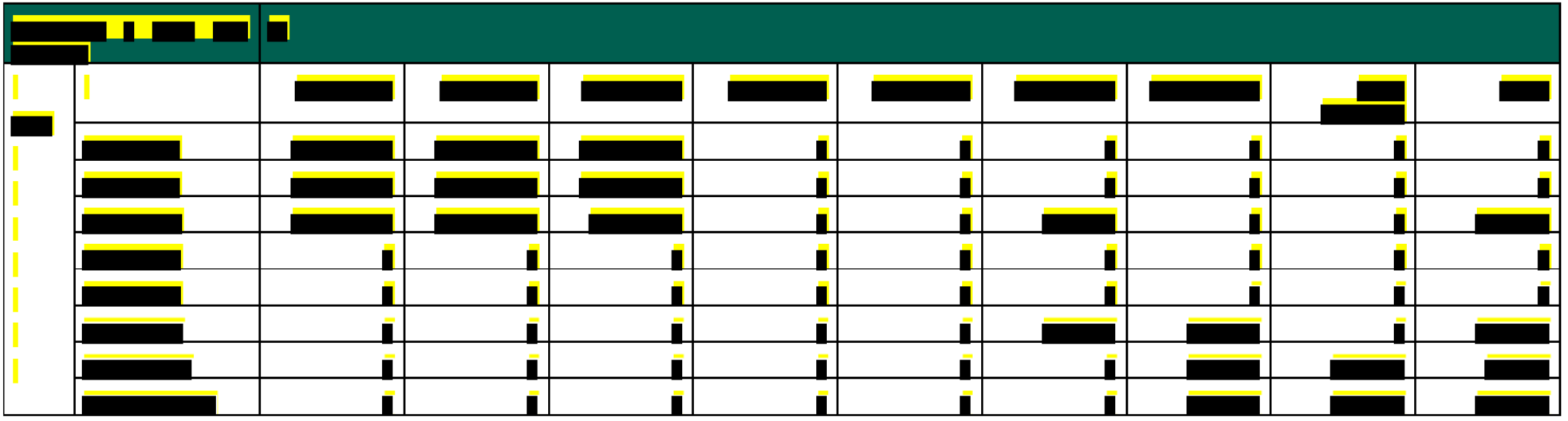

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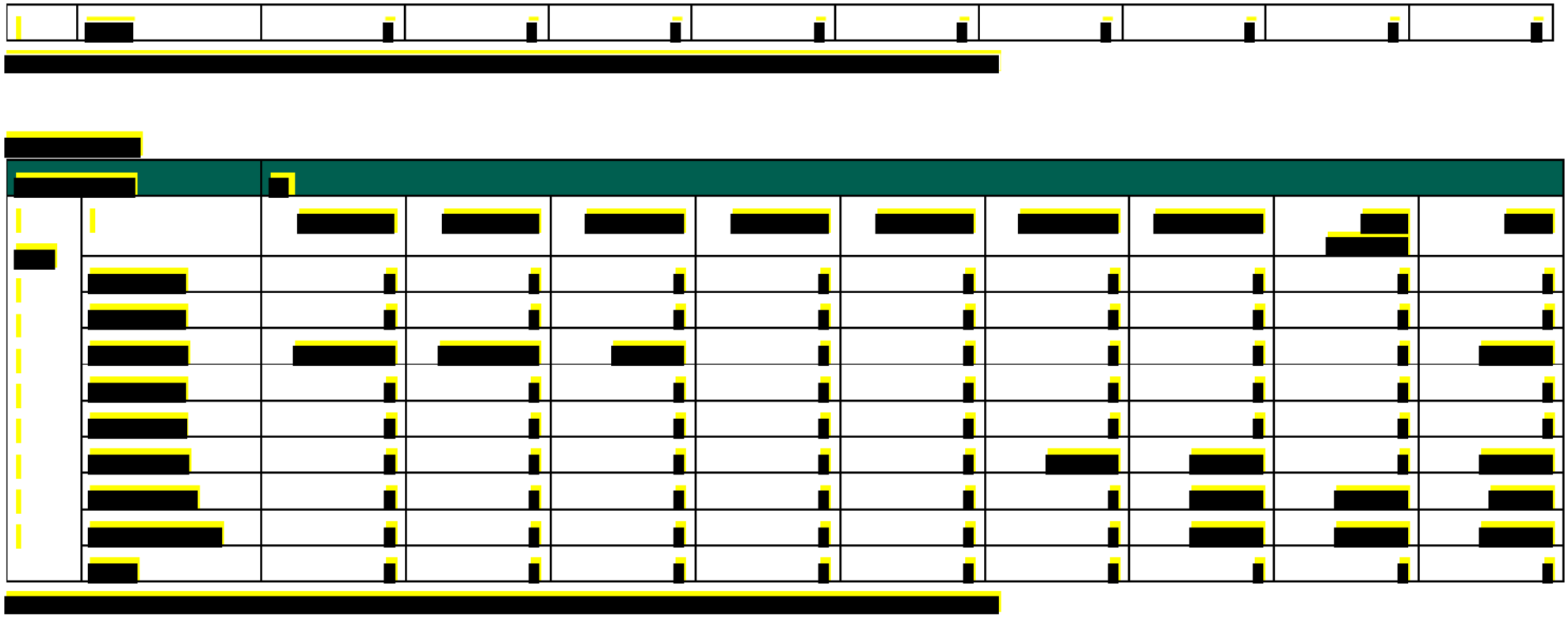

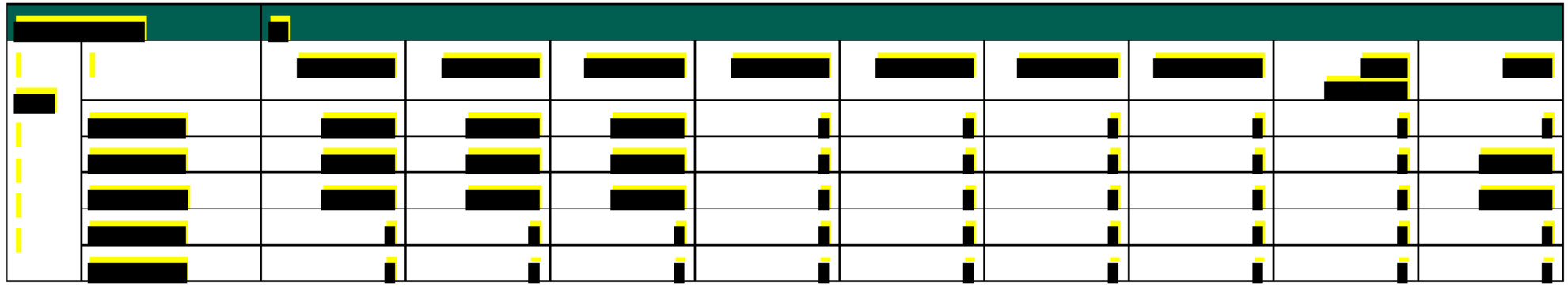

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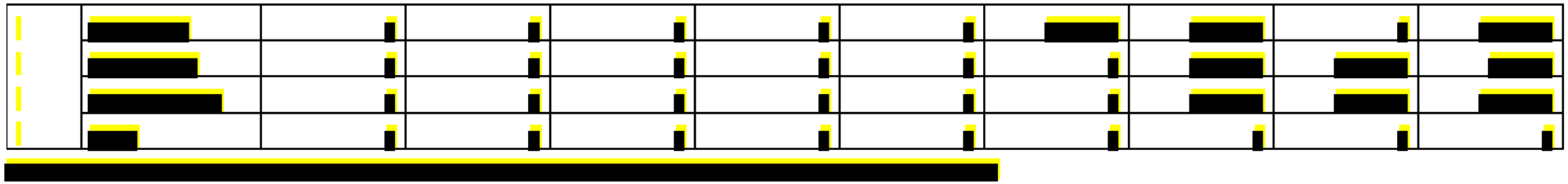

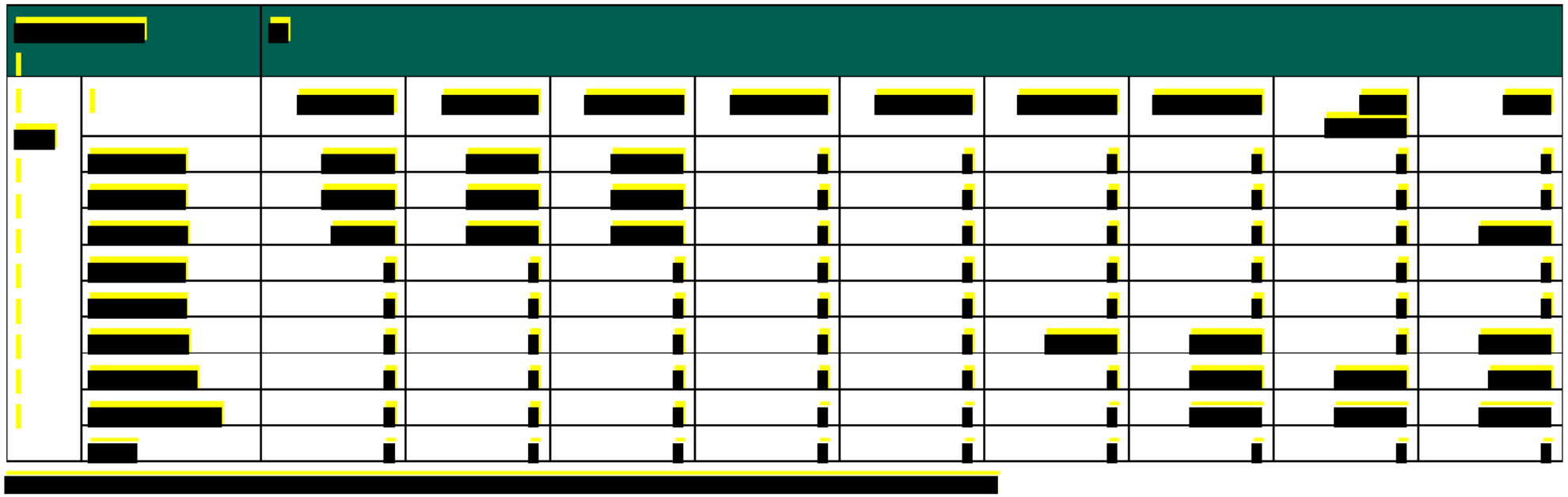

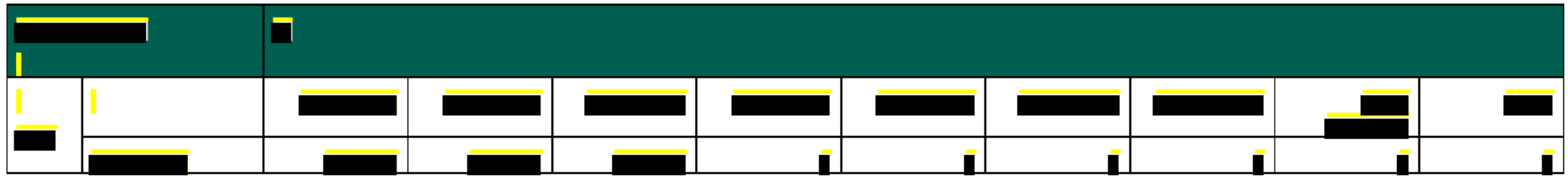

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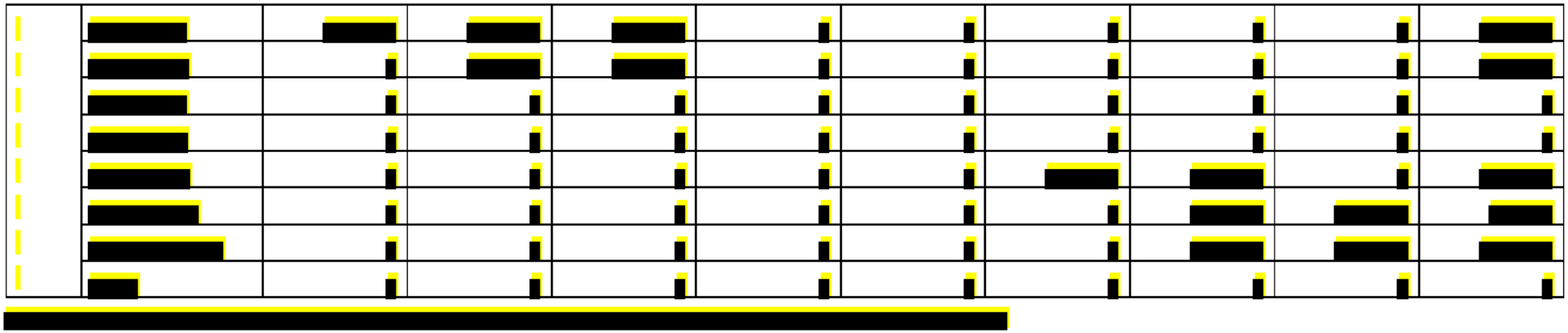

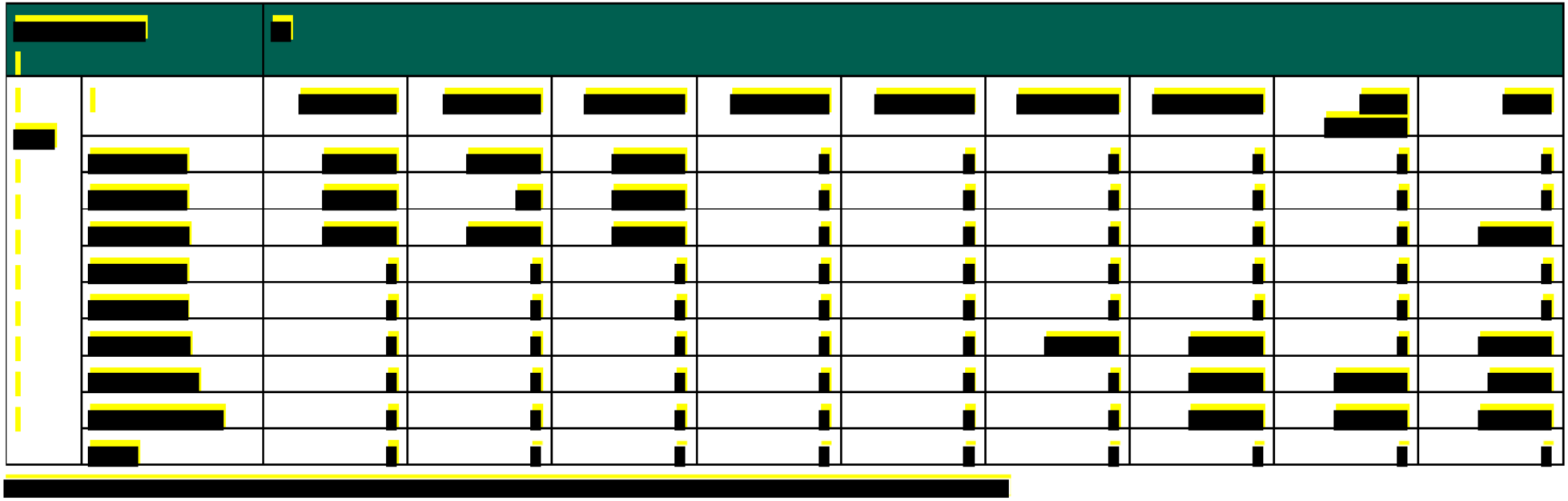

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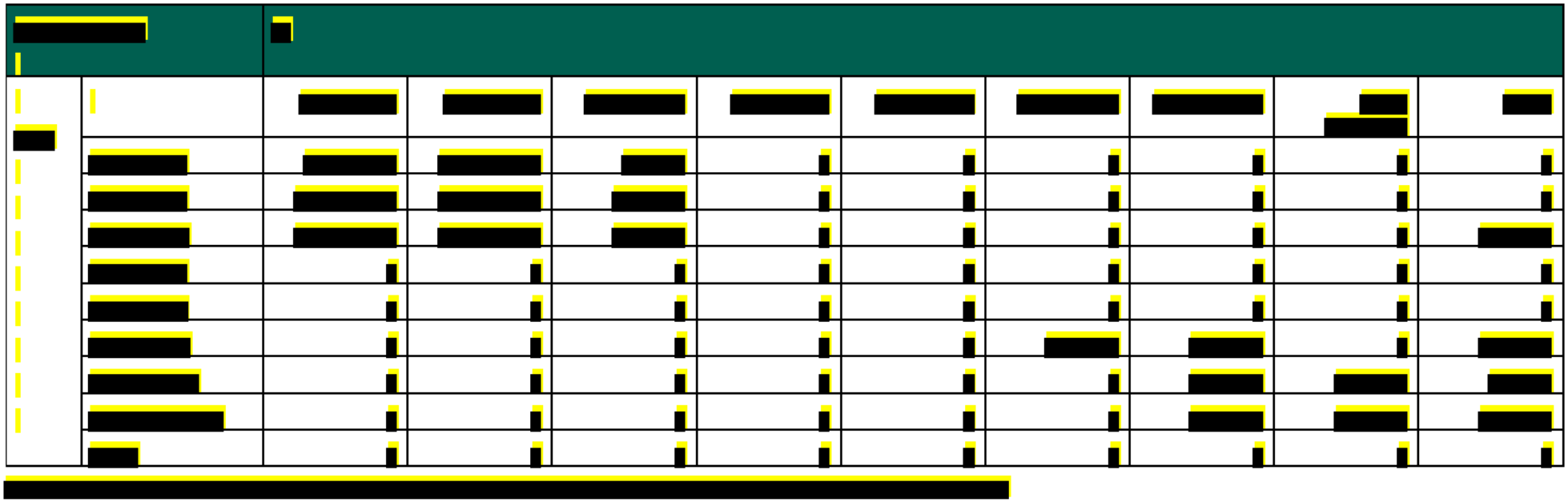

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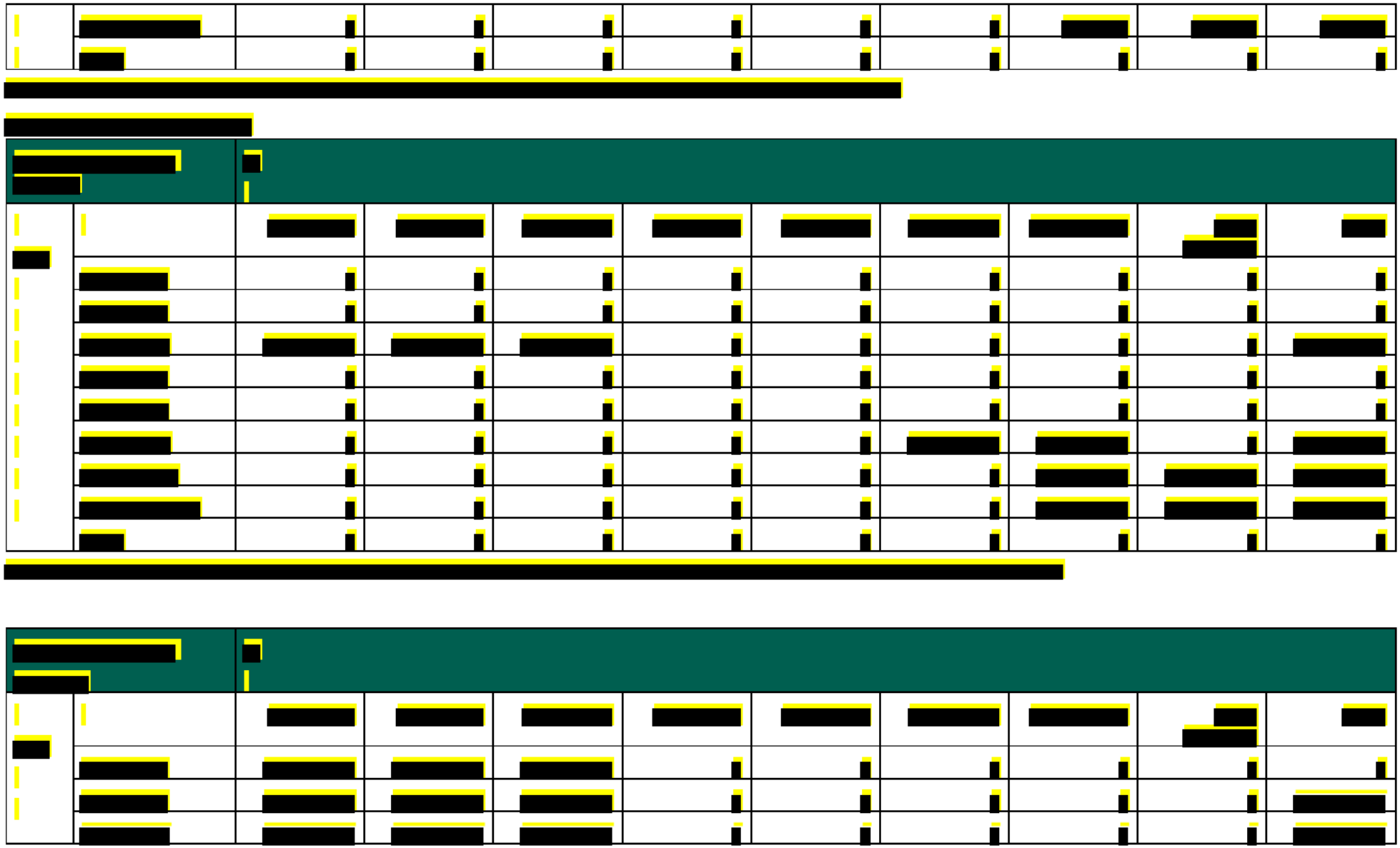

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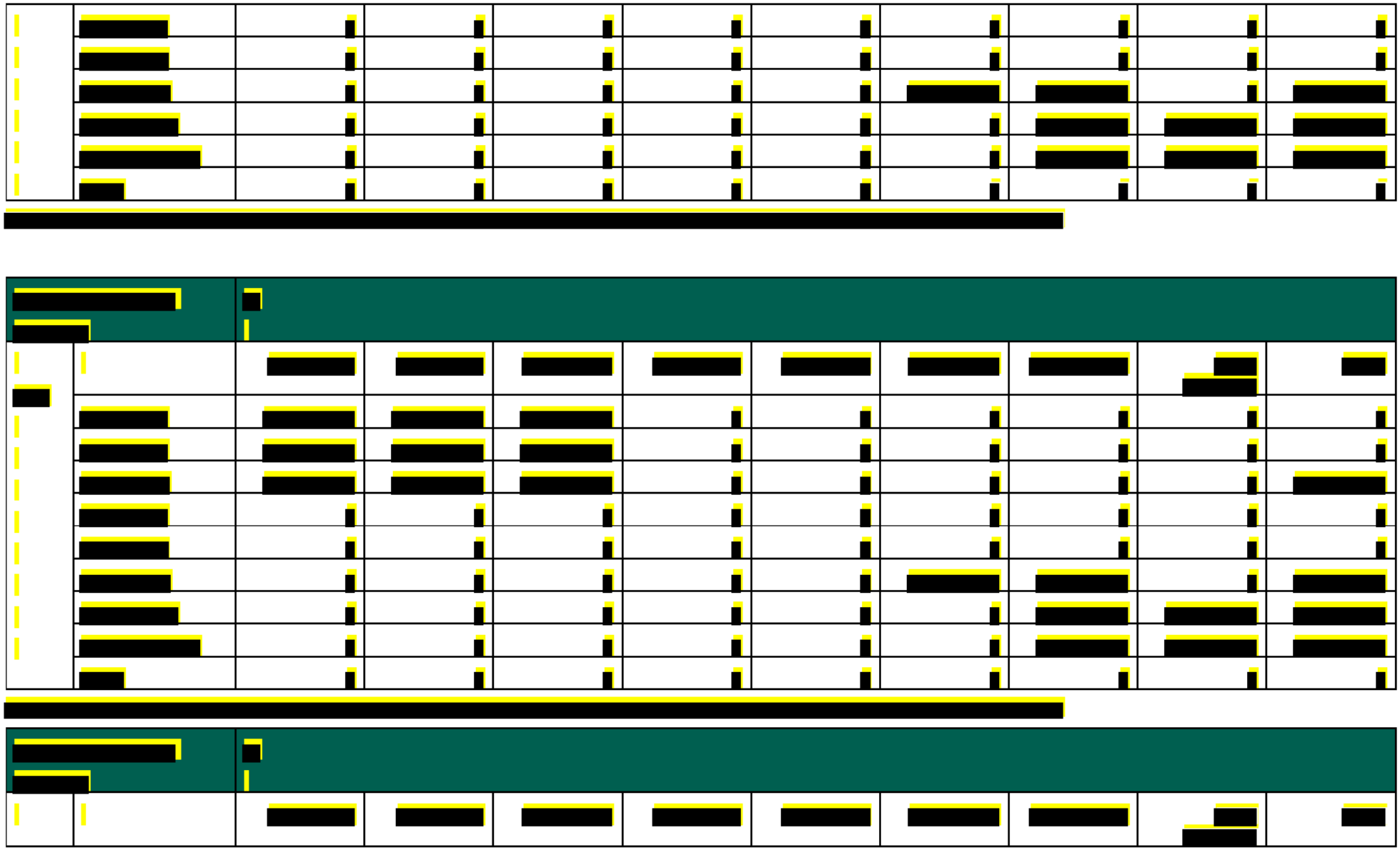

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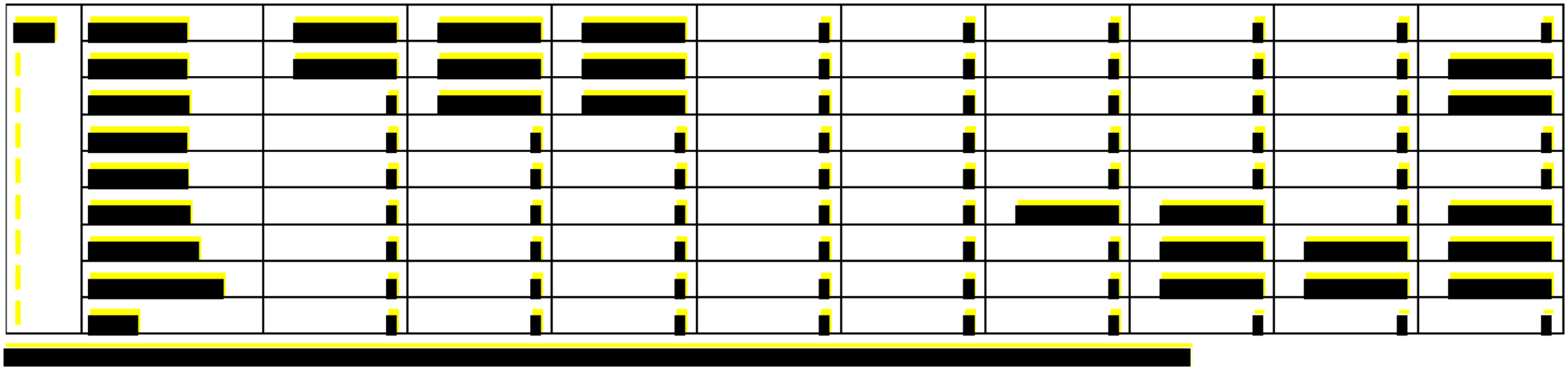

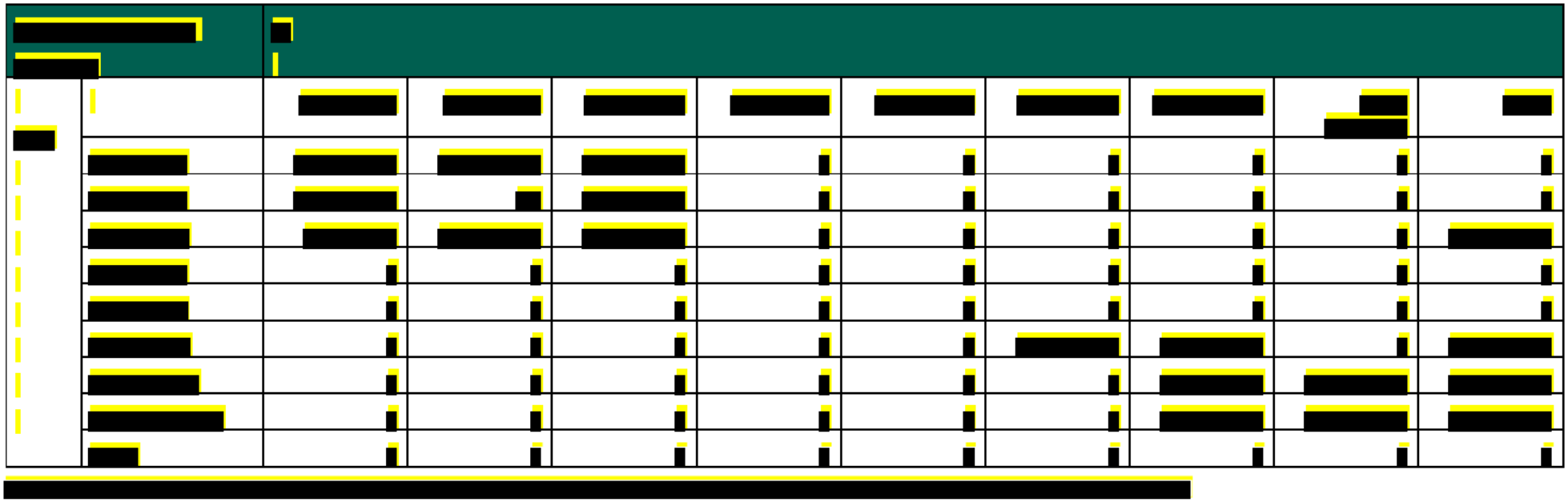

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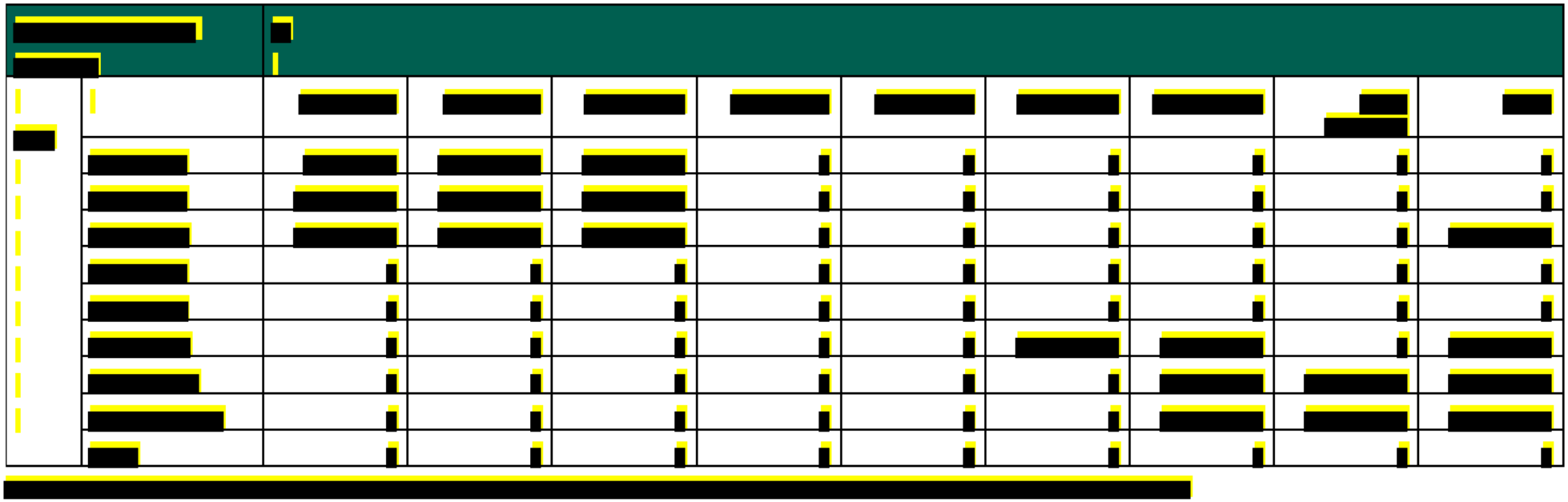

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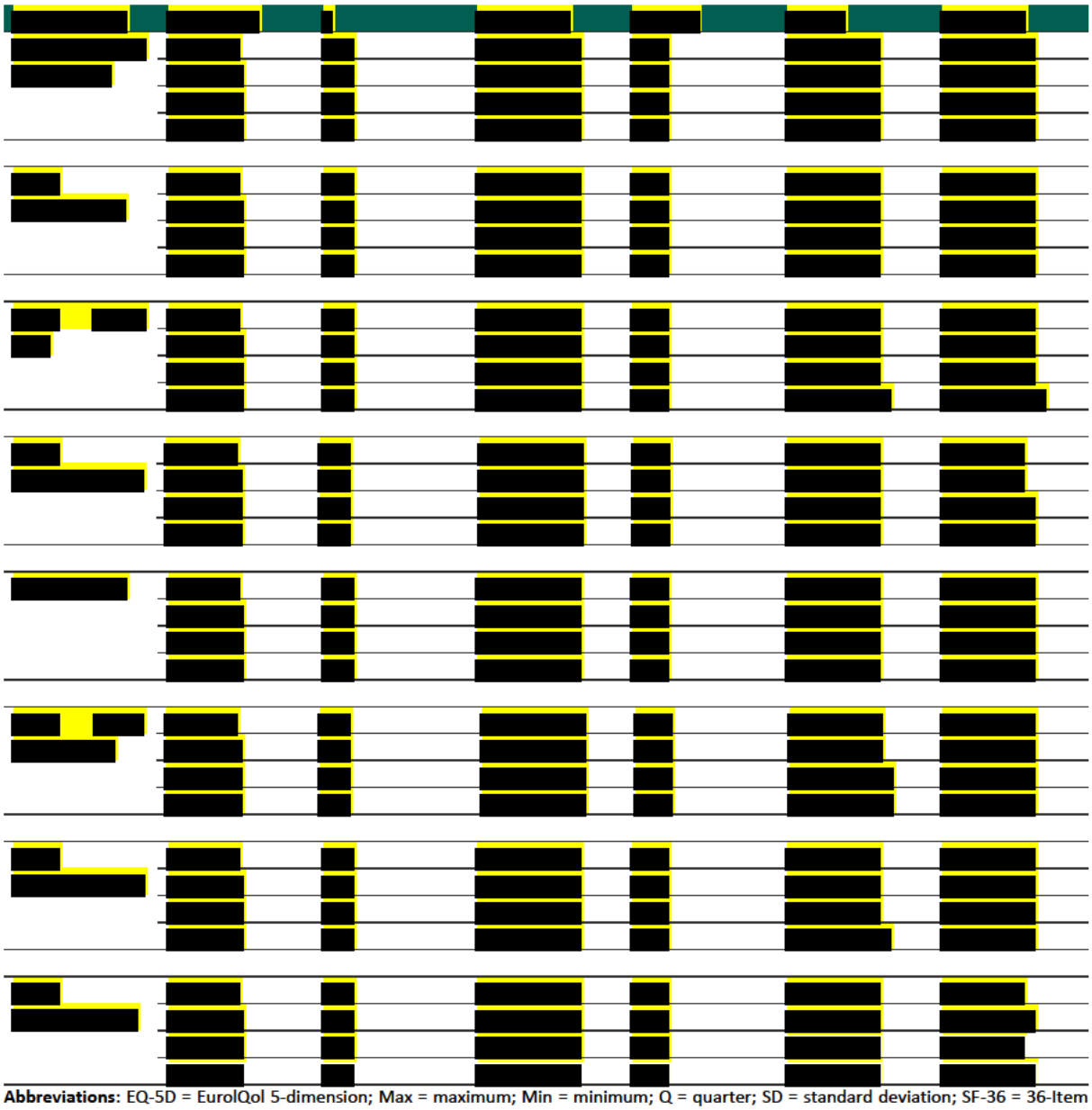
Appendix L Summary of patient-reported outcomes

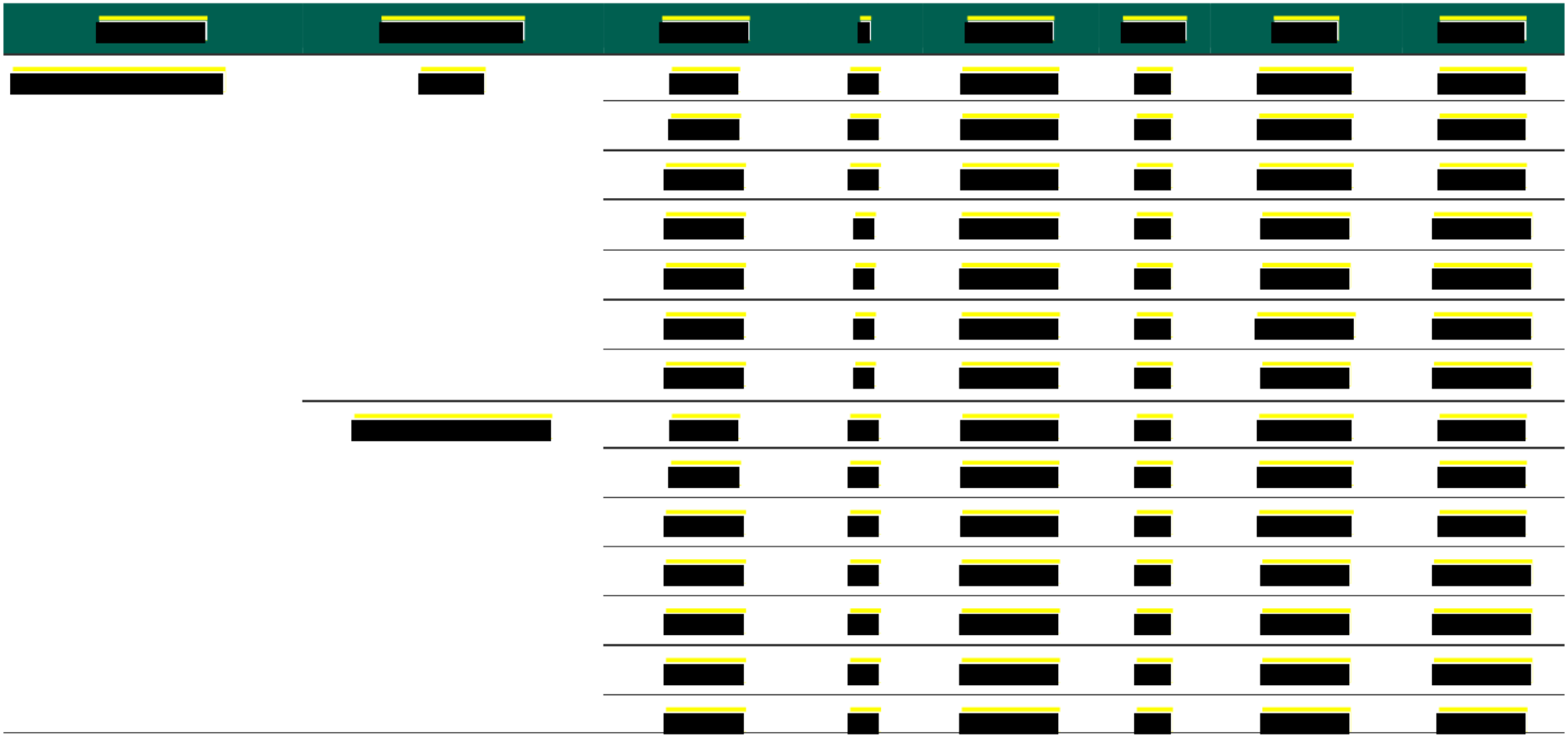
Table 132: Summary of SF-36 and Mapped EQ-5D scores by visit (AURORA)



Abbreviations: EQ-5D = EurolQol 5-dimension; Max = maximum; Min = minimum; Q = quarter; SD = standard deviation; SF-36 = 36-Item Short Form Survey

Below is presented a summary of the integrated AURORA 1 and AURORA 2 SF-36 results.

Table 133: Summary of SF-36 and Mapped EQ-5D scores by visit: Physical functioning (integrated AURORA 1 and AURORA 2)



Abbreviations: BID = twice-daily; EQ-5D = EurolQol 5-dimension; Max = maximum; Min = minimum; Q = quarter; SD = standard deviation; SF-36 = 36-Item Short Form Survey

Table 134: Summary of SF-36 and Mapped EQ-5D scores by visit: Role Physical (integrated AURORA 1 and AURORA 2)

Abbreviations: BID = twice-daily; EQ-5D = EurolQol 5-dimension; Max = maximum; Min = minimum; Q = quarter; SD = standard deviation; SF-36 = 36-Item Short Form Survey

Table 135: Summary of SF-36 and Mapped EQ-5D scores by visit: Bodily Pain (integrated AURORA 1 and AURORA 2)

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[redacted]

Abbreviations: BID = twice-daily; EQ-5D = EurolQol 5-dimension; Max = maximum; Min = minimum; Q = quarter; SD = standard deviation; SF-36 = 36-Item Short Form Survey

Table 136: Summary of SF-36 and Mapped EQ-5D scores by visit: General Health (integrated AURORA 1 and AURORA 2)

[redacted]

[redacted]

Abbreviations: BID = twice-daily; EQ-5D = EurolQol 5-dimension; Max = maximum; Min = minimum; Q = quarter; SD = standard deviation; SF-36 = 36-Item Short Form Survey

Table 137: Summary of SF-36 and Mapped EQ-5D scores by visit: Vitality (integrated AURORA 1 and AURORA 2)

[redacted]

[redacted]

Abbreviations: BID = twice-daily; EQ-5D = EurolQol 5-dimension; Max = maximum; Min = minimum; Q = quarter; SD = standard deviation; SF-36 = 36-Item Short Form Survey

Table 138: Summary of SF-36 and Mapped EQ-5D scores by visit: Social Functioning (integrated AURORA 1 and AURORA 2)

[redacted]

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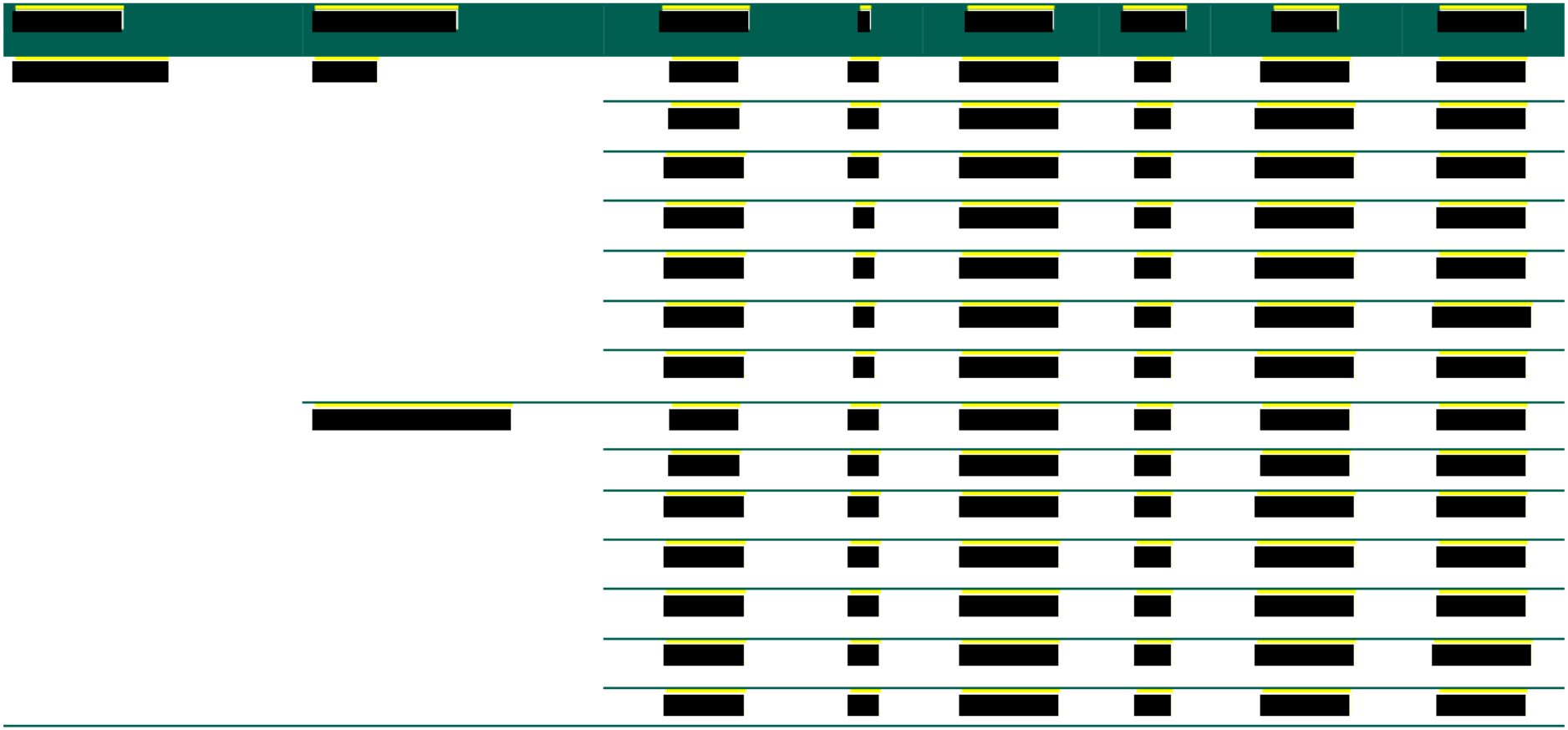
Abbreviations: BID = twice-daily; EQ-5D = EurolQol 5-dimension; Max = maximum; Min = minimum; Q = quarter; SD = standard deviation; SF-36 = 36-Item Short Form Survey

Table 139: Summary of SF-36 and Mapped EQ-5D scores by visit: Role Emotional (integrated AURORA 1 and AURORA 2)



Abbreviations: BID = twice-daily; EQ-5D = EurolQol 5-dimension; Max = maximum; Min = minimum; Q = quarter; SD = standard deviation; SF-36 = 36-Item Short Form Survey

Table 140: Summary of SF-36 and Mapped EQ-5D scores by visit: Mental Health (integrated AURORA 1 and AURORA 2)

[redacted]

Abbreviations: BID = twice-daily; EQ-5D = EurolQol 5-dimension; Max = maximum; Min = minimum; Q = quarter; SD = standard deviation; SF-36 = 36-Item Short Form Survey

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The only lupus-specific patient-reported outcome measure included in the AURORA trials was LupusPRO v1.7, which was collected during AURORA 1 only. Since LupusPRO is collected over 12 domains (Lupus Symptoms, Cognition, Lupus Medications, Procreation, Physical Health, Pain Vitality, Emotional Health, Body Image, Desires-Goals, Social Support, Coping and Satisfaction with Care), the summary statistics from each of these domains is presented at baseline, 24 weeks and 52 weeks in Table 141.

Table 141: AURORA 1 - Summary statistics for LupusPRO

Domain and timepoint	Summary Statistic	Voclosporin n=179	Placebo n=178
Lupus Symptoms			
Baseline	n		
	Mean (SD)		
	Median		
	Min, Max		
Week 12	n		
	Mean (SD)		
	Median		
	Min, Max		
Week 24	n		
	Mean (SD)		
	Median		
	Min, Max		
Week 52	n		
	Mean (SD)		
	Median		
	Min, Max		
Cognition			
Baseline	n		
	Mean (SD)		
	Median		
	Min, Max		
Week 12	n		
	Mean (SD)		
	Median		
	Min, Max		
Week 24	n		
	Mean (SD)		
	Median		
	Min, Max		
Week 52	n		
	Mean (SD)		
	Median		
	Min, Max		
Lupus Medications			

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Baseline	n	[redacted]
	Mean (SD)	
	Median	
	Min, Max	
Week 12	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 24	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 52	n	
	Mean (SD)	
	Median	
	Min, Max	
Procreation		
Baseline	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 12	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 24	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 52	n	
	Mean (SD)	
	Median	
	Min, Max	
Physical Health		
Baseline	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 12	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 24	n	
	Mean (SD)	
	Median	

	Min, Max	[redacted]
Week 52	n	
	Mean (SD)	
	Median	
	Min, Max	
Pain Vitality		
Baseline	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 12	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 24	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 52	n	
	Mean (SD)	
	Median	
	Min, Max	
Emotional Health		
Baseline	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 12	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 24	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 52	n	
	Mean (SD)	
	Median	
	Min, Max	
Body Image		
Baseline	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 12	n	

	Mean (SD)	[redacted]
	Median	
	Min, Max	
Week 24	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 52	n	
	Mean (SD)	
	Median	
	Min, Max	
Desires-Goal		
Baseline	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 12	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 24	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 52	n	
	Mean (SD)	
	Median	
	Min, Max	
Social support		
Baseline	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 12	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 24	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 52	n	
	Mean (SD)	
	Median	
	Min, Max	

Coping		[redacted]
Baseline	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 12	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 24	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 52	n	
	Mean (SD)	
	Median	
	Min, Max	
Satisfaction with care		
Baseline	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 12	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 24	n	
	Mean (SD)	
	Median	
	Min, Max	
Week 52	n	
	Mean (SD)	
	Median	
	Min, Max	

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation
Source: Otsuka 2020(136)

LupusPRO can be summed into two total scores, the HRQOL, as well as non-HRQOL. Correlation pots for both have been presented against EQ-5D, at both baseline (Figure 32 and Figure 33) and month 12 (Figure 34 and

Figure 35). The Spearman's rank correlation coefficient was 0.706 at baseline and 0.685 at month 12 for HRQoL, and 0.338 at baseline and 0.370 at month 12 for non-HRQOL.

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Figure 32: Correlation plot of HRQOL LupusPRO against EQ-5D, baseline

Abbreviations: EQ5D = EuroQoL 5-dimension scale; HRQoL = health-related quality of life; QoL = quality of life

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Figure 33: Correlation plot of non-HRQOL LupusPRO against EQ-5D, baseline

Abbreviations: EQ5D = EuroQoL 5-dimension scale; HRQoL = health-related quality of life; QoL = quality of life

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Figure 34: Correlation plot of HRQOL LupusPRO against EQ-5D, Month 12

Abbreviations: EQ5D = EuroQoL 5-dimension scale; HRQoL = health-related quality of life; QoL = quality of life

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Figure 35: Correlation plot of non-HRQOL LupusPRO against EQ-5D, month 12

Abbreviations: EQ5D = EuroQoL 5-dimension scale; HRQoL = health-related quality of life; QoL = quality of life

Appendix M Subgroup analyses for AURA-LV

Methodology and statistical analysis

No subgroup analyses were stipulated in the Statistical Analysis Plan (SAP). However, post-hoc subgroup analyses were conducted for CRR at Weeks 24 and 48 to explore the impact of the imbalance in randomisation of low gross domestic product (GDP) patients (i.e., low-GDP and non-low GDP) and biopsy class (i.e., class III, III/V, IV, IV/V, and V). TEAEs and serious TEAEs were analysed according to GDP subgroups (139).

Covariate analyses were also conducted for CRR at Week 24 and 48 including the following covariates (139):

Age (≤30 vs >30 years)

Gender (male, female)

Race (White, Asian, other)

Biopsy class (class V, other)

Region (Asia-Pacific, Europe and South Africa, Latin America, North America)

MMF use at screening (yes, no)

Maximum MMF dose (≤2 g vs >2 g)

Subgroup analysis: CRR and TEAES/serious TEAEs in GDP subgroups

At Week 24, the CRR rate was lower for both voclosporin dose groups within the low-GDP subgroup, particularly for those treated with high-dose voclosporin (low GDP: 12.1% vs non-low GDP: 36.4%). The impact was less pronounced at Week 48, with little difference in CRR between the overall population or GDP subgroups (139). Across both voclosporin dose groups, CRR rates at Week 24 increased when low-GDP patients were excluded (i.e., from 32.6% to 38.3% in the low-dose group and from 27.3% to 36.4% in the high-dose group) (139). When low-GDP patients were excluded, the overall incidence of TEAEs was also reduced, especially in the two voclosporin groups. In addition, a similar incidence of serious TEAEs and TEAEs leading to death was observed in patients in non-low GDP countries among all three treatment groups (139). Subgroup analysis of CRR at week 24 and week 48 according to GDP subgroup is presented in Table 142, along with a summary of TEAs and serious TEAs according to GDP in Table 143.

Table 142: AURA-LV - Subgroup analysis of CRR at week 24 and week 48 according to GDP subgroup

GDP subgroup Treatment group		n (%)	OR vs. Placebo (95% CI)	p-value
Week 24 - All	Placebo (N=88)	17 (19.3%)	-	-
	VCS 23.7 mg BID (N=89)	29 (32.6%)	2.03 (1.01, 4.05)	0.045*
	VCS 39.5 mg BID (N=88)	24 (27.3%)	1.59 (0.78, 3.27)	0.204
Week 24 – Low-GDP	Placebo (N=28)	6 (21.4%)		
	VCS 23.7 mg BID (N=42)	11 (26.2%)	1.21 (0.38, 3.85)	0.7509
	VCS 39.5 mg BID (N=33)	4 (12.1%)	0.49 (0.12, 1.97)	0.3162
Week 24 – Non-Low-GDP	Placebo (N=60)	11 (18.3%)		
	VCS 23.7 mg BID (N=47)	18 (38.3%)	2.88 (1.18, 7.01)	0.0199*
	VCS 39.5 mg BID (N=55)	20 (36.4%)	2.51 (1.06, 5.94)	0.0364*

Week 48 – All	Placebo (N=88)	21 (23.9%)		
	VCS 23.7 mg BID (N=89)	44 (49.4%)	3.21 (1.68, 6.13)	<0.001*
	VCS 39.5 mg BID (N=88)	35 (39.8%)	2.10 (1.09, 4.02)	0.0.026*
Week 48 – Low-GDP	Placebo (N=28)	8 (28.6%)		
	VCS 23.7 mg BID (N=42)	21 (50.0%)	2.86 (1.00, 8.22)	0.0504*
	VCS 39.5 mg BID (N=33)	12 (36.4%)	1.49 (0.50, 4.46)	0.4747
Week 48 – Low-GDP Excluded	Placebo (N=60)	13 (21.7%)		
	VCS 23.7 mg BID (N=47)	23 (48.9%)	3.50 (1.51, 8.12)	0.0036*
	VCS 39.5 mg BID (N=55)	23 (41.8%)	2.59 (1.14, 5.86)	0.0228*

Note: *Indicates a statistically significant difference in a logistic regression analysis comparing the OR for achievement of CRR (at Week 24 or Week 48) with voclosporin vs. placebo treatment (p<0.05).

Abbreviations: BID = twice daily; CI = confidence interval; CRR = complete renal response; GDP = gross domestic product; OR = odds ratio; VCS = voclosporin.

Source: Otsuka 2018 (139)

Table 143: Summary of TEAEs and serious TEAEs according to GDP subgroup

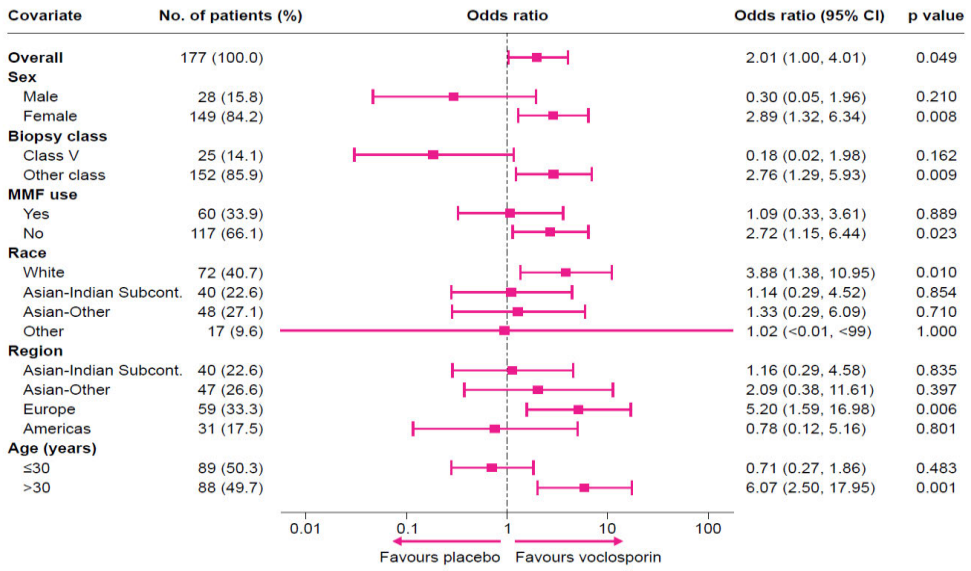
	Placebo			**Voclosporin 23.7 mg BID**			**Voclosporin 39.5 mg BID**		
	All (N=88)	Low-GDP* (N=28)	Non-Low-GDP (N=60	All (N=89)	Low-GDP (N=42)	Non-Low-GDP (N=47)	All (N=88)	Low-GDP (N=33)	Non-Low-GDP (N=55)
TEAE, n (%)	75 (85.2)	27 (96.4)	48 (80.0)	82 (92.1)	40 (95.2)	42 (89.4)	85 (96.6)	33 (100.0)	52 (94.5)
Treatment-related TEAE, n (%)	15 (17.0)	6 (21.4)	9 (15.0)	45 (50.6)	22 (52.4)	23 (48.9)	55 (62.5)	18 (54.5)	37 (67.3)
TEAE in the SOC of Infections and Infestations, n (%)	47 (53.4)	17 (60.7)	30 (50.0)	52 (58.4)	29 (69.0)	23 (48.9)	58 (65.0	27 (81.8)	31 (56.4)
TEAE leading to permanent study drug discontinuation, n (%)	9 (10.2%)	1 (3.6%)	8 (13.3%)	16 (18.0%)	11 (26.2%)	5 (10.6%)	14 (15.9%)	4 (12.1%)	10 (18.2%)
Serious TEAE, n (%)	14 (15.9%)	3 (10.7%)	11 (18.3%)	25 (28.1%)	17 (40.5%)	8 (17.0%)	22 (25.0%)	12 (36.4%)	10 (18.2%)
Serious treatment-related TEAE, n (%)	1 (1.1%)	0 (0.0%)	1 (1.7%)	4 (4.5%)	4 (9.5%)	0 (0.0%)	7 (8.0%)	4 (12.1%)	3 (5.5%)
Serious TEAE in the SOC of Infections and Infestations, n (%)	7 (8.0%)	1 (3.6%)	6 (10.0%)	11 (12.4%)	8 (19.0%)	3 (6.4%)	12 (13.6%)	6 (18.2%)	6 (10.9%)
TEAE leading to death, n (%)	1 (1.1%)	0 (0.0%)	1 (1.7%)	10 (11.2%)	9 (21.4%)	1 (2.1%)	2 (2.3%)	2 (6.1%)	0 (0.0%)

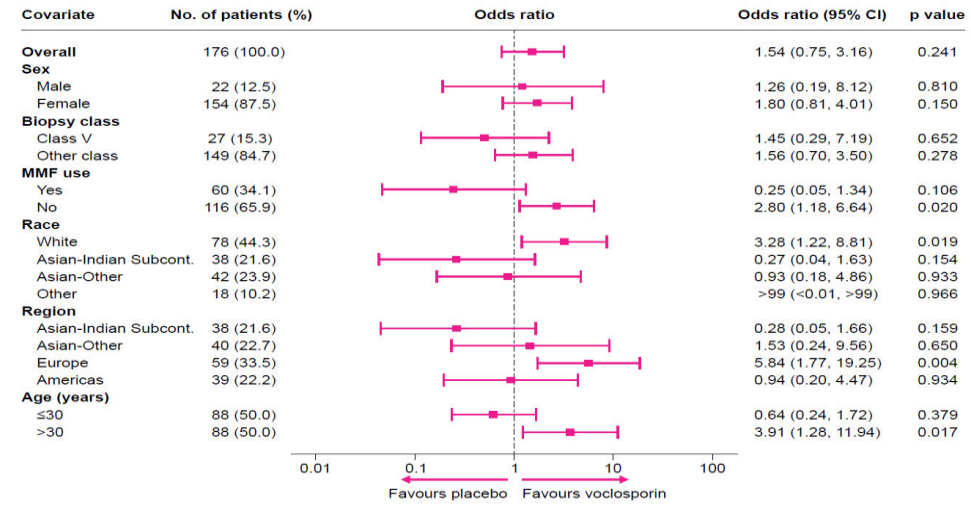
Note: *Low-GDP countries included Bangladesh, Sri Lanka and the Philippines.
Abbreviations: BID = twice daily; GDP = gross domestic product; SOC = system organ class; TEAE = treatment-emergent adverse event
Source: Otsuka 2018(139)

Subgroup analysis: CRR in biopsy subgroups

Figure 36: AURA-LV - Covariate Analyses of CRR at week 24 (Top: Low-dose; Bottom: High-dose voclosporin)

Low-dose voclosporin (Week 24) and High-dose voclosporin (Week 24)





Abbreviations: CI = confidence interval; CRR = complete renal response
Source: Rovin et al. 2019 (202)

At both Week 24 and Week 48, a trend favouring low-dose voclosporin over placebo was maintained across all biopsy classes apart from pure class V. The results for an "all but pure class V" subgroup were consistent with the results for the overall population (139). Results of the covariate analysis examining the effect of gender, biopsy class (at screening), MMF use (at screening), race, region, and age on the primary endpoint are summarised for the full analysis set (FAS) in Figure 36 and Figure 37 for the comparison of placebo vs low-dose and high dose voclosporin (ORs) (202). Subgroup analysis of CRR at week 24 and week 48 according to the biopsy subgroup is presented in Table 144.

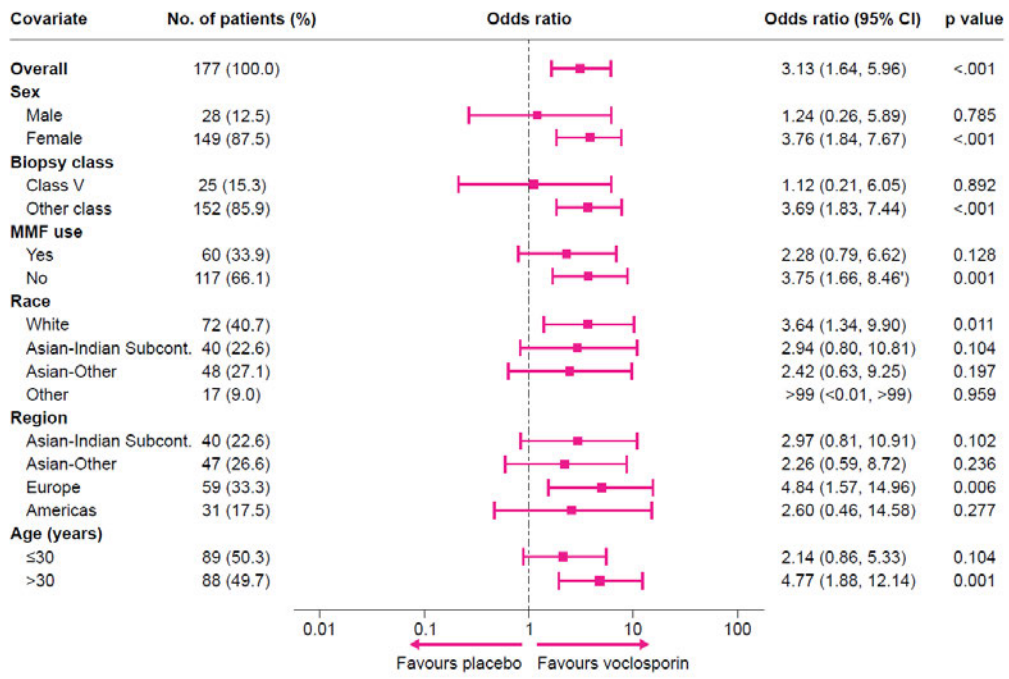
Table 144: AURA-LV - Subgroup analyses of CRR at week 24 and 48 according to biopsy subgroup

Biopsy class	Treatment group	Complete remission at Week 24			Complete remission at Week 48		
		n (%)	OR vs Placebo (95% CI)	p-value vs Placebo	n (%)	OR vs Placebo (95% CI)	p-value vs Placebo
Biopsy class III	Placebo (N=18)	0 (0.0%)	-	-	3 (16.7%)	-	-
	VCS 23.7 mg BID (N=11)	4 (36.4%)	>99.9 (0.00, >99.9)	0.9403	6 (54.5%)	6.00 (1.08, 33.38)	0.0407
	VCS 39.5 mg BID (N=10)	1 (10.0%)	>99.9 (0.00, >99.9)	0.9480	1 (10.0%)	0.56 (0.05, 6.18)	0.6325
Biopsy class III/IV	Placebo (N=8)	1 (12.5%)	-	-	1 (12.5%)	-	-
	VCS 23.7 mg BID (N=11)	3 (27.3%)	2.62 (0.22, 31.35)	0.4457	5 (45.5%)	5.83 (0.52, 64.80)	0.1512
	VCS 39.5 mg BID (N=7)	2 (28.6%)	2.80 (0.20, 40.06)	0.4482	2 (28.6%)	2.80 (0.20, 40.04)	0.4483
Biopsy class IV	Placebo (N=41)	10 (24.4%)	-	-	12 (29.3%)	-	-
	VCS 23.7 mg BID (N=44)	17 (38.6%)	1.95 (0.77, 4.98)	0.1615	24 (54.5%)	2.90 (1.18, 7.11)	0.0200
	VCS 39.5 mg BID (N=53)	15 (28.3%)	1.22 (0.48, 3.10)	0.6707	24 (45.3%)	2.00 (0.84, 4.74)	0.1155
Biopsy class IV/V	Placebo (N=8)	2 (25.0%)	-	-	1 (12.5%)	-	-
	VCS 23.7 mg BID (N=10)	4 (40.0%)	2.00 (0.26, 15.38)	0.5054	5 (50.0%)	7.00 (0.61, 79.83)	0.1172
	VCS 39.5 mg BID (N=4)	0 (0.0%)	0.00 (0.00, >99.9)	0.9472	1 (25.0%)	2.33 (0.11, 50.96)	0.5904
Biopsy class V	Placebo (N=13)	4 (30.8%)	-	-	4 (30.8%)	-	-
	VCS 23.7 mg BID (N=12)	1 (8.3%)	0.20 (0.02, 2.17)	0.1878	4 (33.3)	1.12 (0.21, 6.05)	0.8908
	VCS 39.5 mg BID (N=14)	6 (42.9%)	1.69 (0.35,8.22)	0.5172	7 (50.0)	2.25 (0.47, 10.88)	0.3133
All but pure class V	Placebo (N=75)	13 (17.3%)	-	-	17 (22.7)	-	-
	VCS 23.7 mg BID (N=77)	28 (36.4%)	2.73 (1.28, 5.81)	0.0094	40 (51.9)	3.69 (1.83, 7.44)	0.0003
	VCS 39.5 mg BID (N=74)	18 (24.3%)	1.53 (0.69, 3.41)	0.2951	28 (37.8)	2.08 (1.01, 4.25)	0.0455

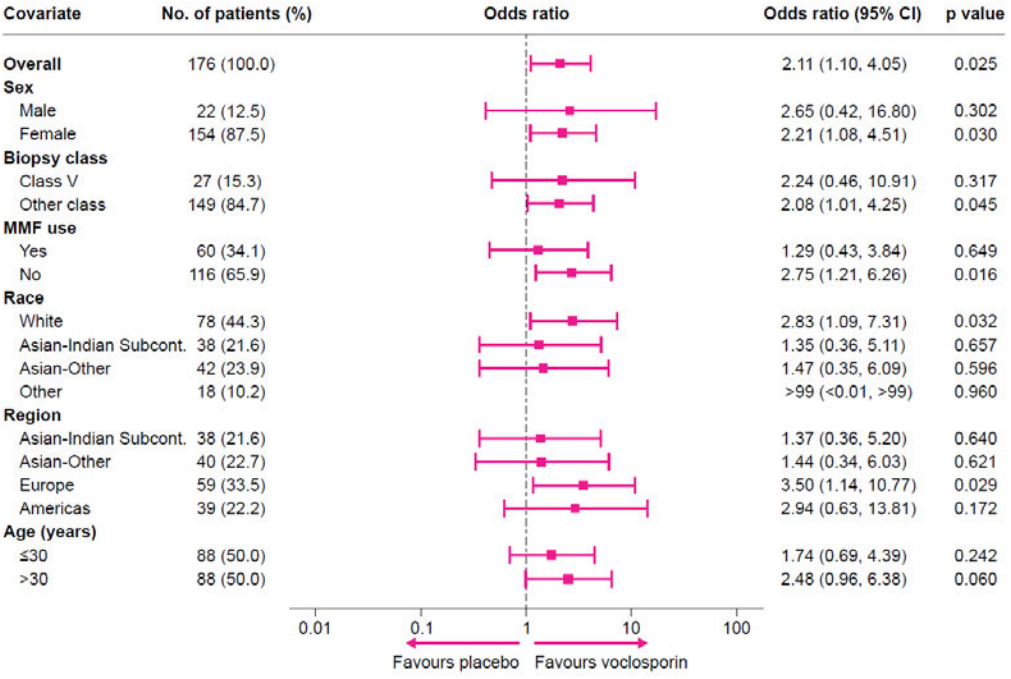
Note: *Indicates a statistically significant difference in a logistic regression analysis comparing the OR for achievement of CRR (at Week 24 or Week 48) with voclosporin vs. placebo treatment (p<0.05).
Abbreviations: BID = twice daily; CI = confidence interval; CRR = complete renal response; OR = odds ratio; VCS = voclosporin
Source: Otsuka 2018 (139)

Figure 37: AURA-LV - Covariate Analyses of CRR at week 48 (*Top:* Low-dose; *Bottom: H*igh-dose voclosporin)

Low-dose voclosporin (Week 48)



High-dose voclosporin (Week 48)



Abbreviations: CI = confidence interval; CRR = complete renal response

Source: Rovin et al. 2019 (202)

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Covariate analyses

Low-dose voclosporin had a beneficial effect in terms of CRR at Week 24 across most covariates compared to placebo. The treatment benefit was not statistically significant for the majority of strata; however, this was likely due to the small sample size (e.g., male gender (n=28) and "other" race (n=17)) (139). ORs in favour of low-dose voclosporin were statistically significant for female gender; "other" biopsy class (i.e., not Class V); no MMF use at screening; White race; the region of Europe; and age >30 years. Odds ratios favoured placebo for male gender (OR 0.30) and Class V biopsy class (OR 0.19), although the results were not statistically significant (p=0.206 and p=0.075, respectively). Overall, similar trends were seen in the covariate analysis for the comparison of high-dose voclosporin vs. placebo (139). Given differences were not significant in scenario analyses, and that patient characteristics in the trial were confirmed to be aligned with those in Denmark, it is not expected that that certain characteristics affect the prognosis or effectiveness of treatment.

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Appendix O BLISS-LN

In a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, 104-week trial conducted at 107 sites in 21 countries, adults with biopsy-proven, active lupus nephritis we assigned in a 1:1 ratio to receive intravenous belimumab (at a dose of 10 mg per kilogram of body weight) or matching placebo, in addition to standard therapy. The primary end point at week 104 was a primary efficacy renal response (a ratio of urinary protein to creatinine of ≤0.7, an eGFR that was no worse than 20% below the value before the renal flare (pre-flare value) or ≥60 ml per minute per 1.73 m2 of body-surface area, and no use of rescue therapy), and the major secondary end point was a complete renal response (a ratio of urinary protein to creatinine of <0.5, an eGFR that was no worse than 10% below the pre-flare value or ≥90 ml per minute per 1.73 m2, and no use of rescue therapy). The time to a renal-related event or death was assessed.

In addition to standard therapy, patients received intravenous belimumab or placebo on days 1 (baseline), 15, and 29 and every 28 days thereafter to week 100, with final assessments at week 104. Standard induction therapy, chosen by the investigators and initiated within 60 days before day 1, consisted of intravenous cyclophosphamide (500 mg every 2 weeks [±3 days] for 6 infusions) or MMF (target dose, 3 g per day). In patients receiving cyclophosphamide–azathioprine, maintenance therapy (target dose, 2 mg per kilogram per day; ≤200 mg per day) until trial end was initiated 2 weeks after the last dose of cyclophosphamide. For MMF induction, maintenance therapy consisted of MMF at a dose of 1 to 3 g per day until the end of the trial, although after 6 months, the dose could be reduced to 1 g per day. At the investigator's discretion, high-dose glucocorticoids (1 to 3 intravenous pulses of methylprednisolone [500 to 1000 mg each]) could be administered during induction, followed by oral prednisone (0.5 to 1.0 mg per kilogram per day; total daily dose, ≤60 mg).

Efficacy and safety

From July 2012 through July 2017, a total of 797 patients underwent screening, and 448 patients underwent randomization (224 in the belimumab group and 224 in the placebo group); the modified ITT population included 223 patients in each group. Randomization was stratified according to induction regimen (59 patients in each group had received cyclophosphamide, and 164 patients in each group had received MMF) and race (31 patients in the belimumab group and 32 patients in the placebo group were Black, and 192 patients in the belimumab group and 191 patients in the placebo group were not Black). A total of 146 of 223 patients (65%) in the belimumab group and 132 of 223 patients (59%) in the placebo group received a trial agent through week 100.

Primary and major secondary endpoints

The results with respect to the primary and major secondary end points are provided in Table 145. At week 104, significantly more patients in the belimumab group than in the placebo group had a primary efficacy renal response (96 of 223 patients [43%] vs. 72 of 223 patients [32%]; odds ratio, 1.6; 95% CI, 1.0 to 2.3; P=0.03). Components of the primary efficacy renal response at week 104, including a decrease in the ratio of urinary protein to creatinine to 0.7 or less and no treatment failure, occurred more often in recipients of belimumab than in recipients of placebo. More patients in the belimumab group than in the placebo group had a primary efficacy renal response at an earlier time point (week 52) (104 of 223 patients [47%] vs. 79 of 223 patients [35%]; odds ratio, 1.6; 95% CI, 1.1 to 2.4; P=0.02). Significantly more patients who received belimumab than those who received placebo had a complete renal response at week 104 (67 of 223 patients [30%] vs. 44 of 223 patients [20%]; odds ratio, 1.7; 95% CI, 1.1 to 2.7; P=0.02). More patients receiving belimumab than those receiving placebo had components of a complete renal response at week 104, including a decrease in the ratio of urinary protein to creatinine to less than 0.5 and no treatment failure.

The results of unadjusted sensitivity analyses for a primary efficacy renal response and a complete renal response at week 104 were consistent with the results of the primary analyses.

Table 145 BLISS-LN - Primary and major secondary endpoints

End point	Belimumab (N=223)	Placebo (N=223)	Odds Ratio or Hazard Ratio (95% CI)[1]	p-value
	n (percent)			
Primary end point: primary efficacy renal response at week 104[2]	96 (43)	72 (32)	1.6 (1.0 to 2.3)	0.03
Major secondary end points				
CRR at week 104[3]	67 (30)	44 (20)	1.7 (1.1 to 2.7)	0.02
Primary efficacy renal response at week 52[4]	104 (47)	79 (35)	1.6 (1.1 to 2.4)	0.02
Time to renal-related event or death[5]	NA	NA	0.5 (0.3 to 0.8)	0.001
Ordinal renal response without urinary sediment at week 104[6]				
CRR	67 (30)	44 (20)	NA	0.01
Partial renal response[7]	39 (18)	38 (17)	NA	
No response	117 (52)	141 (63)	NA	

Footnote:

[1] Odds ratios are provided for the primary end point and the first two major secondary end points. The hazard ratio is provided for the time to a renal-related event or death. Odds ratios with 95% confidence intervals and P values were calculated with the use of a logistic-regression model for the comparison between belimumab and placebo, with covariates of trial group, induction regimen (cyclophosphamide vs. mycophenolate mofetil), race(Black vs. non-Black), baseline ratio of urinary protein to creatinine, and baseline estimated GFR (eGFR). Withdrawal from the trial, treatment failure, and discontinuation of belimumab or placebo were imputed as a nonresponse. NA denotes not applicable.

[2] The primary efficacy renal response at week 104 (week 100, confirmed at week 104) is defined as a ratio of urinary protein to creatinine of 0.7 or less and an eGFR that is no worse than 20% below the pre-flare value or at least 60 ml per minute per 1.73 m2 and no rescue therapy for treatment failure.

[3] The complete renal response at week 104 (week 100, confirmed at week 104) is defined as a ratio of urinary protein to creatinine of less than 0.5, an eGFR that is no worse than 10% below the pre-flare value or at least 90 ml per minute per 1.73 m2, and no rescue therapy.

[4] The primary efficacy renal response at week 52 was the response at week 48, confirmed at week 52.

[5] For this end point, events were defined as the first event that occurred among the following: death; progression to end-stage kidney disease; doubling of the serum creatinine level from the baseline level; increased proteinuria, impaired kidney function, or both; or kidney-related treatment failure. Data on patients who discontinued belimumab or placebo, withdrew from the trial, or were lost to follow-up were censored on the date of the event. Data on patients who completed the 104-week treatment period were censored at the week 104 visit. The time to event in days was defined as the event date minus the treatment start date plus 1. A Cox proportional-

hazards model for the comparison between belimumab and placebo was used, with adjustment for induction regimen, race, baseline ratio of urinary protein to creatinine, and baseline eGFR.

[6] The P value was from a rank analysis-of-covariance model comparing belimumab with placebo, with covariates for trial group, induction regimen (cyclophosphamide vs. mycophenolate mofetil), race (Black vs. non-Black), baseline ratio of urinary protein to creatinine, and baseline eGFR. Withdrawal from the trial, treatment failure, and discontinuation of belimumab or placebo were imputed as a nonresponse.

[7] This end point is defined as an eGFR that is no worse than 10% below the baseline value or within normal range and at least a 50% decrease in the ratio of urinary protein to creatinine with one of the following: a ratio of urinary protein to creatinine of less than 1.0 if the baseline ratio was 3.0 or less, or a ratio of urinary protein to creatinine of less than 3.0 if the baseline ratio was greater 3.0; no treatment failure; and not a complete renal response.

Abbreviations: CI, confidence interval; CRR, complete renal response

Safety

The safety profile for belimumab plus standard therapy was similar to that of standard therapy alone (Table 146). Anti-belimumab antibodies were not detected. A total of 11 patients died during the trial (6 in the belimumab group and 5 in the placebo group). Infection-associated deaths were balanced between the two groups (3 patients in each group), and no deaths were directly attributed to lupus nephritis by the investigators.

Table 146 BLISS-LN - Adverse Events, Adverse Events of Special Interest, and Suicidality in the Safety Population. [1]

Event	Belimumab	Placebo
	(N=224)	(N=224)
	no. of patients (%)	
All adverse events[2]	214 (96)	211 (94)
All treatment-related adverse events[2]	123 (55)	119 (53)
Upper respiratory tract infection	26 (12)	24 (11)
Urinary tract infection	15 (7)	13 (6)
Herpes zoster	13 (6)	10 (4)
Bronchitis	11 (5)	10 (4)
Nasopharyngitis	8 (4)	8 (4)
Headache	9 (4)	5 (2)
Nausea	8 (4)	5 (2)
Rash	6 (3)	5 (2)
All serious adverse events[2]	58 (26)	67 (30)
All treatment-related serious adverse events[2]	23 (10)	25 (11)
Most common treatment-related serious adverse events, according to system organ class, occurring in ≥1% of patients in either group		
Infections and infestations	15 (7)	18 (8)
Respiratory, thoracic, and mediastinal disorders	5 (2)	1 (<1)

Blood and lymphatic system disorders	3 (1)	2 (1)
Nervous system disorders	0	3 (1)
Most common treatment-related serious adverse events occurring in ≥1% of patients in either group		
Pneumonia	3 (1)	4 (2)
Herpes zoster	3 (1)	2 (1)
Adverse events resulting in discontinuation of trial drug	29 (13)	29 (13)
Adverse events of special interest[3]		
Cancer		
Excluding nonmelanoma skin cancer[4]	2 (1)	0
Including nonmelanoma skin cancer[4]	3 (1)	0
Postinfusion reactions[5]	26 (12)	29 (13)
All infections of special interest, including opportunistic infections, herpes zoster, tuberculosis, and sepsis	30 (13)	34 (15)
Serious infections	9 (4)	7 (3)
Depression, suicide, or self-injury	11 (5)	16 (7)
C-SSRS suicidal ideation or behavior during trial intervention	7 (3)	12 (5)
Death	6 (3)	5 (2)
Fatal serious adverse events that began during trial intervention	4 (2)	3 (1)
Fatal serious adverse events that did not begin during trial intervention	2 (1)	2 (1)

Footnote:

[1] Only adverse events that occurred during the intervention period (from the first infusion to the first missed infusion or the last infusion, whichever was later, plus 28 days) are listed. Patients were counted once in each row and column for any adverse event that met the criterion. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 22.0.

[2] This category includes all patients who had at least one event. Relatedness of the intervention to the event was determined by the site investigators.

[3] These events were determined according to a custom MedDRA query.

[4] This category includes tumors of unspecified cancer that were adjudicated as cancer.

[5] These events were determined according to a custom MedDRA query or sponsor adjudication.

Abbreviations: C-SSRS, Columbia suicide severity rating scale; MedDRA, medical dictionary for regulatory activities

Appendix P Change in UPCR from baseline

Prior to starting treatment in AURORA 1, baseline mean UPCR levels (defined as the average of the last 2 pre-randomization values) was similar in both treatment arms for subjects entering the AURORA 2 study (3.87 mg/mg in the placebo arm and 3.94 mg/mg in the voclosporin arm at baseline) (Table 147). Early decreases in mean UPCR were observed for both treatments with a greater decrease seen with voclosporin by Month 3 which was sustained across the 3 years of study (Figure 38 and Figure 39).

Table 147 MMRM Model of Change from Baseline in UPCR (mg/mg) - AURORA 2 ITT Population

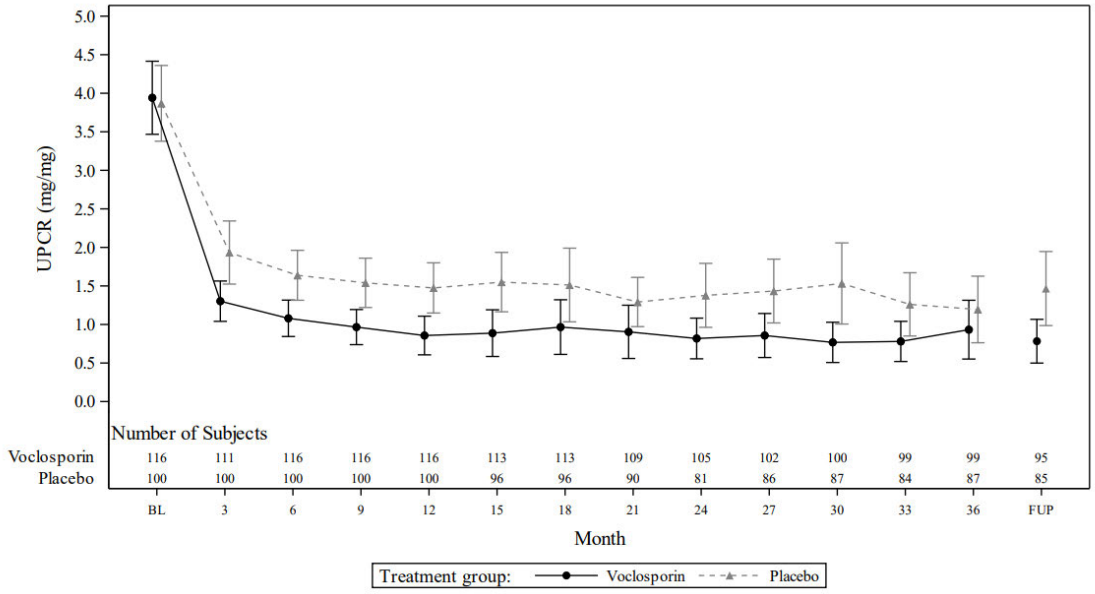
		Placebo (N=100)		Voclosporin (N=116)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from baseline
Baseline (AURORA 1)	n	100	NA	116	NA
	Mean (SD)	3.87 (2.476)	NA	3.94 (2.577)	NA
	Median	2.96	NA	2.81	NA
	Min, Max	0.8, 14.5	NA	0.2, 13.1	NA
Overall	n	100	100	116	116
	Mean (SD)	1.67 (2.092)	-2.41 (2.859)	1.15 (1.802)	-3.01 (2.712)
	Median	0.90	-1.95	0.42	-2.21
	Min, Max	0.0, 17.7	-14.4, 10.1	0.0, 14.4	-13.1, 7.6
	LS mean (SE)		-2.40 (0.172)		-3.05 (0.162)
	95% CI		-2.74, -2.06		-3.37, -2.73
	Comparison to Placebo				
	LS mean of Difference (SE)				-0.65 (0.195)
	95% of LS mean CI				-1.03, -0.26
	P-value				0.001

Note: Results are based on a Mixed Effect Model Repeated Measures analysis with Change from baseline at each visit as the response variable, while treatment arm, visit, treatment by visit interaction, biopsy class, MMF use at baseline, Region and baseline UPCR are included effects in the model Model is using unstructured covariance structure Baseline UPCR is defined as the average of the latest 2 pre-randomization values.

Abbreviations: CI, confidence interval; ITT, intention to treat LS, least square; MMF, mycophenolate; MMRM, mixed effect model repeated measures; SD, standard deviation; SE, standard error; UPCR, urine protein creatinine ratio

Source: AURORA 2 CSR (15)

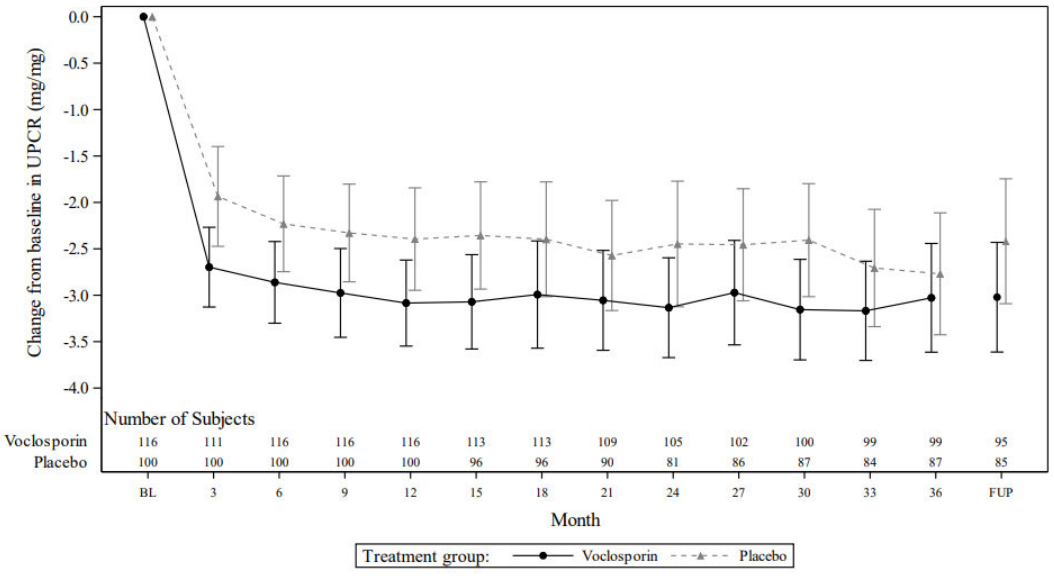
Figure 38 Mean (±95% CI) Observed UPCR (mg/mg) by Visit (AURORA 1 and AURORA 2)



Abbreviations: BL, baseline; CI, confidence interval; FUP, follow-up; UPCR, urine protein creatinine ratio

Source: AURORA 2 CSR (15)

Figure 39 Mean (±95% CI) Change in UPCR (mg/mg) from AURORA 1 Baseline by Visit (AURORA 1 and AURORA 2)



Abbreviations: BL, baseline; CI, confidence interval; FUP, follow-up; UPCR, urine protein creatinine ratio

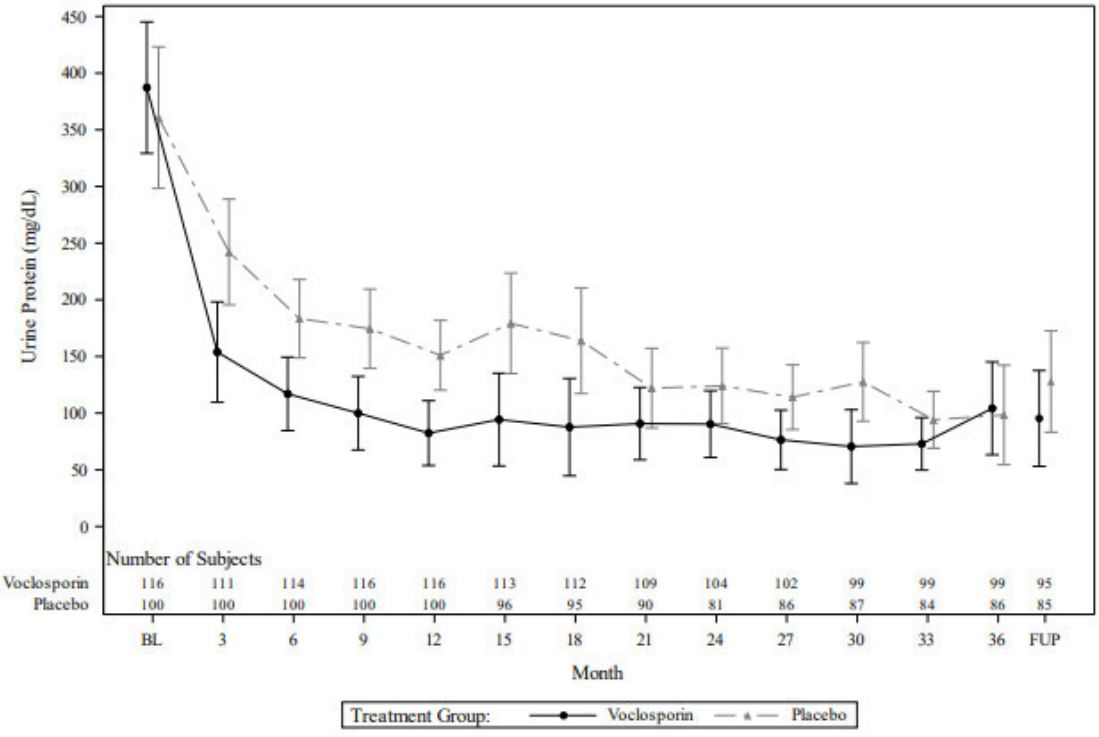
Source: AURORA 2 CSR (15)

Appendix Q Change in urine protein, serum creatinine and eGFR from baseline

Urine Protein

Urine protein decreased across the 3 years of observation during the AURORA 1 and AURORA 2 studies (Figure 40). In both arms, urine protein levels showed expected fluctuations over the course of the studies but levels in the voclosporin arm remained lower than those in the placebo arm

Figure 40 Mean (±95% CI) Observed Urine Protein (mg/dL) by Visit (AURORA 1 and AURORA 2)



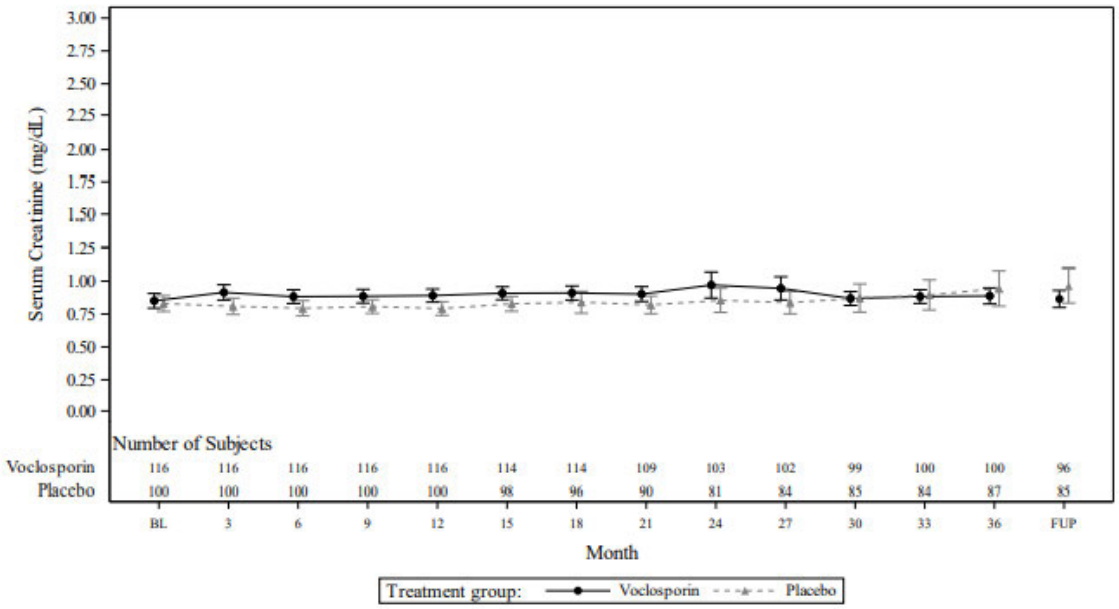
Abbreviations: BL, baseline; CI, confidence interval; FUP, follow-up

Source: AURORA 2 CSR (15)

Serum Creatinine

Mean serum creatinine levels at baseline prior to the start of treatment in AURORA 1 were within normal range and similar in both treatment arms. Over the first 15 months of treatment, small but not clinically relevant increases (i.e., within normal range) in mean levels were observed in the voclosporin arm while levels in the placebo arm decreased slightly (Figure 41).

Figure 41 Mean (±95% CI) Observed Serum Creatinine (mg/dL) by Visit (AURORA 1 and AURORA 2)



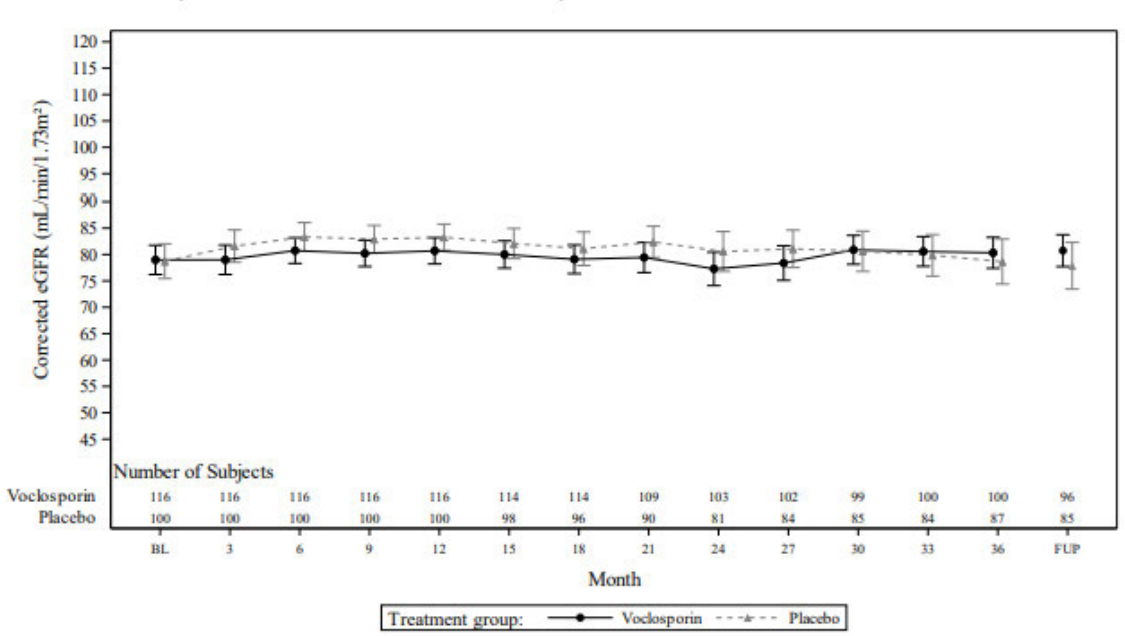
Abbreviations: BL, baseline; CI, confidence interval; FUP, follow-up

Source: AURORA 2 CSR (15)

eGFR

For subjects who continued treatment in AURORA 2, mean corrected eGFR values were similar in both arms prior to the start of study treatment in AURORA 1 (79.0 mL/min/1.73 m2in the voclosporin arm and 78.7 mL/min/1.73 m2 in the placebo arm). Over the first 3 months of treatment, the mean corrected eGFR were stable in the voclosporin arm while the mean value in the placebo arm showed a small increase (Figure 42 and Figure 43)**.** The small difference between the arms remained through to Month 27, after which the mean eGFR value increased slightly in the voclosporin arm and started to decline in the placebo arm. On stopping study treatment, the LS mean corrected eGFR values increased by 1.4 mL/min/1.73 m2 in the voclosporin arm whereas in the placebo arm, the mean corrected eGFR value dropped by 3.3 mL/min/1.73 m2 leading to a difference between the treatment arms of 4.8 mL/min/1.73 m2. The difference was more pronounced when using the raw eGFR values (9.4 mL/min/1.73 m2). This demonstrates that the early differences between treatment arms are due to the reversible hemodynamic effect of voclosporin and not the result of a permanent adverse impact on renal function.

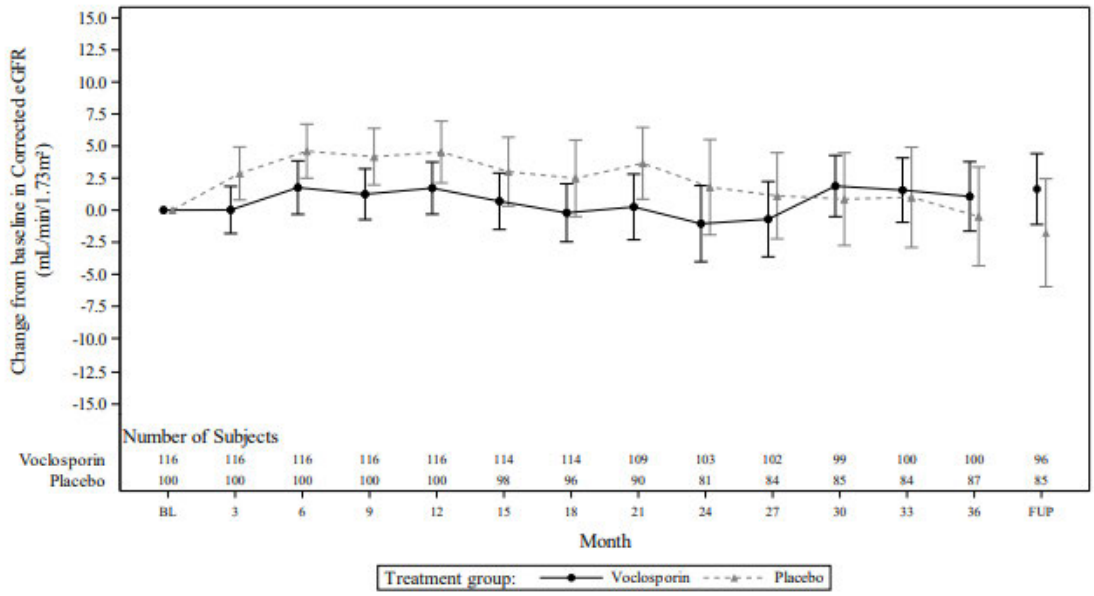
Figure 42 Mean (±95% CI) Corrected eGFR (mL/min/1.73 m2) by Visit (AURORA 1 and AURORA 2)



Abbreviations: BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; FUP, follow-up

Source: AURORA 2 CSR (15)

Figure 43 Mean (±95% CI) Change from AURORA 1 Baseline in Corrected eGFR (mL/min/1.73 m2) by Visit (AURORA 1 and AURORA 2)



Abbreviations: BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; FUP, follow-up

Source: AURORA 2 CSR (15)