Medicinrådet

Bilag til Medicinrådets anbefaling vedr. difelikefalin til behandling af moderat til svær uræmisk kløe i forbindelse med kronisk nyresygdom hos voksne patienter i hæmodialyse

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. difelikefalin
2. Ansøgers endelige ansøgning vedr. difelikefalin

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24.05.2024
BMC/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	19.06.2024
Leverandør	CSL Vifor
Lægemiddel	Kapruvia (difelikefalin)
Ansøgt indikation	Behandling af moderat til svær uræmisk kløe i forbindelse med kronisk nyresygdom hos voksne patienter i hæmodialyse
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Kapruvia (difelikefalin):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Kapruvia	50 µg/ml	12 * 1 ml	4.022	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Hvis Medicinrådet ikke anbefaler Kapruvia, indkøbes lægemidlet til følgende forhandlede SAIP.

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Kapruvia	50 µg/ml	12 * 1 ml	4.022	[redacted]	[redacted]	[redacted]

Aftaleforhold

Amgros har en eksisterende aftale med leverandøren, som vil blive tilpasset afhængig af udfaldet i Medicinrådet. Ved anbefaling kan den forhandlede SAIP gælde fra den 20.06.2024.

Konkurrencesituationen

Der er på nuværende tidspunkt ingen behandlingsvejledningsvejledning eller defineret standardbehandling til uræmisk kløe.

Tabel 2: lægemiddeludgifter pr. patient pr. år

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Kapruvia	50 µg/ml	12 * 1 ml	0,5 µg/kg tre gange ugentligt	[redacted]	[redacted]

*Med antagelse om at patienten modtager ét hætteglas pr. behandling jf. Medicinrådets vurderingsrapport

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Application for the assessment of Kapruvia® for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information

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Abbreviations

Abbreviation	Definition
ANCOVA	Analysis of covariance
BBB	Blood-brain barrier
CI	Confidence interval
CKD	Chronic kidney disease
CKD-aP	Chronic kidney disease associated pruritus
CNS	Central nervous system
CR845	Difelikefalin
CTCAE	Common Terminology Criteria for Adverse Events
DNSL	Dansk Nefrologisk Selskabs Landsregister
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
HR	Hazard ratio
GFR	Glomerular filtration rate
HRQoL	Health-related quality of life
HD	Haemodialysis
IL	Interleukin
ITT	Intention-to-treat

IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KDQoL-36	Kidney Disease Quality of Life-36
KOR	Kappa opioid receptor
LH	Lawrence, Hung
LS	Least-squares
MCS	Mental component summary score
MOR	Mu opioid receptor
N/A	Not applicable
OLE	Open-label extension
OR	Odds ratio
PCS	Physical component summary score
PD	Peritoneal dialysis
PRO	Patient-reported outcomes
QoL	Quality of Life
SD	Standard deviation
SE	Standard error
SF-12	12-item Short Form Survey
TEAE	Treatment-emergent adverse event
US	United States
WI-NRS	Worst Itching Intensity Numerical Rating Scale
SDQ	Sleep disability question

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Kapruvia
Generic name	Difelikefalin
Therapeutic indication as defined by EMA	Difelikefalin is indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis.
Marketing authorization holder in Denmark	Vifor Fresenius Medical Care Renal Pharma France
ATC code	V03AX04
Combination therapy and/or co-medication	Given as monotherapy
Date of EC approval	25-04-2022
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation	No
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC	No
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Kapruvia (difelikefalin) 50 microgram/ml, 1 ml solution for injection, 12 vials

Abbreviations: N/A = not applicable

Sources: European Medicines Agency, 2022 (1); European Medicines Agency, 2022 (2); Danish Medicines Agency, 2023 (3)

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Difelikefalin is indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis.
Dosage regiment and administration	Difelikefalin is administered 3 times per week by intravenous (IV) bolus injection into the venous line of the dialysis circuit at the end of the haemodialysis treatment during rinse-back or after rinse-back. The recommended dose of difelikefalin is 0.5 micrograms/kg dry body weight (i.e., the target post dialysis weight). For patients with a dry body weight equal to or above 195 kg the recommended dose is 100 micrograms (2 ml).
Choice of comparator	Placebo
Prognosis with current treatment (comparator)	Chronic kidney disease associated pruritus (CKD-aP) patients on haemodialysis (HD) experience a higher mortality rate than chronic kidney disease (CKD) patients without pruritus. In an analysis of DOPPS phase 1 (1996–2001) data, HD patients with moderate to severe CKD-aP had a 13% higher adjusted mortality risk than those not bothered by CKD-aP and a 21% higher risk of mortality in DOPPS phase II (2002–2004) (4).
Type of evidence for the clinical evaluation	Head-to-Head

Most important efficacy endpoints (Difference/gain compared to comparator)	Proportion of patients achieving a ≥3-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12
	• KALM-1
	  ○ Difelikefalin: LS mean = 51.0% (95% CI: 42.9%–58.9%)
	  ○ Placebo: LS mean = 27.6% (95% CI: 20.2%–36.6%)
	• KALM-2
	  ○ Difelikefalin: LS mean = 54.0% (43.9%–63.9%)
	  ○ Placebo: LS mean = 42.2% (32.5%–52.5%)

Most important serious adverse events for the intervention and comparator	In the double-blind phase of KALM-1 infections and infestations were the most serious adverse events, as most patients both in the difelikefalin and placebo group experienced this (7.9% and 8.0%, respectively). The same applies for the double-blind and open-label extension phase of KALM-2 (8.9% in the difelikefalin group and 5.9% in the placebo group in the double-blind phase, as well as 12.2% in the difelikefalin group and 14.8% in the placebo group in the open-label extension phase experienced a serious adverse event of the type *infections and infestations*).
Impact on health-related quality of life	**Clinical documentation:** Significantly greater proportions of participants in the difelikefalin group achieved clinically meaningful improvements in itch-related QoL vs. the placebo group (≥5-point improvements in 5-D Itch) over 12 weeks of treatment. Itch (52.1% vs. 42.3%, P=0.01).

Summary					
	Health economic model: 0.218 QALYs better than comparator				
Type of economic analysis that is submitted	Cost utility using a Markov model				
Data sources used to model the clinical effects	Patient-level data from KALM-1 and KALM-2, supplemented by published literature (DNSL report 2022(5), Boenink et al. 2020 (6), Sørensen et al., 2007) (7), and Krajewski et al., 2021 (8)				
Data sources used to model the health-related quality of life	Patient-level data from KALM-1 and KALM-2 used to inform 5-D itch scale disease-specific quality-of-life, while Hernandez et al., 2023(9) is used to generate generic utilities. Ratio calculated from Eriksson et al., 2017 (10)				
Life years gained	0 years (equal survival assumed)				
QALYs gained	0.218 incremental QALYs compared to standard of care				
Incremental costs	DKK -24,024 DKK				
ICER (DKK/QALY)	Difelikefalin dominates standard of care				
Uncertainty associated with the ICER estimate	Resource use is the biggest cost driver. Efficacy beyond trial data. Utilities in haemodialysis.				
Number of eligible patients in Denmark	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
	710*	115**	115**	115**	115**
	*Eligible prevalence and incidence, **Eligible incidence				
Budget impact (in year 5)	DKK -1,522,709				

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; CKD-aP = chronic kidney disease associated pruritus; HD = haemodialysis; IV = intravenous; LS = least-squares; QALY = Quality-adjusted life-years

Sources: European Medicines Agency, 2022 (1); Pisoni et al., 2006 (4).

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

CKD is a progressive disease associated with high morbidity and mortality (11). CKD is defined by Kidney Disease: Improving Global Outcomes (KDIGO) as “abnormalities of kidney structure or function, present for >3 months, with implications for health” (12, 13). According to KDIGO guidelines, a patient should be diagnosed with CKD if they fulfil either of the following criteria for a period of >3 months: A glomerular filtration rate (GFR) <60

ml/min/1.73 m^2, or at least one marker of kidney damage such as albuminuria, urine sediment abnormalities, electrolyte abnormalities, or structural abnormalities (12, 13).

CKD is often caused by underlying diseases such as hypertension, diabetes mellitus (types 1 and 2), and glomerulonephritis, and is also an age-associated condition (11). A range of symptoms are associated with CKD, including electrolyte disturbances, fatigue, oedema of the feet and ankles, dyspnoea, haematuria, and nausea. Symptoms can be particularly severe in stage 5 CKD (estimated glomerular filtration rate [eGFR] <1ml/min/1.73m^2) as the kidneys are nearing failure or may have already failed, meaning that waste products accumulate in the body. At this point (chronic kidney failure or end-stage renal disease [ESRD]), the kidneys do not function sufficiently for the patient to survive without either dialysis (HD or peritoneal dialysis [PD]) or kidney transplantation (14).

A common symptom experienced by CKD patients undergoing dialysis is relentless itchy skin, known as CKD-aP. The focus of this application is moderate to severe CKD-aP in the HD population, aligned with the difelikefalin indication.

3.1.1 Pathophysiology

The aetiology and pathophysiology of CKD-aP have not yet been fully elucidated. There are several hypotheses, including histamine release by mast cells, immune-mediated responses, opioid receptor-mediated nervous system responses, and uraemic toxins.

3.1.1.1 Histamine hypothesis

Histamine is the most widely studied mediator of itch (15). Histamine released by mast cells binds to H1 receptors on sensory nerve fibres and endothelial vessel walls, and H4 receptors on immune cells (mast cells, granulocytes, and T lymphocytes). These interactions cause swelling, redness, and inflammation, which are postulated to cause itch. H4 receptor stimulation specifically leads to upregulation of the pruritogenic interleukin (IL)-31 (15, 16).

Increased levels of histamine have been observed in patients with pruritus and it has been suggested that histamine accumulation is an important contributing factor in chronic pruritus (17). However, the frequent failure of these treatments, and evidence for non-histamine-mediated itch in CKD-aP suggest that factors other than histamine are involved (17-19).

3.1.1.2 Inflammatory hypothesis

According to the inflammatory hypothesis, CKD-aP is the result of systemic and dermal microinflammation mediated by inflammatory factors like cytokines (20-22). Studies have demonstrated that HD patients have elevated levels of inflammatory markers, including IL-6, T helper type 1 cells, and C-reactive protein. Some studies have indicated that immunomodulators can reduce pro-inflammatory cytokine production and reduce itch (23). However, these studies are generally small and out of date.

3.1.1.3 Nervous system hypothesis

The nervous system hypothesis suggests that CKD-aP arises from an imbalance in the activation of different opioid receptor subtypes. Neurons with sensory endings in the skin transmit itch signals to the central nervous system (CNS) via their cell bodies in the kappa opioid receptor (KOR)-rich dorsal root ganglia.

Stimulation of mu opioid receptors (MORs), e.g., by analgesic opioid drugs, is known to cause itch, whereas stimulation of KORs attenuates itch. A pathological imbalance of MOR and KOR activation has therefore been proposed as a cause of CKD-aP (24). The likely role of inflammation and the nervous system in the pathophysiology of CKD-aP has been the basis for several recent developments in the treatment of this disease.

3.1.1.4 Uraemic toxins

The uraemic toxin hypothesis is based on data suggesting that CKD-aP is associated with markers of inefficient dialysis, including elevated levels of serum phosphorus and calcium (25). Early studies from the 1960s and 1970s indicated an improvement in CKD-aP after treatment of high calcium and phosphorous levels (17, 24). However, subsequent trials could not confirm these associations (26), leading to the conclusion that insufficient dialysis frequency and elevated calcium or phosphorous may be responsible for CKD-aP in only a small subset of patients (24). In a study by Lim et al. (2020), the use of high efficiency (medium cut-off) dialysers appeared to improve patients' self-reported outcomes compared to high flux dialysers in HD CKD-aP patients , suggesting that increased molecule removal might help in reducing the physical components responsible for CKD-aP. However, the small sample size and short duration of this study limits the reliability and generalizability of its results. Furthermore, an analysis of patient serum phosphate levels in recent clinical trials found no correlation with reported itch severity in CKD-aP patients (27). Overall, there is limited evidence to suggest that uraemic toxins are a principal driver of CKD-aP.

3.1.2 Clinical presentation/symptoms of the condition

CKD-aP tends to present symmetrically and can be either generalised or localised, affecting only specific areas of the body such as the scalp, face, upper back, arms (particularly the dialysis access arm) or groin. The itch can occur either intermittently or persistently, and it may present before, during, and/or after dialysis. It can vary throughout the day, with many patients reporting being bothered by itch most often at night, and 25% reporting peak severity during or immediately after dialysis (17, 28). CKD-aP in ESRD patients may be associated with xerosis (dry skin) or complications of excoriation (skin lesions resulting from scratching) like impetigo, linear crusts, papules, ulcerations, and prurigo nodularis (17). Typical skin manifestations of CKD-aP also include scarring. While skin lesions can be severe, some patients have no skin manifestations of CKD-aP, and the severity of the itch is not correlated to the skin damage observed (17).

3.1.3 Prognosis

CKD-aP patients on HD experience a higher mortality rate than CKD patients without pruritus. In an analysis of DOPPS phase 1 (1996–2001) data, HD patients with moderate to severe CKD-aP had a 13% higher adjusted mortality risk than those not bothered by CKD-aP and a 21% higher risk of mortality in DOPPS phase II (2002–2004) (4).

An analysis of DOPPS data by Sukul et al. 2021 showed that, compared to patients who reported being not at all bothered by itchy skin, patients who were extremely bothered had a higher rate of all-cause mortality (HR 1.24; 95% confidence interval [CI]: 1.08–1.41). In the unadjusted model, the HR was 1.59 (95% CI: 1.41–1.81). Patients extremely bothered by itching also had higher rates of cardiovascular-related mortality (HR 1.29, 95% CI: 1.06–1.57) and infection-related mortality (HR 1.44, 95% CI: 1.05–1.96) (29).

In a longitudinal assessment of DOPPS data (phases 4–6) by Sukul et al. 2022, patients were categorised into four groups: those at least moderately bothered by itchy skin at baseline only (Yes/No), one year later only (No/Yes), neither (No/No), or both (Yes/Yes) time points. The all-cause mortality HR, compared to the No/No reference group, was 1.22 (95% CI: 0.99–1.51) for Yes/No, 1.32 (95% CI:1.07–1.63) for No/Yes, and 1.31 (95% CI:1.11–1.56) for Yes/Yes (30).

3.1.4 Patients' functioning and health-related quality of life

Studies of CKD-aP patients have consistently demonstrated the negative impact of pruritus on health-related quality of life (HRQoL). Patients with moderate to severe CKD-aP are more likely to suffer from comorbidities such as fatigue, poor sleep quality, and depression than patients with no or mild CKD-aP (4, 31). Several of these factors increase the HRQoL burden of CKD-aP.

Poku et al. 2020 conducted a systematic literature review to evaluate the relationship between CKD-aP and HRQoL in ESRD patients receiving HD. CKD-aP severity was found to be associated with a decrease in HRQoL in the majority of the studies and persistent pruritus resulted in worsening HRQoL over time. Sleep disturbances were found to partially explain the relationship between pruritus severity and HRQoL. Disease-specific HRQoL instruments, in contrast to generic instruments, showed a more consistent relationship between pruritus and HRQoL (32).

The Kidney Disease Quality of Life-36 (KDQoL-36) scoring system is a tool developed to assess HRQoL in patients with kidney disease undergoing dialysis, where higher scores indicate better HRQoL (33). The KDQoL-36 is a self-reported measure that includes a 12-item health survey as the generic core (12-item Short Form Survey [SF-12]-36), supplemented with multi-item scales targeted at particular concerns of individuals with kidney disease who are on dialysis: burden of the disease, the disease symptoms, and the effect of the disease. The SF-12 has both a mental and physical component summary score (MCS and PCS) (34).

Ramakrishnan et al. (2014) used the KDQoL-36 scoring system to assess HRQoL in a population of >70,000 CKD-aP patients undergoing dialysis. There was a statistically

significant association between increased itch severity and worse PCS and MCS scores (both P<0.0001 (35). Sukul et al. 2021 reported similar findings (29). These consistent findings demonstrate that CKD-aP negatively affects both physical and mental aspects of HRQoL (35).

More recent results from van der Willik (2022) align with previous findings that CKD-aP patients experience lower HRQoL in both mental and physical dimensions, and that pruritus severity is associated with a decrease in HRQoL. Throughout the whole study period, the prevalence of pruritus was approximately 50% with a moderate burden (mean burden scores between 2.8 and 3.4 on a 1–5 scale). In 70% of affected patients the pruritus was persistent. In total, 773 patients (26.1%) had moderate to severe pruritus (36). Patients with pruritus experienced a lower physical (–3.35 [95% CI: –4.12 to –2.59; P<0.001]) and mental HRQoL (–3.79 [95% CI: –4.56 to -3.03; P<0.001]), compared to patients without pruritus. Patients with moderate to severe pruritus experienced a lower physical (-3.98 [95% CI: –4.82 to –3.14; P<0.001]) and mental (–4.66 [95% CI: –5.49 to –-3.83; P<0.001]) HRQoL compared to patients with no or mild pruritus (36). Sleep problems (70% vs 52%) and psychological symptoms (36% vs 19%) were more common in patients with pruritus. These symptoms had an additional negative effect on HRQoL when controlled for pruritus (36).

In a post hoc analysis of DOPPS data, associations between Skindex-10 scores and other patient-reported outcomes (PROs) were assessed (37). The result showed that just under half of the responders (48%) were bothered by CKD-aP. The mean Skindex-10 score (with higher scores indicating poorer HRQoL) was 12.2 among all patients and 27.4 among those bothered by CKD-aP. After adjustment for covariates including age, sex, and comorbidities, higher Skindex-10 scores were associated with worse SF-12 PCS and MCS scores, as well as an increased risk of poor sleep and depressive symptoms (37).

3.2 Patient population

Limited information is available to inform on Danish specific incidence and prevalence rates of moderate to severe CKD-aP on HD, as there are no treatment guidelines available. To best inform this, the Dansk Nefrologisk Selskabs Landsregister (DNSL) 2022 annual report (5) was used to estimate the number of HD patients in Denmark, together with inputs from Danish clinical experts to estimate the number of CKD-aP patients (38).

The DNSL reported 415 new HD patients per year on average in 2018-2022, with an average prevalence of 2,153 undergoing HD in Denmark (5). From these patients, the clinical experts agreed that patients with moderate to severe CKD-aP on HD would be a subset of these patients from the DNSL report (38). The clinical experts estimated 30% of these patients would be classified with moderate to severe CKD-aP and expected patient numbers to be relatively stable over the next 5 years (38).

Therefore, the incidence of moderate to severe CKD-aP patients on HD in Denmark is estimated to be 124 patients per year and the average prevalence is estimated to be 646 patients in Denmark. Table 1 presents the estimated incidence and prevalence of moderate to severe CKD-aP on HD patients in Denmark in the past 5 years.

Table 1: Incidence and prevalence of moderate to severe CDK-aP patients on HD in the past 5 years

Year	2018	2019	2020	2021	2022
Incidence in Denmark	129	114	124	139	116
Prevalence in Denmark	662	647	642	643	636
Global prevalence *	23,260 patients on haemodialysis				

* For small patient groups, also describe the worldwide prevalence.

Sources: DNSL 2022 Annual Report (5); Danish Clinical Experts (38); DOPPS Phase 4-6 Global study (29)

The Danish patient population relevant for this application consists of HD patients with moderate to severe CKD-aP. However, as difelikefalin is only administrated in-center, patients in home-haemodialysis were not considered eligible. Based on the DNSL 2022 report, approximately 92% of patients are treated in-center. Estimated patient numbers over the next five years in Denmark is provided in Table 2 below. Year 1 is estimated as eligible incidence (~595 patients) + eligible prevalence (~115 patients), resulting in 710 eligible patients in year 1. Patient number in the remaining years are estimated as eligible incidence, resulting in 115 patients per year.

Table 2: Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	710	115	115	115	115

3.3 Current treatment options

The Danish Medicines Council (DMC) has not developed treatment guidelines for patients with moderate to severe CKD-aP in HD. Clinical experts were consulted to inform on the relevant treatment options available in Danish clinical practice (38).

Treatment for moderate to severe CKD-aP includes a range of treatments, both systematic and topical, with the main treatment outcomes aimed at providing these patients with a reduction in pruritus (38). All current treatments are used as off-label treatments. Clinical experts primarily use systematic oral gabapentinoids as current treatment options for this patient population (38). The first option is gabapentin 300 mg every second or third day. The second option is gabapentin 100 mg (Neurontin) daily. The third option is pregabalin with a starting dose of 25 mg daily and can be titrated up to 75 mg daily. Antihistamines are rarely used in clinical practice as they do not provide sufficient efficacy for this patient population (38). Beyond systematic oral gabapentinoids, there are no further treatment options available for these patients.

Patients with moderate-to-severe pruritus CKD-aP on HD are expected to be on this treatment for a lifetime, until end of treatment effect or if the treatment is not tolerated (38).

3.3.1 Gabapentin

Four randomised, double-blind, placebo-controlled studies have investigated the effectiveness of gabapentin in treating CKD-aP (39-42). Although gabapentin was more effective than placebo in reducing pruritus in these studies, this conclusion was based on small sample sizes (25-54 patients per study), with a total of only 82 patients receiving gabapentin. The study durations were limited to between two and four weeks, resulting in a lack of evidence for long-term efficacy or safety. Other studies of gabapentin are limited by a lack of blinding, randomisation, or placebo control, leading to an overall limited and poor-quality data set in support of the efficacy of gabapentin.

Gabapentin is also associated with a high rate of adverse events, the most common of which are somnolence, dizziness, and fatigue (41-43). Other side effects include confusion, dry mouth, visual changes, weight gain, angioedema, and increased suicide risk (24). The study by Cheikh Hassan et al. (2015) reported that approximately 47% of patients treated with gabapentin experienced at least one side effect and 17% of patients permanently discontinued treatment. In one open-label study, 20% of patients terminated treatment due to side-effects (44). Furthermore, a study of 140,899 chronic HD patients showed that patients taking gabapentin were significantly more likely to experience altered mental status, a fall, or a fracture than those not taking the drug (45).

3.3.2 Pregabalin

A small, single-centre prospective study (N16) found that a daily dose of 25 mg pregabalin could significantly improve CKD-aP in HD patients who were resistant to conventional treatment (46). However, 25% of patients discontinued treatment because of side effects (dizziness and somnolence in three patients and blurred vision and hand tremor in one patient). The efficacy of pregabalin has been shown to be similar to that of gabapentin in improving symptoms of pruritus in a 14-week, randomised, prospective, crossover trial with ESRD patients on HD (n=50) with established neuropathy and/or neuropathic pain (47). However, in a prospective study of 71 consecutive patients with severe pruritus, gabapentin relieved pruritus in 66% of patients vs. 81% of patients for pregabalin. In this cohort, 30% of patients suffered significant side effects with gabapentin and 12% with pregabalin, the most common of which was oversedation (44). Altered mental status, fall, and fracture were also shown to be significantly more likely among patients taking pregabalin compared to those not prescribed this drug (45).

3.4 The intervention

Table 3: Overview of the intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Difelikefalin is indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis.
Method of administration	Difelikefalin is administered 3 times per week by IV bolus injection into the venous line of the dialysis circuit at the

Overview of intervention	
	end of the haemodialysis treatment during rinse-back or after rinse-back.
Dosing	0.5 micrograms of difelikafalin per kg dry body weight (i.e., the target postdialysis weight). For patients with a dry body weight ≥ 195 kg the recommended dose is 100 micrograms (2 ml).
Dosing in the health economic model (including relative dose intensity)	In the model, this it is assumed that 1 vial is used per administration. The rest of the vial is wasted.
Should the pharmaceutical be administered with other medicines?	Given as monotherapy
Treatment duration / criteria for end of treatment	Until patient does not respond to treatment
Necessary monitoring, both during administration and during the treatment period	Hyperkalaemia Hyperkalaemia frequently occurs in chronic kidney disease patients on haemodialysis. In the placebo-controlled clinical studies a numerically higher rate of adverse events of hyperkalaemia was reported for the difelikefalin treated patients (4.7%; 20 / 424 patients) compared to placebo (3.5%; 15 / 424 patients). No causal relationship was established. Frequent monitoring of potassium levels is recommended. Cardiac failure and atrial fibrillation Difelikefalin has not been studied in patients with New York Heart Association class IV heart failure. In the pivotal clinical studies, a small numerical imbalance of cardiac failure and atrial fibrillation events was observed in the difelikefalin treated patients compared to placebo, in particular among patients with a medical history of atrial fibrillation who discontinued or missed their atrial fibrillation treatment. No causal relationship was established. Patients with impaired blood-brain barrier Difelikefalin is a peripherally acting kappa opioid receptor agonist with restricted access to the central nervous system (CNS). The blood-brain barrier (BBB) integrity is important for minimizing difelikefalin uptake into the CNS. Patients with clinically important disruptions to the BBB (e.g., primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis, advanced Alzheimer's disease) may be at risk for difelikefalin entry into the CNS. Kapruvia should be prescribed with caution in such patients taking into account their individual benefit-risk balance with observation for potential CNS effects. Dizziness and somnolence Dizziness and somnolence have occurred in patients taking difelikefalin and may subside over time with continued treatment. Concomitant use of sedating antihistamines, opioid analgesics or other CNS depressants may increase the likelihood of these adverse reactions and should be used with caution during treatment with difelikefalin. Compared to placebo, the incidence of somnolence was higher in difelikefalin treated subjects 65 years of age and older

Overview of intervention	
	(7.0%) than in difelikefalin treated subjects less than 65 years of age (2.8%). Excipients with known effect This medicinal product contains less than 1 mmol sodium per vial, that is to say essentially sodium-free
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	Kapruvia (difelikefalin) 50 microgram/ml, 1 ml solution for infection, 12 vials

Abbreviations: BBB = blood-brain barrier; CNS = central nervous system; IV = intravenous.

Sources: European Medicines Agency, 2022 (1); Danish Medicines Agency, 2023 (3).

3.4.1 Treatment with difelikefalin

Difelikefalin offers patients an effective and well-tolerated treatment for CKD-aP and has been approved in the European Union (48) and is the only approved treatment for CKD-aP. All other available pharmaceutical treatments (e.g., antihistamines, gabapentinoids) are used off-label (49).

3.4.1.1 Mechanism of action

Difelikefalin is a selective KOR agonist with low CNS penetration. The physicochemical properties of difelikefalin (hydrophilic, synthetic D-amino acid peptide with high polar surface area and charge at physiological pH) minimise its passive diffusion (permeability) and active transport across membranes, thus limiting penetration into the CNS. The activation of KOR on peripheral sensory neurons and immune cells by difelikefalin are considered mechanistically responsible for the antipruritic and anti-inflammatory effects (1).

3.4.2 The intervention in relation to Danish clinical practice

Difelikefalin is expected to be used after patients have not responded to systematic gabapentinoid therapy (see section 3.3). This is based on the opinions from Danish clinical experts (38), who have stated that no additional therapies exist beyond gabapentinoid therapy. Thus, the current clinical practice will be altered to include difelikefalin as an additional treatment option for patients with moderate to severe CKD-aP on HD.

3.5 Choice of comparator(s)

As there is no existing label-specific treatment alternative for CKD-aP (see section 3.3), the comparator included in this submission is placebo. In the health economic analysis, the comparator is modelled as standard of care (SoC) applying the placebo effect of the clinical trials. SoC includes treatment of pruritus, treatment of dialysis, and treatment following transplantation. Treatment of pruritus includes gabapentinoids, antihistamine, topical preparations. Treatment related to CKD and dialysis included erythropoiesis-stimulating

agents (ESA), iron, and phosphate binders. Treatment following transplantation includes Tacrolimus, mycophenolate, and methylprednisolone.

All patients using anti-itch medication in difelikefalin trials are modelled to use an antihistamine, in line with the difelikefalin trials (50). In the KALM-1 and -2 trials, 5.8 % (n=30/517) of patients with difelikefalin exposure and with anti-itch medication used hydrocortisone (Fishbane et al. 2022, Table 1) (50). This proportion was modelled to be equal for all severities. All CKD patients are modelled to use emollients (standard practice). In total 20.2 % of all trial patients in KALM-1 and KALM-2 used gabapentin or pregabalin for any condition (Topf et al. 2022). Proportions and doses are presented in Table 4. Treatment and dosing in relation to dialysis and transplantation is presented in Appendix K.

Table 4: Pruritus treatment proportions and dose

Treatment	None	Mild	Moderate	Severe	Overwhelming	Dose
Antihistamine	0 %	30 %	32 %	41 %	51 %	25 mg daily
Topical corticosteroid	0 %	2 %	2 %	2 %	3 %	3 mg daily
Emollient	0 %	100 %	100 %	100 %	100 %	5 mg daily
Gabapentin	0 %	10 %	10 %	10 %	10 %	300 mg every 2nd day
Pregabalin	0 %	10 %	10 %	10 %	10 %	25 mg daily

3.6 Cost-effectiveness of the comparator(s)

N/A

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 5: Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
≥3-point reduction in Worst Itching Intensity Numerical Rating Scale (WI-NRS) scores	Week 12	Proportion of participants achieving a ≥3-point improvement (reduction) in the weekly mean of daily 24-hour WI-NRS scores at week 12.	Each day, participants were asked to indicate, using the WI-NRS, the intensity of the worst itching they had experienced over the past 24 hours, on a scale from 0 (no itching) to 10 (worst itching imaginable). Proportions of patients achieving a ≥3-point reduction were assessed weekly from week 1-week 12 (51).

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
≥4-point reduction in WI-NRS scores	Week 12	Proportion of participants achieving a ≥4-point improvement (reduction) in the weekly mean of daily 24-hour WI-NRS scores at week 12.	Each day, participants were asked to indicate, using the WI-NRS, the intensity of the worst itching they had experienced over the past 24 hours, on a scale from 0 (no itching) to 10 (worst itching imaginable). Proportions of patients achieving a ≥4-point reduction were assessed weekly from week 1-week 12 (51).
Complete WI-NRS response	Week 12	Proportion of participants achieving a complete WI-NRS response over 12 weeks. For each week, a complete response was defined as reporting 0 or 1 on at least 80% of the daily WI-NRS scores. The cutoff of at least 80% represents 6 of the 7 daily scores collected in 1 week, assuming no data are missing.	N/A
Improvement in itch-related quality of life (QoL) assessed by the Skindex-10 Scale Score	Week 12	Achievement of a clinically meaningful improvement in itch-related QoL assessments evaluated over 12 weeks. In patients treated by haemodialysis, clinically meaningful thresholds were determined to be a ≥15-point reduction in Skindex-10 scores.	N/A
Improvement in itch-related QoL assessed by the 5-D Itch Scale Score	Week 12	Achievement of a clinically meaningful improvement in itch-related QoL assessments evaluated over 12 weeks. In patients treated by haemodialysis, clinically meaningful thresholds were determined to be a ≥5-point reduction in 5-D Itch total scores.	N/A
The long-term impacts of difelikefalin on itch intensity and itch-related QoL	Weeks 24, 36, and 52	The long-term impacts of difelikefalin on itch intensity and itch-related QoL measured by the 5-D Itch scale.	This outcome was assessed using the 5-D Itch scale during the open-label extension (OLE); beyond week 12, participants completed the 5-D Itch scale at weeks 24, 36, and 52 of the open-label phase.
Sleep quality**	Week 12	Measured by the sleep question on the 5-D Itch Scale	A paired t-test was performed to compare the sleep score at

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		sleep disability question (SDQ).	baseline and Week 12 for each WI-NRS improvement category. All P values are exploratory and should be interpreted descriptively.

Abbreviations: N/A = not applicable; OLE = open-label extension; QoL = quality of life; WI-NRS = Worst Itching Intensity Numerical Rating Scale; 5-D SDQ = 5-D Itch Scale sleep disability question.

Notes: * Time point for data collection used in analysis (follow up time for time-to-event measures). **This endpoint was investigated in an *post hoc* exploratory analysis and is therefore only presented pooled for KALM-1 and -2.

Sources: Topf et al., 2022 (51); Weiner et al., 2023 (52).

Validity of outcomes

The WI-NRS is a validated 11-point scale, with scores ranging from 0 to 10 and with higher scores indicating greater itch intensity (53, 54). The scale has been validated for this patient population and is identical to the primary efficacy endpoint used in the dose-ranging, phase 2 study, CR845-CLIN2101 (55). The categorical threshold of a decrease of at least 3 points was selected on the basis of a psychometric analysis of data from a previous phase 2 trial that showed that a 3-point decrease represented a clinically meaningful improvement in itch intensity in this patient population (patients undergoing haemodialysis with moderate-to-severe pruritus) (56). A change of 4 points has been estimated as the minimal clinically important difference in patients with psoriasis (57).

The Skindex-10 scale evaluates itch-related QoL across three domains (disease, mood or emotional distress, and social functioning), with total scores ranging from 0-60 and higher scores indicating a worse itch-related QoL (53). The Skindex-10 scale have been assessed as relevant in a population with CKD-aP (51). The 5-D Itch scale evaluates five dimensions of itch (duration, degree, direction, disability, and distribution), with total scores ranging from 5-25 and higher scores indicating a worse itch and worse itch-related QoL (58). The scale has been validated in patients with chronic pruritus, including haemodialysis patients, and has been shown to be sensitive to changes in pruritus over time (58). In patients treated by HD, clinically meaningful thresholds were determined to be a ≥15-point reduction in Skindex-10 and a ≥5-point reduction in 5-D Itch total scores (51).

4. Health economic analysis

4.1 Model structure

The cost-effectiveness model is essentially a new three-state Markov model (haemodialysis, renal transplant, and death), where two of the stages have five substates for the severity of CKD-aP (none, mild, moderate, severe, and overwhelming; Figure 1). The model structure is presented in Figure 1.

In the model, CKD-aP severity was defined with the 5-D itch scale, a validated measure for pruritus with a total score varying from 5 to 25 (58). It has five domains: duration and

degree of pruritus, direction (worsening or improvement), and disability (impact of pruritus on everyday activities). The scale gives a good view of the long-term quality of life related to pruritus because patients are asked to assess pruritus-related quality of life for the past two weeks. The definition of pruritus severity substates are defined in Table 6.

Figure 1: Model structure

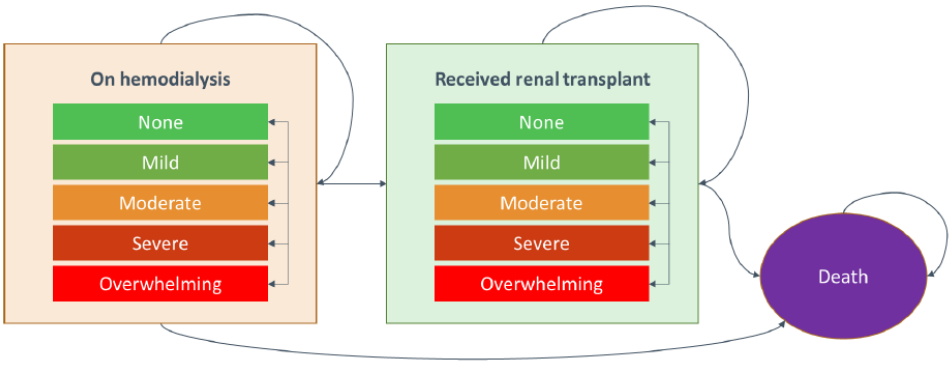


Table 6: Definition of model subhealth states

Pruritus severity categorisation	5-D Itch scale
None	5 to 8
Mild	9 to 11
Moderate	12 to 17
Severe	18 to 20
Overwhelming	21 to 25

Abbreviation: 5-D = Five dimensions

All modelled patients start with haemodialysis and have moderate, severe, or overwhelming CKD-aP at the model baseline. Over time, patients may receive a renal transplant (at which point difelikefalin is stopped).

At model baseline, patients are started on treatment with difelikefalin or the comparator. Difelikefalin is modelled to be continued until the patient receives a renal transplant, dies, or stops treatment for another reason. Reasons other than death and renal transplant only apply for the first 64 weeks. To align with the difelikefalin trial data, up to 64 weeks, the overall difelikefalin discontinuation is modelled to include patients who receive a renal transplant or die. This essentially means that the modelled total proportion of patients stopping difelikefalin by week 64 is independent of mortality rate or probability of receiving a renal transplant, unless mortality or transplantations are specifically added to input values denoting the probability of stopping difelikefalin before week 64.

To generate QALYs, each health state and substate was associated with a state-specific health utility weight, which is scored on a scale that assigns a value of 1 to the state equivalent to perfect health and 0 to the state equivalent to death. Conservatively, health states worse than death were not modelled. Each health state had specific costs, which were applied for the duration of the given health state. Life years, QALYs, and costs are accrued over time and aggregated at the end of the modelled time horizon.

4.2 Model features

The model features are presented in Table 7.

Table 7: Features of the economic model

Model features	Description	Justification
Model type	Markov model	To reflect the development of the disease
Patient population	Adult patients with chronic kidney disease-associated moderate to severe pruritus (CKD-aP), undergoing central haemodialysis.	Based om difelikefalin SMPC (1)
Perspective	Limited societal perspective	According to DMC guidelines (59)
Time horizon	Lifetime (40 years)	To capture all health benefits and costs in line with DMC guidelines. (59)
Cycle length	Weekly	To match the difelikefalin treatment cycle
Half-cycle correction	No	Due to the short cycle length
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years (59)
Intervention	Kapruvia® (difelikefalin) injection intravenously (IV) three times a week after each haemodialysis session	Treatment of interest
Comparator(s)	Current Danish Standard of Care (SoC)	No other approved treatments
Outcomes	Aggregated and disaggregated costs, life years, and quality-adjusted life years (QALY). Incremental cost-effectiveness ratio (ICER) measured as cost per QALY gained. Net monetary benefit (NMB)	N/a
Handling of uncertainty	Probabilistic sensitivity analysis and deterministic sensitivity analysis for all relevant parameters including scenarios.	To match the DMC standard analysis (59)
Utilities	Based on published literature, which estimates the EQ-5D-3L value associated with each severity state, as defined by the 5-D itch scale. A ratio was applied to utility values of transplanted patients.	Due to lack of relevant utility data in clinical trials.
Discontinuation	Difelikefalin is modelled to be continued until the patient receives a renal transplant, dies, or stops treatment for another reason. Reasons other than death and renal transplant only apply for the first 64 weeks. SoC is not modelled to be discontinued for either the difelikefalin arm nor the SoC arm.	To reflect the available data. Patients are expected to continue on some SoC treatment for lifetime. Variations modelled via proportions. (38)

Abbreviations: CKD-aP = chronic kidney disease associated pruritus; DMC = Danish Medicines Council; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version; ICER = Incremental cost-effectiveness ratio; NMB = net monetary benefit QALY = quality-adjusted life years; SoC = Standard of Care

5. Overview of literature

5.1 Literature used for the clinical assessment

As the main comparator of interest for this submission is placebo, a systematic literature review (SLR) was not carried out as the main studies included this submission are head-to-head studies that directly compare difelikefalin vs placebo. This is the case as difelikefalin is expected to be used after the aforementioned off-label treatments that are currently used in Danish clinical practice, thus the most relevant comparator is placebo.

The primary studies included in this submission to inform the comparative efficacy and safety of difelikefalin vs placebo for patients with moderate to severe CKD-aP on HD are KALM-1 and KALM-2 studies.

CR845-CLIN3105 is a single arm study which assesses the safety of difelikefalin in the same population. No efficacy data is available from this study and will merely provide data on the relation between WI-NRS and sleep quality as well as additional safety data. In addition, itis used in the health economic model.

Table 8: Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F; KALM-1 Trial Investigators. A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus. N Engl J Med. 2020 Jan 16;382(3):222-232. doi: 10.1056/NEJMoa1912770. Epub 2019 Nov 8. PMID: 31702883 (60) Fishbane S, Wen W, Munera C, Lin R, Bagal S, McCafferty K, Menzaghi F, Goncalves J, Safety and Tolerability of Difelikefalin for the Treatment of Moderate-to-Severe Pruritus in Hemodialysis Patients: Pooled Analysis From the Phase 3 Clinical Trial Program, Kidney Medicine (2022), doi: https://doi.org/10.1016/j.xkme.2022.100513 (50) Topf J, Wooldridge T, McCafferty K, Schömig M, Csiky B, Zwiech R, Wen W, Bhaduri S, Munera C, Lin R, Jebara A, Cirulli J, Menzaghi F, Efficacy of Difelikefalin for the Treatment of Moderate-to-Severe Pruritus in Hemodialysis Patients: Pooled Analysis of KALM-1 and KALM-2 Phase 3 Studies, Kidney Medicine (2022), doi: https://doi.org/10.1016/j.xkme.2022.100512 (51) Weiner DE, Schaufler T, McCafferty K, Kalantar-Zadeh K, Germain M, Ruessmann D, Morin I, Menzaghi F, Wen W, Ständer S. Difelikefalin improves itch-related sleep disruption in patients undergoing haemodialysis. Nephrol Dial Transplant. 2023 Nov 15:gfad245. doi: 10.1093/ndt/gfad245. Epub ahead of print. PMID: 37968132 (52)	KALM-1	NCT03422653	Start: 06/02/18 Completion: 26/04/22	Difelikefalin vs. placebo for haemodialysis patients with moderate-to-severe CKD-aP
Fishbane S, Wen W, Munera C, Lin R, Bagal S, McCafferty K, Menzaghi F, Goncalves J, Safety and Tolerability of Difelikefalin for the Treatment of Moderate-to-Severe Pruritus in Hemodialysis Patients: Pooled Analysis From the Phase 3 Clinical Trial Program,	KALM-2	NCT03636269	Start: 17/08/18 Completion: 26/04/22	Difelikefalin vs. placebo for haemodialysis patients with moderate-to-severe CKD-aP

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Kidney Medicine (2022), doi: https://doi.org/10.1016/j.xkme.2022.100513 (50) Topf J, Wooldridge T, McCafferty K, Schömig M, Csiky B, Zwiech R, Wen W, Bhaduri S, Munera C, Lin R, Jebara A, Cirulli J, Menzaghi F, Efficacy of Difelikefalin for the Treatment of Moderate-to-Severe Pruritus in Hemodialysis Patients: Pooled Analysis of KALM-1 and KALM-2 Phase 3 Studies, Kidney Medicine (2022), doi: https://doi.org/10.1016/j.xkme.2022.100512 (51) Weiner DE, Schaufler T, McCafferty K, Kalantar-Zadeh K, Germain M, Ruessmann D, Morin I, Menzaghi F, Wen W, Ständer S. Difelikefalin improves itch-related sleep disruption in patients undergoing haemodialysis. Nephrol Dial Transplant. 2023 Nov 15:gfad245. doi: 10.1093/ndt/gfad245. Epub ahead of print. PMID: 37968132 (52)				
Fishbane S, Wen W, Munera C, Lin R, Bagal S, McCafferty K, Menzaghi F, Goncalves J, Safety and Tolerability of Difelikefalin for the Treatment of Moderate-to-Severe Pruritus in Hemodialysis Patients: Pooled Analysis From the Phase 3 Clinical Trial Program, Kidney Medicine (2022), doi: https://doi.org/10.1016/j.xkme.2022.100513 (50) Weiner DE, Schaufler T, McCafferty K, Kalantar-Zadeh K, Germain M, Ruessmann D, Morin I, Menzaghi F, Wen W, Ständer S. Difelikefalin improves itch-related sleep disruption in patients undergoing haemodialysis. Nephrol Dial Transplant. 2023 Nov 15:gfad245. doi: 10.1093/ndt/gfad245. Epub ahead of print. PMID: 37968132 (52) Weiner DE, Vervloet MG, Walpen S, Schaufler T, Munera C, Menzaghi F, Wen W, Bhaduri S, Germain MJ; trial investigators. Safety and Effectiveness of Difelikefalin in Patients With Moderate-to-Severe Pruritus Undergoing Hemodialysis: An Open-Label,	CR845-CLIN3105	NCT03998163	Start: 26/06/19 Completion: 15/10/21	Difelikefalin (single arm study) for haemodialysis patients with moderate-to-severe CKD-aP

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Multicenter Study. Kidney Med. 2022 Aug 24;4(10):100542. doi: 10.1016/j.xkme.2022.100542 (61)				

Abbreviations: CKD-aP = chronic kidney disease-associated pruritus.

Notes: * If there are several publications connected to a trial, include all publications used.

Sources: ClinicalTrials.gov, 2018 (62); ClinicalTrials.gov, 2018 (63); ClinicalTrials.gov, 2019 (64); Fishbane et al., 2020 (60); Fishbane et al., 2022 (50); Topf et al., 2022 (51); Weiner et al., 2022 (61).

5.2 Literature used for the assessment of health-related quality of life

As an SLR was not considered to bring any further information (described in section 5.1), a HRQoL SLR was not carried out either. Thus, desktop research was carried out to identify utility values. No Danish studies have been identified to adapt CKD-aP specific HRQoL measures to generic HRQoL measures.

In relation to other HTA submissions for difelikefalin, a study was carried out in order to convert CKD-aP specific HRQoL measures to generic HRQoL values. To create a standardised input for the model, the findings from the Hernandez et al., 2023 (9) study was utilised. The study establishes a correlation between pruritus severity, assessed using WI-NRS and the 5-D itch scale, and health utility, measured through EQ-5D (9). The desktop search also identified Eriksson et al., 2017 (10) which was used to establish a ratio between dialysis utilities and utilities of transplanted patients.

Table 9: Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Hernandez M, Sasso A, Hnynn P, Gittus M, Powell R, Dunn L, Thokala P, Fotheringham J, Relationship Between Standardized Measures of Chronic Kidney Disease-associated Pruritus Intensity and Health-related Quality of Life Measured with the EQ-5D Questionnaire: A Mapping Study, Acta Derm Venereol (2023), DOI: 10.2340/actadv.v103.11604.(9)	Conversion algorithm between CKD-aP pruritus measures and generic EQ-5D health-related quality of life. This publication is used to estimate the EQ-5D-3L values associated with each pruritus severity health state in the health economic model.	Described in section 10.3

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Eriksson, D., Karlsson, L., Eklund, O., Dieperink, H., Honkanen, E., Melin, J., Selvig, K., & Lundberg, J. (2017). Health-related quality of life across all stages of autosomal dominant polycystic kidney disease. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 32(12), 2106–2111. https://doi.org/10.1093/ndt/gfw335 (10)	Ratio is calculated based on utility values in Eriksson et al., 2017. The ratio is calculated as utility value for transplanted patients divided with utility value for dialysis patients. The ratio is used to calculate the utility values for transplanted patients in the model.	Described in section 10.3

Sources: Hernandez et al., 2023 (9) and Eriksson et al., 2017 (10)

5.3 Literature used for inputs for the health economic model

No economic SLR was done to provide input for the health economic model, as the SLR was not expected to bring further information (described in section 5.1). The clinical trials (KALM-1, KALM-2, and CLIN-3105) were used for baseline characteristics in the economic model and for the regression model that is running the transitions between pruritus health states of the economic model. Because the CLIN3015 trial did not include a week 4 follow-up point, that trial efficacy data could not be used for regression analyses, and therefore only the KALM-1 and KALM-2 efficacy data was used in the regression model. The publications of the clinical trials (KALM-1, KALM-2 and CLIN3105) are already listed in Table 8, and therefore these are not listed in Table 10.Based on clinical expert feedback, the applicant was made aware of the DNSL annual report (5), which includes information on all Danish dialysis patients and transplantations. Further, the applicant was made aware of the Boenink et al. 2020 (6) publication during a dialogue meeting with the DMC, which were included to model age-dependent mortality in renal replacement therapies. Krajewski et al., 2021 (8) was used to model pruritus severity following transplantation, and was found via targeted literature review (desktop search). Sørensen et al., 2007 (7) was used to model hazard ratios for patients with diabetes versus those without diabetes. Publications are presented in Table 10

Table 10: Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described
Dansk Nefrologisk Selskabs Landsregister (DNSL). Dansk Nefrologisk Selskabs Landsregister (DNSL) Landsdækkende database for patienter med kronisk nyresvigt - Årsrapport for 2022. Published: Regionernes Kliniske Kvalitetsudviklingsprogram. Published in 2023. Version. 0.1 (5)	Dialysis mortality Mortality transplanted patients Patient proportions for transplantations, diabetes, age, dialysis before transplantation.	Identified by clinicians / targeted literature search	Section 8.2
Boenink, R., Stel, V. S., Waldum-Grevbo, B. E., Collart, F., Kerschbaum, J., Heaf, J. G., de Meester, J., Finne, P., García-Marcos, S. A., Evans, M., Ambühl, P. M., Arici, M., Ayav, C., Steenkamp, R., Cases, A., Traynor, J. P., Palsson, R., Zoccali, C., Massy, Z. A., Jager, K. J., … Kramer, A. (2020). Data from the ERA-EDTA Registry were examined for trends in excess mortality in European adults on kidney replacement therapy. Kidney international, 98(4), 999–1008. https://doi.org/10.1016/j.kint.2020.05.039 (6)	Age-dependent mortality renal replacement therapy	Identified by the DMC / Targeted literature search	Section 8.2
Sørensen, V. R., Mathiesen, E. R., Heaf, J., & Feldt-Rasmussen, B. (2007). Improved survival rate in patients with diabetes and end-stage renal disease in Denmark. Diabetologia, 50(5), 922–929. https://doi.org/10.1007/s00125-007-0612-5 (7)	Hazard ratios for patients with diabetes versus patients without diabetes	Targeted literature search	Section 8.2
Krajewski PK, Olczyk P, Krajewska M, Krajewski W, Szepietowski JC. Clinical Characteristics of Itch in Renal Transplant Recipients. Front Med (Lausanne). 2021 Jan 20;7:615334. doi: 10.3389/fmed.2020.615334. PMID: 33553209; PMCID: PMC7854568.(8)	Distribution of pruritus severity after renal transplant	Targeted literature search	Section 8.2

Sources: DNSL 2022 (5), Boenink et al., 2020 (6), Sørensen et al., 2007 (7), Krajewski et al., 2021 (8)

6. Efficacy

6.1 Efficacy of difelikefalin compared to placebo for adult patients with moderate-to-severe pruritus associated with chronic kidney disease on haemodialysis

6.1.1 Relevant studies

The comparative efficacy of difelikefalin vs placebo is informed by the head-to-head KALM-1 and KALM-2 studies.

The main efficacy results are derived from the double-blind treatment phase of both studies and are presented in the section below. The open label extension phase of KALM-2 is only used to provide supplementary efficacy results for the 5-D Itch Score. No results from the KALM-1 open label extension are presented. As mentioned above, CR845-CLIN3105 will only be used to provide data on the relation between WI-NRS and sleep quality. In addition, supplementary safety data is presented in the safety section (section 9.1).

When treating pruritus, the placebo effect needs to be taken into account. The 'placebo effect' describes positive outcomes experienced by patients that cannot be attributed to a biological treatment mechanism. Although this can be leveraged to reduce symptoms in certain conditions such as depression and anxiety (55), the placebo effect presents a challenge in the analysis of clinical study outcomes as it can be difficult to establish the true effect of the active treatment.

In contrast to other conditions such as chronic pain, there is less research on the role of placebo effects in the treatment of pruritus. Studies of treatments for pruritus are particularly subject to placebo effects because of the multiple aspects that influence a patient's perception of their pruritus; pruritus is a complex comorbidity that is affected by a range of environmental and psychological factors. A meta-analysis of 34 studies of chronic pruritus treatments revealed that patients receiving placebo experienced a 24 % decrease in their pruritus compared to baseline (65). This occurred regardless of the administration mode and means that an IV administration (e.g., as used in difelikefalin studies) is as susceptible to the placebo effect as oral or topical administration. The size of the effect was higher than that reported in other meta-analyses of patients experiencing pain, suggesting that the placebo effect is a key consideration in studies of chronic pruritus treatments (65). A considerable placebo effect has also seen in other itch-related treatments recommended by the DMC (66).

Due to considerable placebo effect, the real-world benefits of difelikefalin are likely to be underestimated in the difelikefalin studies, as they examine the efficacy of difelikefalin in comparison to placebo IV-treatment. Placebo IV-treatment is not administered in clinical practice.

Table 11: Overview of study design for studies included in the comparison difelikefalin vs placebo

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
KALM1, NCT03422653 Fishbane et al. 2020 (60) Fishbane et al., 2022 (50) Topf et al., 2022 (51) Weiner et al., 2023 (52)	Multicentre randomised phase III double-blind, placebo-controlled study of difelikefalin vs. placebo. The study includes double-blind phase and an OLE phase.	12-week double-blind phase and 52-week OLE phase. Patients who received at least 30 doses of study drug (active or placebo) during the 12-week double-blind phase could receive open label difelikefalin for an additional 52 weeks.	Patients with ESRD on haemodialysis moderate to severe uremic pruritus.	Difelikefalin (IV administration), 0.5 mcg/kg after each dialysis session (3 times/week)	Placebo (IV administration), after each dialysis session (3 times/week)	Proportion of participants achieving a ≥3-point improvement (reduction) in the weekly mean of daily 24-hour WI-NRS scores (week 12). Itch-related QoL (change from baseline in 5-D itch scale score, week 12). Itch-related QoL (change from baseline in total Skindex-10 scale score, week 12). Proportion of participants achieving a ≥4-point improvement (reduction) in the weekly mean of daily 24-hour WI-NRS scores (week 12).
KALM2, NCT03636269 Fishbane et al., 2022 (50) Topf et al., 2022 (51) Weiner et al., 2023 (52)	Multicentre randomised phase III double-blind, placebo-controlled study of difelikefalin vs. placebo. The study includes double-blind phase and an OLE phase.	12-week double-blind phase and 52-week OLE phase. Patients who received at least 30 doses of study drug (active or placebo) during the 12-week double-blind phase could receive open label difelikefalin for an additional 52 weeks.	Patients with ESRD on haemodialysis moderate to severe uremic pruritus.	Difelikefalin (IV administration), 0.5 mcg/kg after each dialysis session (3 times/week)	Placebo (IV administration), after each dialysis session (3 times/week)	Proportion of participants achieving a ≥3-point improvement (reduction) in the weekly mean of daily 24-hour WI-NRS scores (week 12). Proportion of participants achieving a ≥4-point improvement (reduction) in the weekly mean of daily 24-hour WI-NRS scores (week 12). Itch-related QoL (change from baseline in total Skindex-10 scale score, week 12). Itch-related QoL (change from baseline in 5-D itch scale score, week 12).
CR845-CLIN3105, NCT03998163* Fishbane et al., 2022 (50)	Multicentre, open-label, phase III study of the safety and	Up to 12-week treatment period.	Patients ESRD on haemodialysis with moderate to	Difelikefalin (IV administration) 0.5 mcg/kg after each dialysis	N/A	Number of participants with adverse events (up to follow-up visit in week 13-14).

Weiner et al., 2023 (52) Weiner et al., 2022 (61)	effectiveness of difelikefalin.	severe uremic pruritus.	session (3 times/week).

Abbreviations: ESRD = end-stage renal disease; IV = intravenous; OLE = open-label extension; N/A = not applicable; QoL = quality of life; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Notes: * The trial CR845-CLIN3105 is not included in the comparative analysis. However, it is presented here, as is used in the health economic model. The primary outcome is reported in 9.1.

Sources: ClinicalTrials.gov 2018 (62); ClinicalTrials.gov, 2018 (63); ClinicalTrials.gov, 2019 (64).

6.1.2 Comparability of studies

KALM-1 and KALM-2 were multicentre, randomised, double-blind, placebo-controlled studies to evaluate the safety and efficacy of difelikefalin at a dose of 0.5 mcg/kg administered after each haemodialysis session (3 times a week) in subjects with moderate-to-severe pruritus. Both studies included a double-blind phase and OLE phase (62, 63). KALM-1 was a United States (US) study, and KALM-2 was a global study conducted in North America (US and Canada), Europe (Czech Republic, Germany, Great Britain, Hungary, and Poland), and the Asia Pacific region (Australia, New Zealand, South Korea, and Taiwan) (51). In addition, in KALM-1 patients 18 years of age or older were eligible for inclusion, while in KALM-2 patient 18-85 years of age were eligible for inclusion (55, 67).

The double-blind phase consisted of a screening visit, a 7-day run-in period during the week prior to randomisation and a 12-week double-blind treatment period where difelikefalin was evaluated relative to placebo. Participants completed the 7-day run-in period to confirm they had moderate-to-severe CKD-aP, defined as weekly mean WI-NRS score of >4 in KALM-1 or ≥5 in KALM-2. However, the mean WI-NRS at baseline was similar in the two studies (in KALM-1, 7.06 and 7.25 in the difelikefalin and placebo group, respectively, and in KALM-2, 7.27 and 7.12 in the difelikefalin and placebo group, respectively,) (see Table 12, section 6.1.2.1). For KALM-1 the double-blind treatment period was followed by a 2-week discontinuation period, during which no study drug was administered, and subjects were monitored for potential signs or symptoms of physical dependence, before advancing to the OLE phase (51, 62, 63, 67).

Both studies also included an OLE phase. No separate objectives were specified for the OLE phase. The open-label part of the study was designed to evaluate the safety of difelikefalin at a dose of 0.5 mcg/kg administered IV after each dialysis session (generally 3 times per week) during long-term use (for up to 52 weeks) in subjects who had completed the 12-week double-blind treatment period. It also evaluated the maintenance of treatment effect during long-term use. The OLE phase consisted of the open-label treatment period and the follow-up period. The first visit and first dosing for the OLE phase occurred during the week following the discontinuation period in KALM-1. For KALM-2 the dose is given either on the day of the last visit of the double-blind treatment period or on the next visit up to 1 week following the double-blind treatment period. The last dose of the study drug was administered at the last haemodialysis treatment of week 52. A final safety follow-up visit was conducted 7 to 10 days after the end of treatment/early termination visit (62, 63, 68).

6.1.2.1 Comparability of patients across studies

In Table 12 baseline characteristics of patients included in the studies included in the comparative analysis, KALM-1 and KALM-2, are presented. In addition, baseline characteristics of patients included in the CR845-CLIN3105 are presented.

Table 12: Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety in KALM-1 and KALM-2

	KALM-1		KALM-2		CR845-CLIN3105
	Difelikefalin (n = 189)[¥]	Placebo (n = 188)[¥]	Difelikefalin (n = 235)[¥]	Placebo (n = 236)[¥]	Difelikefalin (n = 222)[Ω]
Mean age, years (standard deviation [SD])	58.2 (11.16)	56.8 (13.89)	59.7 (13.11)	59.6 (13.07)	58.1 (12.81)
Age group, n (%)					
<45	22 (11.6)	35 (18.6)	28 (11.9)	28 (11.9)	31 (14.0)
≥45 - <65	113 (59.8)	101 (53.7)	118 (50.2)	125 (53.0)	119 (53.6)
≥65 - <75	44 (23.3)	32 (17.0)	55 (23.4)	49 (20.8)	48 (21.6)
≥75	10 (5.3)	20 (10.6)	34 (14.5)	34 (14.4)	24 (10.8)
Sex, n (%)					
Male	112 (59.3)	118 (62.8)	135 (57.4)	139 (58.9)	121 (54.5)
Female	77 (40.7)	70 (37.2)	100 (42.6)	97 (41.1)	101 (45.5)
Race, n (%)					
American Indian or Alaska Native	6 (3.2)	5 (2.7)	1 (0.4)	1 (0.4)	2 (0.9)
Asian	6 (3.2)	7 (3.7)	12 (5.1)	20 (8.5)	7 (3.2)
Black or African American	82 (43.4)	75 (39.9)	53 (22.6)	38 (16.1)	110 (49.5)
Native Hawaiian or Other Pacific Islander	2 (1.1)	4 (2.1)	1 (0.4)	3 (1.3)	3 (1.4)
White	91 (48.1)	94 (49.5)	162 (68.9)	169 (71.6)	96 (43.2)
Unknown	1 (0.5)	2 (1.1)	N/A	N/A	N/A
Other	1 (0.5)	2 (1.1)	6 (2.6)	5 (2.1)	4 (1.8)
Region, n (%)					
USA	N/A	N/A	145 (61.7)	133 (56.4)	203 (91.4)
Asia	N/A	N/A	8 (3.4)	12 (5.1)	N/A
Eastern Europe	N/A	N/A	54 (23.0)	60 (25.4)	19 (8.6)
Western Europe/European Origin	N/A	N/A	28 (11.9)	31 (13.1)	N/A
Mean prescription dry body weight, kg (SD)	85.91 (20.264)	84.98 (21.084)	81.56 (19.731)	79.95 (19.450)	86.64 (23.548)
Baseline WI-NRS, mean (SD)	7.06 (1.439)	7.25 (1.606)	7.27 (1.358)	7.12 (1.363)	7.57 (1.331)
Baseline anti-itch medication use?*, n (%)					
Yes	72 (38.1)	78 (41.5)	87 (37.0)	85 (36.0)	70 (31.5)
No	117 (61.9)	110 (58.5)	148 (63.0)	151 (64.0)	152 (68.5)

	KALM-1		KALM-2		CR845-CLIN3105
	Difelikefalin (n = 189)¥	Placebo (n = 188)¥	Difelikefalin (n = 235)¥	Placebo (n = 236)¥	Difelikefalin (n = 222)Ω
Specific medical condition?*, n (%)					
Yes	25 (13.2)	28 (14.9)	41 (17.4)	37 (15.7)	N/A
No	164 (86.8)	160 (85.1)	194 (82.6)	199 (84.3)	N/A
Mean duration of pruritus, years (SD)	3.19 (3.244)	3.45 (3.369)	3.21 (4.567)	3.20 (3.184)	3.89 (3.312)
Mean years since diagnosis of ESRD, years (SD)	4.66 (3.898)	5.66 (5.178)	5.23 (4.677)	5.46 (4.509)	5.87 (4.690)
Years since diagnosis of CKD					
n	189	187	234	232	222
Mean (SD)	6.92 (5.926)	7.03 (5.739)	9.28 (7.638)	9.76 (7.009)	8.51 (6.878)
Years on chronic haemodialysis, mean (SD)	4.37 (3.982)	4.73 (4.219)	4.83 (4.588)	5.09 (4.327)	5.42 (4.413)
Aetiology of CKD, n (%)**					
Diabetes	107 (56.6)	94 (50.0)	118 (50.2)	112 (47.5)	110 (49.5)
Hypertension	129 (68.3)	139 (73.9)	121 (51.5)	114 (48.3)	135 (60.8)
Large vessel disease	4 (2.1)	4 (2.1)	4 (1.7)	3 (1.3)	4 (1.8)
Glomerulonephritis	7 (3.7)	8 (4.3)	14 (6.0)	17 (7.2)	11 (5.0)
Vasculitis	0	0	3 (1.3)	2 (0.8)	1 (0.5)
Interstitial nephritis	0	1 (0.5)	2 (0.9)	1 (0.4)	1 (0.5)
Pyelonephritis	0	0	3 (1.3)	1 (0.4)	2 (0.9)
Cystic	1 (0.5)	2 (1.1)	18 (7.7)	16 (6.8)	2 (0.9)
Hereditary	1 (0.5)	2 (1.1)	13 (5.5)	6 (2.5)	0
Congenital	0	0	1 (0.4)	3 (1.3)	0
Neoplasms	1 (0.5)	1 (0.5)	0	2 (0.8)	0
Tumours	2 (1.1)	0	1 (0.4)	1 (0.4)	1 (0.5)
Urologic	0	0	6 (2.6)	9 (3.8)	3 (1.4)
Nephrotic syndrome	2 (1.1)	4 (2.1)	3 (1.3)	6 (2.5)	1 (0.5)
Unknown	7 (3.7)	6 (3.2)	8 (3.4)	14 (5.9)	N/A
Other	11 (5.8)	16 (8.5)	26 (11.1)	28 (11.9)	N/A
Dialysis type					
Haemofiltration	N/A	N/A	0	0	0
Haemodialysis	N/A	N/A	220 (93.6)	199 (84.3)	216 (97.3)

	KALM-1		KALM-2		CR845-CLIN3105
	Difelikefalin (n = 189)¥	Placebo (n = 188)¥	Difelikefalin (n = 235)¥	Placebo (n = 236)¥	Difelikefalin (n = 222)Ω
Haemodiafiltration	N/A	N/A	15 (6.4)	37 (15.7)	6 (2.7)
Haemodialysis and haemodiafiltration	N/A	N/A	0	0	0
Haemofiltration and haemodialysis	N/A	N/A	0	0	0
Haemofiltration and haemodiafiltration	N/A	N/A	0	0	0

Abbreviations: CKD = chronic kidney disease; ESRD = end-stage renal disease; N/A = not applicable; SD = standard deviation; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Notes: *Observed stratum values. ** More than one item may have been checked. ¥ Baseline characteristics are reported for the safety population defined as randomised subjects who received at least 1 dose of double-blind study drug during the Double-blind Treatment Period. The only difference between the intention-to-treat (ITT) population (defined as subjects who were randomized to a treatment group) and the safety population in the KALM-1 study is that the placebo arm in the safety population comprise 188 patients while comprising 189 patients in the ITT population. In the KALM-2 study, 237 patient are in difelikefalin arm in the ITT population and 235 patients in the difelikefalin arm in the safety population. Ω The data is based on the safety population. The safety population was defined as the group of subjects who received at least 1 dose of difelikefalin in the study.

Sources: Cara Therapeutics, 2020 (67); Cara Therapeutics, 2020 (55).

The proportion of Black or African American participants was slightly greater in the difelikefalin group vs. the placebo group in KALM-2 (22.6% vs. 16.1%, respectively), similar between the difelikefalin and placebo groups in KALM-1 (43.4% vs. 39.9%, respectively), and higher in KALM-1 vs. KALM-2 (51). The proportion of white participants was higher in KALM-2 (approximately 70%) than in KALM-1 (approximately 49%).

In addition, a difference between studies in years since CKD diagnosis appeared. In KALM-1 the mean number of years since diagnosis was approximately 7, while the mean number of years since diagnosis was more than 9 years in KALM-2.

In KALM-2, the proportion of participants on haemodialysis was higher in the difelikefalin group than in the placebo group (93.6% vs. 84.3%, respectively), while the proportion of participants on haemodfiltration was lower in the difelikefalin group than in the placebo group (6.4% vs. 15.7%, respectively).

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Table 13: Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population DNSL 2022	Value used in health economic model (reference if relevant)
Age (mean)**	63.86	58.70
Male %	63.6 %	59.6 %
Diabetes	50.6 %	24.1 %*

Proportion of patients with 2 years or less of haemodialysis	Not reported	26.8 %
Proportion older than 65 years	54.7 %**	30.2 %

* Likely underestimation. Only includes patients with diabetic renal disease.

** estimated based on age distribution

6.1.4 Efficacy – results per KALM-1

The number and proportion of patients that discontinued the study in the difelikefalin and placebo arm, respectively, and the reason for discontinuation is presented in Table 14 and Table 15.

Table 14: Discontinuation in the double-blind treatment period of KALM-1

	Difelikefalin (N=189)	Placebo (N=188)
Number (%) of subjects who discontinued the double-blind treatment period	27 (14.3)	18 (9.6)
Adverse event, n (%)	14 (7.4)	9 (4.8)
Lack of therapeutic efficacy, n (%)	0	0
Lost to follow-up, n (%)	0	0
Pregnancy, n (%)	0	0
Eligibility (inclusion/exclusion criteria), n (%)	1 (0.5)	2 (1.1)
Subject non-compliance, n (%)	1 (0.5)	1 (0.5)
Subject withdrew consent, n (%)	8 (4.2)	6 (3.2)
Administrative, n (%)	0	0
Other, n (%)	3 (1.6)	0

Source: KALM-1 double-blind CSR, 2020; table 5 (67)

Table 15: Discontinuation in the OLE phase of KALM-1

	Difelikefalin/difelikefalin (N=151)	Placebo/difelikefalin (N=162)
Number (%) of subjects who discontinued the OLE phase, except due to sponsor stopping study	**38 (25.2)**	**49 (30.2)**
Adverse event, n (%)	11 (7.3)	15 (9.3)
Lack of therapeutic efficacy, n (%)	0 (0)	0 (0)
Lost to follow-up, n (%)	1 (0.7)	4 (2.5)
Pregnancy, n (%)	0 (0)	0 (0)
Eligibility (inclusion/exclusion criteria), n (%)	0 (0)	0 (0)
Subject non-compliance, n (%)	1 (0.7)	4 (2.5)
Subject withdrew consent, n (%)	9 (6.0)	8 (4.9)
Administrative, n (%)	0 (0)	0 (0)

Other, n (%)	16 (10.6)	18 (11.1)
Could not complete treatment due to sponsor stopping study early	**19 (12.6)**	**18 (11.1)**

Abbreviations: OLE = open-label extension.

Notes: The difelikefalin/difelikefalin group includes participants randomised to difelikefalin group during double-blind phase/received difelikefalin during OLE phase. The placebo/difelikefalin group includes participants randomised to placebo group during double-blind phase/received difelikefalin during OLE phase.

Source: Fishbane et al. 2022; supplementary figure 4 (50).

6.1.4.1 WI-NRS scores

The primary efficacy endpoint was the proportion of subjects achieving a ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at week 12 of the double-blind treatment period. Table 16 summarises the results for the ITT population based on the combined imputed data from interim and post-interim analysis subjects. At week 12, the least-squares (LS) mean percentage of subjects with at least a 3-point improvement from baseline in the WI-NRS was 51.0% in the difelikefalin group, compared with 27.6% in the placebo group. The odds ratio (OR) for a ≥3 point improvement from baseline with difelikefalin versus placebo was 2.72 (95% CI: 1.72-4.30), which was statistically significant (*P* <.001).

The third secondary efficacy endpoint (the first and second secondary efficacy endpoint is presented in section 6.1.4.2) was the proportion of subjects achieving a ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at week 12. Table 16 summarises the analysis of this endpoint for the ITT population, which was conducted in a manner identical to that employed in the primary analysis of the primary endpoint. At week 12, the LS mean percentage of subjects with a ≥4-point improvement in WI-NRS from baseline was 38.9% in the difelikefalin group and 18.0% in the placebo group; the OR with difelikefalin was 2.89 (95% CI: 1.75-4.76), which was statistically significant (*P* <.001).

Table 16: Analysis of efficacy outcomes based on WI-NRS scores*, KALM-1, double-blind treatment period

Outcomes	Placebo (N=189)	Difelikefalin (N=189)	P Value **
Proportion of patients achieving a ≥3-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12***			
Observed, no./total no. (%)	51/165 (30.9)	82/157 (52.2)	
LS mean$^{\Omega}$, % (95% CI)	27.6 (20.2–36.6)	51.0 (42.9–58.9)	
Lawrence, Hung (LH) OR$^{\Omega}$ (95% CI)		2.72 (1.72-4.30)	
Relative risk (95% CI)		1.72 (1.32-2.24)	P<0.001$^{\Omega}$
Proportion of patients achieving a ≥4-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12***			
Observed, no./total no. (%)	35/165 (21.2)	64/157 (40.8)	

LS mean$^{\Omega}$, % (95% CI)	18.0 (12.1–26.0)	38.9 (29.8–48.7)	
LH OR$^{\Omega}$ (95% CI)		2.89 (1.75-4.76)	
Relative risk (95% CI)		1.99 (1.43-2.78)	P<0.001$^{\Omega}$

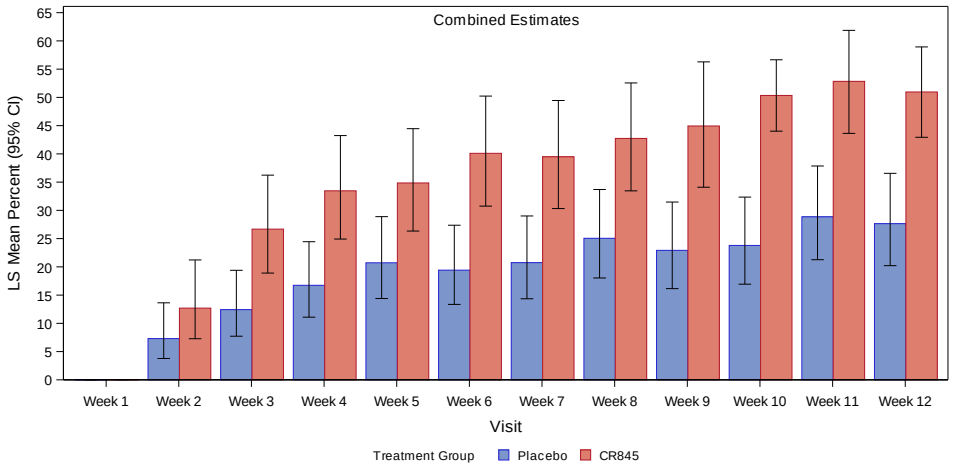
Abbreviations: CI = confidence interval; ITT = intention-to-treat; LH = Lawrence, Hung; LS = least-squares; OR = odds ratio; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Notes: * Efficacy analyses were performed on the ITT population. The primary and secondary outcomes were evaluated using a prespecified hierarchical statistical testing procedure; the P value for each outcome was considered inferential if the preceding end point in the sequential testing procedure was statistically significant at a two-sided 0.05 significance level. ** Cui, Hung, Wang procedure. *** Includes scores on-treatment only. $^{\Omega}$ Estimated percent, OR, and *P* value used a logistic regression model with terms for treatment group, baseline WI-NRS score, use of anti-itch medication during the week prior to randomisation, and the presence of specific medical conditions. Missing values were imputed using multiple imputation under missing-at-random missing data assumption for interim subjects and post-interim subjects separately.

Source: Fishbane et al. 2020; table S7 (60); KALM-1 double-blind CSR, 2020; table 13 and 17 (67)

Figure 2 depicts the LS mean percentage of ITT subjects with a ≥3-point improvement from baseline in WI-NRS by study week (week 12 being the primary efficacy time point). A statistically significant treatment group difference favouring difelikefalin was observed as early as week 3 (*P* <.001) and was maintained throughout the remainder of the double-blind treatment period. At week 4, the LS mean percentage of subjects in the difelikefalin group with a ≥3 point improvement from baseline in WI-NRS was 33.5% vs. 16.7% for the placebo group (*P* <.001), and at week 8, the respective percentages were 42.7% vs. 25.1% (*P* <.001).

Figure 2: Percentage of subjects with a ≥3-point improvement in WI-NRS score by week (primary efficacy imputation) (population: ITT)



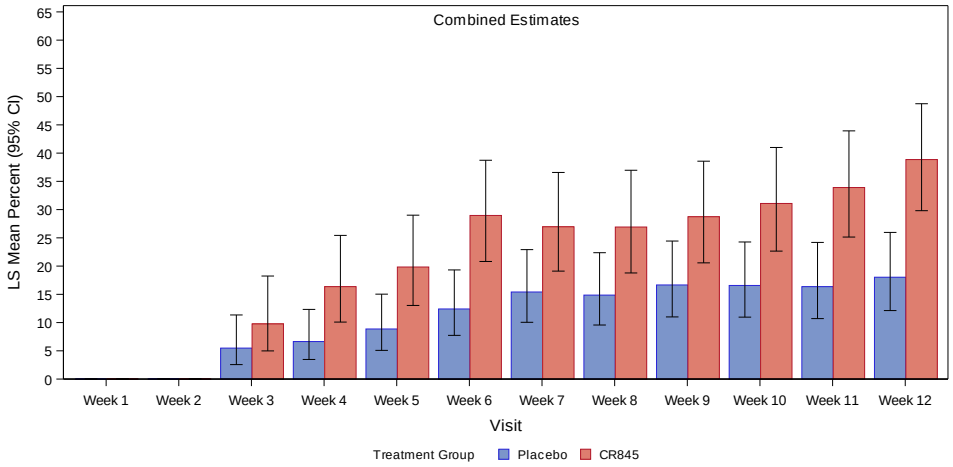
Abbreviations: CI = confidence interval; CR845 = difelikefalin; ITT= Intent-to-treat; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Note: Estimated percentages and CIs used a logistic regression model with terms for treatment group, baseline WI-NRS score, use of anti-itch medication during the week prior to randomisation, and the presence of specific medical conditions. Missing values were imputed using multiple imputation under a missing-at-random missing data assumption for interim subjects and post-interim subjects separately. Combined analysis used the separate interim and post-interim results to generate an adjusted overall estimate and P value using the Lawrence, Hung/Cui, Hung, Wang methodology.

Source: KALM-1 double-blind CSR, 2020; figure 3 (67).

Figure 3 depicts the percentage of ITT subjects with a ≥4-point improvement in the WI-NRS by study week. A statistically significant (*P* ≤.05) treatment group difference favouring difelikefalin was observed by Week 4 (*P* = .003) and maintained throughout the remainder of the double-blind treatment period. At week 4, the LS mean percentage of subjects in the difelikefalin group with a ≥4-point improvement from baseline in WI-NRS was 16.4% vs. 6.6% for the placebo group (*P* = .003), and at Week 8, the respective percentages were 26.9% versus 14.9% (*P* = .005).

Figure 3: Percentage of subjects with a ≥4-point improvement in WI-NRS score by week (multiple imputation with missing at random assumption) (population: ITT)



Abbviations: CI = confidence interval; CR845 = difelikefalin; ITT= Intent-to-treat; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Note: Estimated percentages and CIs used a logistic regression model with terms for treatment group, baseline WI-NRS score, use of anti-itch medication during the week prior to randomisation, and the presence of specific medical conditions. Missing values were imputed using multiple imputation under a missing-at-random missing data assumption for interim subjects and post-interim subjects separately. Combined analysis used the separate interim and post-interim results to generate an adjusted overall estimate and *P* value using the Lawrence, Hung/Cui, Hung, Wang methodology.

Source: KALM-1 double-blind CSR, 2020; figure 4 (67).

6.1.4.2 Itch-related quality of life results

The first secondary efficacy endpoint was the change from baseline in itch-related QoL at the end of week 12, as assessed by the 5-D Itch Scale (total score). Table 17 summarises the change from baseline in total 5-D Itch Scale score at the end of week 12 using analysis of covariance (ANCOVA) with multiple imputation. Compared with the placebo group, the difelikefalin group showed a statistically significant (P <.001) greater reduction in total 5-D Itch Scale score at the end of week 12, with a LS mean treatment group difference of 1.3 (95% CI: -2.0, -0.5).

The second secondary efficacy endpoint was the change from baseline in itch-related QoL at the end of week 12, as assessed by the total Skindex-10 Scale score. Table 17 summarise the change from baseline in total Skindex 10 Scale score at the end of week 12 for the ITT population using ANCOVA with multiple imputation. At the end of week 12, the LS mean change in total Skindex-10 Scale score was greater in the difelikefalin group than in

the placebo group (-17.2 versus -12.0), with a statistically significant LS mean difference: -5.1 (95% CI, -8.0 to -2.3); P <.001.

Table 17: Itch-related quality of life results, KALM-1, double-blind treatment period

Outcomes	Placebo (N=189)	Difelikefalin (N=189)	Difference in LS Means (difelikefalin – placebo)	P Value
LS mean change from baseline at week 12 in 5-D itch scale total score	–3.7 (standard error [SE]: 0.33; CI: -4.4, -3.1)	–5.0 (SE: 0.33; CI: (-5.7, -4.4)	-1.3 (SE: 0.38; CI: -2.0, -0.5)	<0.001
LS mean change from baseline at week 12 in Skindex-10 scale total score	–12.0 (SE: 1.24; CI: -14.5, -9.6)	–17.2 (SE: 1.26; CI: -19.6, -14.7)	-5.1 (SE: 1.44; CI: -8.0, -2.3)	<0.001

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LS = least-squares; SE = standard error.

Note: LS means, SEs, and 95% CIs were based on ANCOVA with fixed effects for treatment, with baseline score and the randomisation stratification variables as covariates. Missing values were imputed using multiple imputation under missing-at-random missing data assumption.

Source: KALM-1 double-blind CSR, 2020; table 15 and 16 (67).

6.1.5 Efficacy – results per KALM-2

The number and proportion of patients that discontinued the study in the difelikefalin and placebo arm, respectively, and the reason for discontinuation is presented in Table 18 and Table 19.

Table 18: Discontinuation in the double-blind treatment period of KALM-2

	Difelikefalin (N=237)	Placebo (N=236)
Number (%) of subjects who discontinued the double-blind treatment period	29 (12.3)	13 (5.5)
Adverse event, n (%)	13 (5.5)	7 (3.0)
Lack of therapeutic efficacy, n (%)	1 (0.4)	0
Lost to follow-up, n (%)	1 (0.4)	0
Pregnancy, n (%)	0	0
Eligibility (inclusion/exclusion criteria), n (%)	2 (0.9)	0
Subject non-compliance, n (%)	1 (0.4)	2 (0.8)
Subject withdrew consent, n (%)	5 (2.1)	1 (0.4)
Administrative, n (%)	0	0
Other, n (%)	6 (2.6)	3 (1.3)

Source: KALM-2 double-blind CSR, 2020; table 5 (55).

Table 19: Discontinuation in the double-blind treatment period and open-label extension phase of KALM-2

	Difelikefalin/difelikefalin (N=189)	Placebo/difelikefalin (N=210)
Number (%) of subjects discontinued open-label treatment (except due to sponsor stopping study)	41 (21.7)	40 (19.0)
Adverse event, n (%)	9 (4.8)	12 (5.7)
Lack of therapeutic efficacy, n (%)	0	2 (1.0)
Lost to follow-up, n (%)	0	0
Pregnancy, n (%)	0	0
Eligibility (inclusion/exclusion criteria) , n (%)	1 (0.5)	1 (0.5)
Subject non-compliance, n (%)	0	0
Subject withdrew consent, n (%)	7 (3.7)	4 (1.9)
Administrative, n (%)	19 (10.1)	17 (8.1)
Other, n (%)	5 (2.6)	4 (1.9)
Number (%) of subjects discontinued (i.e., who could not complete) open-label treatment due to sponsor stopping study early	146 (77.2)	167 (79.5)

Source: KALM-2 OLE CSR, 2020; table 4 (68).

6.1.5.1 WI-NRS scores

The primary efficacy endpoint was the proportion of subjects achieving a ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at week 12. Table 20 summarises these results for the ITT population based on the combined data from interim and post-interim analysis subjects. At week 12, the LS mean percentage of subjects with at least a 3-point improvement from baseline in the WI-NRS was 54.0% in the difelikefalin group compared with 42.2% in the placebo group. The estimated OR for a ≥3 point improvement from baseline with difelikefalin versus placebo was 1.61 (95% CI: 1.08 to 2.41), which was statistically significant (P = .020).

The first key secondary efficacy endpoint was the proportion of subjects achieving a ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at week 12. Table 20 summarises the analysis of this endpoint for the ITT population, which was conducted in a manner identical to that employed in the primary analysis of the primary endpoint. At week 12, the LS mean percentage of subjects with a ≥4-point improvement in WI-NRS from baseline was 41.2% in the difelikefalin group and 28.4% in the placebo group; the OR was 1.77 (95% CI: 1.14 to 2.74), which was statistically significant (P = .010).

Table 20: Analysis of efficacy outcomes based on WI-NRS scores, KALM-2, double-blind treatment period

Outcomes	Placebo (N=236)	Difelikefalin (N=237)	P Value*

Proportion of patients achieving a ≥3-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12			
Observed**, no. (%)	77 (37.2%)	95 (49.7%)	
LS mean***, % (95% CI)	42.2 (32.5, 52.5)	54.0 (43.9, 63.9)	
LH OR*** (95% CI)		1.61 (1.08, 2.41)	0.020
Proportion of patients achieving a ≥4-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12			
Observed**, no. (%)	52 (25.1%)	72 (37.7%)	
LS mean***, % (95% CI)	28.4 (21.3, 36.7)	41.2 (33.0, 50.0)	
LH OR*** (95% CI)		1.77 (1.14, 2.74)	0.010

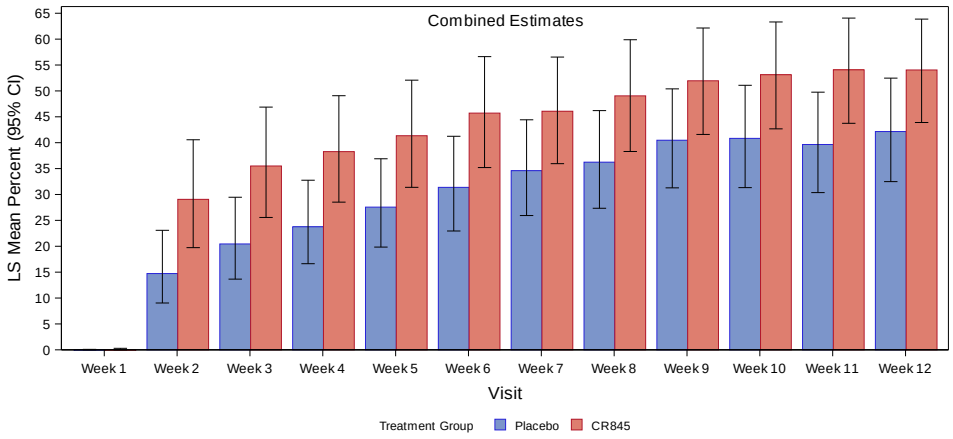
Abbreviations: CI = confidence interval; LH = Lawrence, Hung; LS = least-squares; OR = odds ratio; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Notes: Combined analysis used the separate interim and post-interim results to generate an adjusted overall estimate and P value using the LH or Cui, Hung, Wang methodology. * Cui, Hung, Wang procedure. ** Counts and percentages were based on non-missing data. *** Estimated percentage, OR and P value used a logistic regression model with terms for treatment group, baseline WI-NRS score, region, use of anti-itch medication during the week prior to randomisation, and the presence of specific medical conditions. Missing values were imputed using multiple imputation under missing-at-random missing data assumption for interim subjects and post-interim subjects separately.

Source: KALM-2 double-blind CSR, 2020; table 13 and 16 (55).

Figure 4 depicts the LS mean percentage of ITT subjects with a ≥3-point improvement from baseline in WI-NRS score by study week (week 12 being the primary efficacy time point). A statistically significant treatment group difference favouring difelikefalin was observed as early as week 2 (*P* = .003) and was maintained throughout the remainder of the double-blind treatment period.

Figure 4: Percentage of subjects with a ≥3-point improvement in WI-NRS score by week (primary efficacy imputation) (population: ITT)



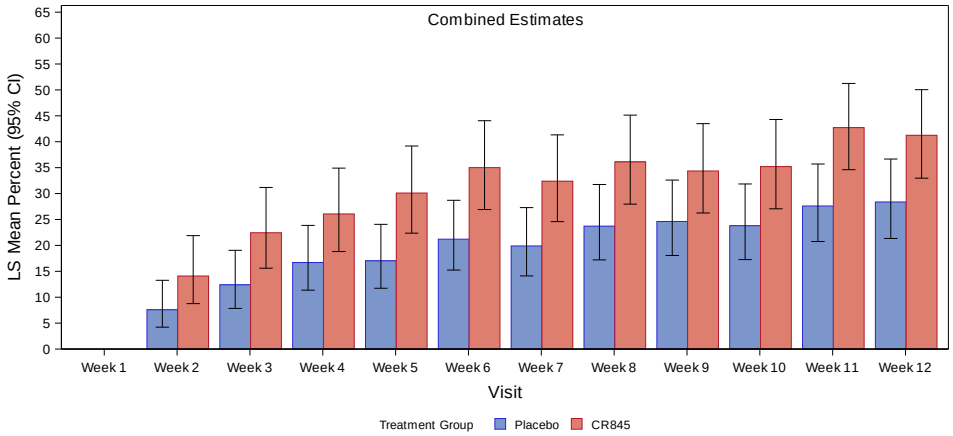
Abbreviations: CI = confidence interval; CR845 = difelikefalin; ITT= Intent-to-treat; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Note: Estimated percentages and CIs used a logistic regression model with terms for treatment group, baseline WI-NRS score, region, use of anti-itch medication during the week prior to randomisation, and the presence of specific medical conditions. Missing values were imputed using multiple imputation under a missing-at-random missing data assumption for interim subjects and post-interim subjects separately. Combined analysis used the separate interim and post-interim results to generate an adjusted overall estimate and *P* value using the Lawrence, Hung/Cui, Hung, Wang methodology.

Source: KALM-2 double-blind CSR, 2020; figure 3 (55).

Figure 5 depicts the percentage of ITT population with a ≥4-point improvement in the WI-NRS by study week. A statistically significant treatment group difference favouring difelikefalin was observed by week 3 (*P* = .018) and maintained throughout the remainder of the double-blind treatment period.

Figure 5: Percentage of subjects with a ≥4-point improvement in WI-NRS score by week (multiple imputation with missing at random assumption) (population: ITT)



Abbreviations: CI = confidence interval; CR845 = difelikefalin; ITT= Intent-to-treat; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Note: Estimated percentages and CIs used a logistic regression model with terms for treatment group, baseline WI-NRS score, region, use of anti-itch medication during the week prior to randomisation, and the presence of specific medical conditions. Missing values were imputed using multiple imputation under a missing-at-random missing data assumption for interim subjects and post-interim subjects separately. Combined analysis used the separate interim and post-interim results to generate an adjusted overall estimate and *P* value using the Lawrence, Hung/Cui, Hung, Wang methodology.

Source: KALM-2 double-blind CSR, 2020; figure 4 (55).

6.1.5.2 Itch-related quality of life results

One secondary efficacy endpoint was the change from baseline in itch-related QoL at the end of week 12, as assessed by the total Skindex-10 Scale score. Table 21 summarise the change from baseline in total Skindex 10 Scale score at the end of Week 12 for the ITT population using ANCOVA with multiple imputation under missing at random assumption. Compared with the placebo group, the difelikefalin group showed a numerically greater reduction in LS Mean total Skindex-10 Scale score (-16.6 vs. -14.8) at the end of Week 12, with a LS mean treatment group difference of 1.8 (95% CI: -4.3 to 0.8), which was not statistically significant (*P* = .171).

The last secondary efficacy endpoint was the change from baseline in itch-related QoL at the end of week 12, as assessed by the total score of the 5-D Itch Scale. Table 21 and

summarise the change from baseline in total 5-D Itch Scale score at the end of Week 12 using ANCOVA with multiple imputation of missing data under a missing-at-random assumption. Compared with the placebo group, the difelikefalin group showed a greater reduction in total 5 D Itch Scale score at the end of week 12, with a LS mean treatment group difference of 1.1 (95% CI: 1.7 to -0.4). Although the nominal P value was 0.002, this difference could not be declared as statistically significant based on the hierarchical testing order, as the prior secondary endpoint (Skindex-10 at Week 12) was not statistically significant.

Table 21: Itch-related quality of life results, KALM-2, double-blind treatment period

Outcomes	Placebo (N=236)	Difelikefalin (N=237)	Difference in LS Means (difelikefalin – placebo)	P Value
LS mean change from baseline at week 12 in Skindex-10 scale total score	-14.8 (SE: 1.32; 95% CI: -17.4, -12.2)	-16.6 (SE: 1.35; 95% CI: -19.3, -14.0)	-1.8 (SE: 1.29; 95% CI: -4.3, 0.8)	0.171
LS mean change from baseline at week 12 in 5-D itch scale total score	-3.8 (SE: 0.36; 95% CI: -4.5, -3.1)	-4.9 (SE: 0.36; CI: -5.6, -4.2)	-1.1 (SE: 0.35; CI: -1.7, -0.4)	0.002

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LS = least-squares; SE = standard error.

Note: LS means, SEs, and 95% Cis were based on ANCOVA with fixed effects for treatment, with baseline score and the randomisation stratification variables as covariates. Missing values were imputed using multiple imputation under missing-at-random missing data assumption.

Source: KALM-2 double-blind CSR, 2020; table 20 and 21 (55).

6.1.5.3 Efficacy assessment in the OLE phase

The maintenance of the effect of difelikefalin on itch was measured by the 5-D Itch scale with which data were already recorded during the double-blind treatment period. The 5-D Itch Scale was completed by subjects periodically during the OLE phase and was used to evaluate the effect of difelikefalin, focusing on the change in total score and change by domain score from baseline.

Table 22: Mixed model for repeated measures analysis of change from double-blind baseline in total 5-D Itch Score double-blind and open-label visits - no imputation (population: open-label safety)

Change from baseline	Placebo/difelikefalin (N=210)	Difelikefalin/difelikefalin (N=189)
n, double-blind end of week 4	204	182
LS mean, double-blind end of week 4	-2.9 (SE: 0.31; 95% CI: -3.5, -2.3)	-4.2 (SE: 0.33; 95% CI: -4.9, -3.6)
n, double-blind end of week 12	207	185
LS mean, double-blind end of week 12	-3.9 (SE: 0.33; 95% CI: -4.6, -3.3)	-5.3 (SE: 0.35; 95% CI: -6.0, -4.6)
n, OLE end of week 4	200	167

LS mean, OLE end of week 4	-6.3 (SE: 0.32; 95% CI: -7.0, -5.7)	-5.7 (SE: 0.35; 95% CI: -6.4, -5.0)
n, OLE end of week 36	30	22
LS mean, OLE end of week 36	-6.7 (SE: 0.60; 95% CI: -7.9, -5.5)	-7.0 (SE: 0.68; 95% CI -8.3, -5.6)

Abbreviations: CI = confidence interval; LS = least-squares; OLE = open-label extension; SE = standard error.

Notes:

- Least square means, SEs, and CIs were based on a mixed model repeated measures analysis with effects for treatment sequence, visit, treatment-by-visit interaction, baseline score, region, and randomisation stratification variables. The model was fit using an unstructured covariance structure. End of week 52 data was excluded from the model due to small cell size.

- Baseline was the last assessment prior to the start of double-blind treatment.

- Open-label safety population was defined as the group of subjects who received at least 1 dose of open-label study drug during the open-label treatment period. Subjects in the open-label safety population were analysed according to the sequence of treatments received in the double-blind treatment period and the open-label treatment period (i.e., placebo/difelikefalin and difelikefalin/difelikefalin), and all sequences pooled.

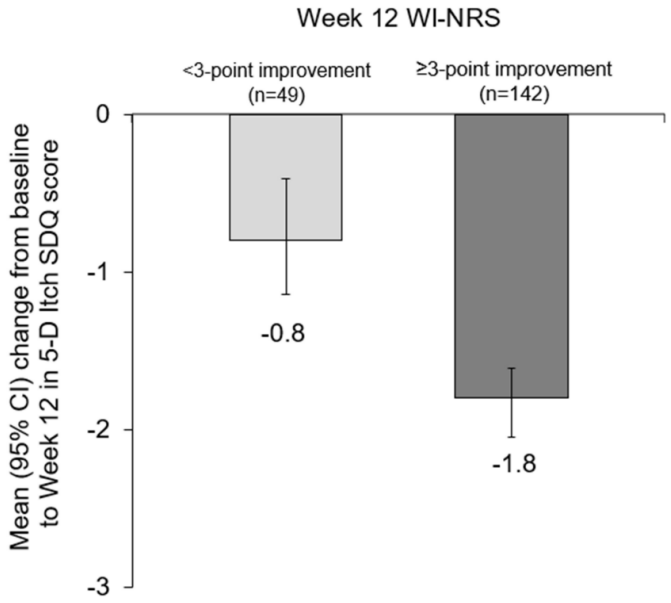
Source: KALM-2 OLE CSR, 2020; table 13 (68).

6.1.6 Efficacy – results per CLIN3105

6.1.6.1 Sleep improvement

An exploratory, post-hoc analysis of sleep quality was conducted for CLIN3105 to explore the impact in the reduction of pruritis severity on sleep quality based on the SDQ score (42). Figure 6 shows the mean change (95% CI) from baseline to week 12 for 5-D SDQ score by WI-NRS score improvement from baseline to week 12 (≥3 point vs <3-point). Patients with a ≥3 point improvement vs <3-point improvement in WI-NRS had a -1.8 (95% CI: -2.1, -1.6, P<0.001) change compared to a -0.8 (95% CI: -1.1, -0.4, P<0.001) change in 5-D SDQ score from baseline, following 12 weeks difelikefalin treatment. This equated to a relative percentage improvement in 5-D SDQ score from baseline to week 12 of -45.9% (-51.2, -40.5, P<0.001) for patients with ≥3-point WI-NRS improvement, and -13.1% (-32.5, 6.4, P=0.184), for patients with a <3-point WI-NRS improvement (52).

Figure 6: Mean change in 5-D Itch SDQ Score (CLIN3105)*



	<3-point improvement (n=49)	≥3-point improvement (n=142)
Mean (95% CI) relative change	–13.1% (–32.5, 6.4), p=0.184	–45.9% (–51.2, –40.5), p<0.001

Abbreviations: CI = confidence interval; WI-NRS = Worst Itching In-tensity Numerical Rating Scale; SDQ = sleep disability question.

* A paired t test was performed to compare the sleep score at baseline and Week 12 for each WI-NRS improvement catego-ry. All P values are exploratory and should be interpreted descriptively.

Source: Weiner et al., 2023, figure 3a (52).

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

There were no discrepancies in the definition of outcomes between studies.

7.1.2 Method of synthesis

The comparative analysis included in this submission is a pooled analysis of KALM-1 and KALM-2 evaluating difelikefalin's efficacy and the itch-related QoL overall and in sub-groups (51). Pooled data from the KALM-1 and KALM-2 studies was analysed to obtain a combined estimate of the treatment effects of difelikefalin in HD participants with mod-erate to severe pruritus, including QoL endpoints (51).

Efficacy analyses were conducted in the ITT population from the pooled KALM-1 and KALM-2 studies, which consisted of all randomised participants. Differences between pla-cebo and difelikefalin were analysed using a logistic regression model. For the analysis of the proportions of participants who achieved ≥3-point or ≥4-point reductions in the weekly mean WI-NRS scores, missing weekly WI-NRS scores were imputed by multiple

imputation under a missing-at-random assumption. Proportions of participants achieving a ≥5-point improvement in the 5-D Itch total score and a ≥15-point improvement in the Skindex-10 total score were analysed without imputation for missing values (51).

Continuous efficacy endpoints were analysed by a mixed model for repeated measures. An unstructured covariance structure was applied to model the within-participant errors. Missing values were not imputed (51).

The subgroup analyses of ≥3-point and ≥4-point reductions from baseline in the weekly mean WI-NRS scores were performed using the same methodology as that employed for the full ITT population (51).

Additional details are provided in Appendix C.

7.1.3 Results from the comparative analysis

Table 23 presents the results of the comparative analysis of difelikefalin vs. placebo for the ITT population. The odds of achieving a ≥3-point reduction in the weekly mean WI-NRS score at week 12 were almost twice as great with difelikefalin vs. placebo (OR = 1.93; 95% CI: 1.44-2.57). Achievement of a ≥4-point reduction in the weekly mean of daily WI-NRS scores was significantly greater with difelikefalin vs. placebo (LS mean estimate, 38.7% [95% CI: 32.8%-45.0%] vs. 23.4% [95% CI: 18.7%-28.8%], respectively; $P < 0.001$) (51).

The proportion of participants who achieved a complete response on the WI-NRS was significantly greater with difelikefalin vs. placebo at week 12 (12.0% vs. 6.7%, respectively; $P = 0.006$) (51).

Table 23 also shows that significantly greater proportions of participants in the difelikefalin group achieved clinically meaningful improvements in itch-related QoL vs. the placebo group, as measured by ≥15-point improvements in Skindex-10 total scores (55.5% vs. 40.5%, respectively, at week 12; $P < 0.001$) and ≥5-point improvements in 5-D Itch total scores (52.1% vs. 42.3%, respectively, at week 12; $P = 0.01$) (51).

Results from the subgroup analyses are presented in Appendix C.

Table 23: Results from the comparative analysis of difelikefalin vs. placebo for patients in haemodialysis with moderate-to-severe pruritus

Outcome measure	Difelikefalin (N=426)	Placebo (N=425)	Result
≥3-point reduction in WI-NRS scores, week 12	51.1%	35.2%	OR: 1.93 (95% CI: 1.44-2.57) P < 0.001
≥4-point reduction in WI-NRS scores, week 12	LS mean: 38.7% (95% CI: 32.8%-45.0%)	LS mean: 23.4% (95% CI: 18.7%-28.8%)	P < 0.001
≥15-point improvements in Skindex-10 total scores, week 12	55.5%	40.5%	P < 0.001
≥5-point improvements in 5-D Itch total scores, week 12	52.1%	42.3%	P = 0.01

Outcome measure	Difelikefalin (N=426)	Placebo (N=425)	Result
LS mean change from baseline to week 12 in Skindex-10 total scores	−16.9 (95% CI: −18.6 to −15.2)	−13.5 (95% CI: −15.1 to −11.8)	P = 0.001
LS mean change from baseline to week 12 in 5-D Itch total scores	−4.9 (95% CI: −5.4 to −4.5)	−3.7 (95% CI: −4.1 to −3.3)	P < 0.001

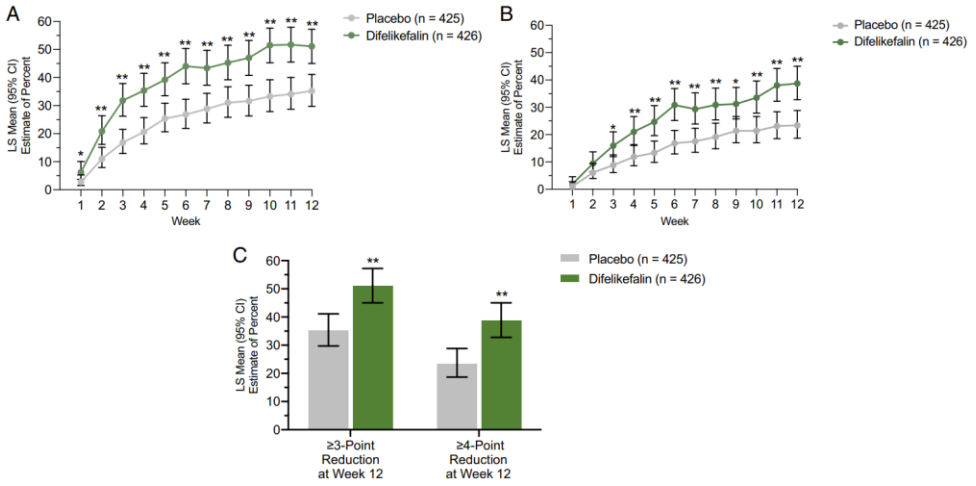
Abbreviations: CI = confidence interval; LS = least-squares; OR = odds ratio; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Source: Topf et al. 2022 (51).

7.1.4 Efficacy – results per WI-NRS outcome

Figure 7 present results for ≥3-point and ≥4-point reduction in WI-NRS scores. A significantly greater proportion of participants achieved a ≥3-point reduction in the weekly mean of daily WI-NRS scores with difelikefalin vs. placebo, observed as early as week 1 and sustained at all time points up to week 12 (Figure 7A and C). Achievement of a ≥4-point reduction in the weekly mean of daily WI-NRS scores was significantly greater with difelikefalin vs. placebo at all time points from week 3 to week 12 (Figure 7B and C) (51).

Figure 7: Proportions of participants with (A) A ≥3-point reduction in the weekly mean of the daily WI-NRS scores over 12 weeks, (B) A ≥4-point reduction in the weekly mean of the daily WI-NRS scores over 12 weeks, and (C) ≥3-point and ≥4-point reductions in week



Abbreviations: CI = confidence interval; LS = least-squares; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

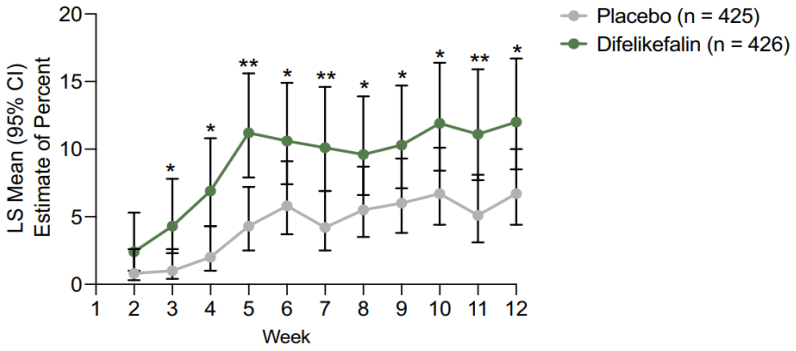
Notes: *P < 0.05 and **P < 0.001 difelikefalin vs. placebo. Differences between placebo and difelikefalin with respect to proportions were analysed using a logistic regression model with terms for the treatment group, baseline WI-NRS score, use of an anti-itch medication during the week before randomsation, presence of specific medical conditions, and geographic region. Missing weekly WI-NRS scores were imputed by multiple imputation under a missing-at-random assumption.

Source: Topf et al. 2022 (51).

The proportion of participants who achieved a complete response on the WI-NRS was significantly greater with difelikefalin vs. placebo with significant differences between

difelikefalin and placebo starting at week 3 and sustained at all time points up to week 12 (Figure 8) (51).

Figure 8: Achievement of complete response on the WI-NRS over 12 weeks



Abbreviations: CI = confidence interval; LS = least-squares; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

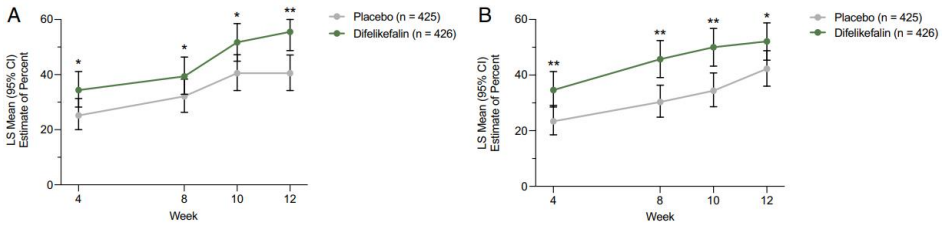
Notes: *$P < 0.05$ and **$P < 0.001$ difelikefalin vs. placebo. A complete response was defined as ≥80% of daily WI-NRS scores being equal to 0 or 1 for the preceding week. Differences between placebo and difelikefalin with respect to proportions were analysed using a logistic regression model containing terms for the treatment group, baseline WI-NRS score, use of an anti-itch medication during the week before randomisation, presence of specific medical conditions, and geographic region. Missing weekly WI-NRS scores were imputed by multiple imputation under a missing-at-random assumption.

Source: Topf et al. 2022 (51).

7.1.5 Efficacy – results per itch-related QoL outcome

Figure 9 shows that significantly greater proportions of participants in the difelikefalin group achieved clinically meaningful improvements in itch-related QoL vs. the placebo group (measured by ≥15-point improvements in Skindex-10 total scores and ≥5-point improvements in 5-D Itch total scores) over 12 weeks of treatment (51).

Figure 9: Achievement of clinically meaningful improvements in (A) Skindex-10 and (B) 5-D Itch total scores over 12 weeks



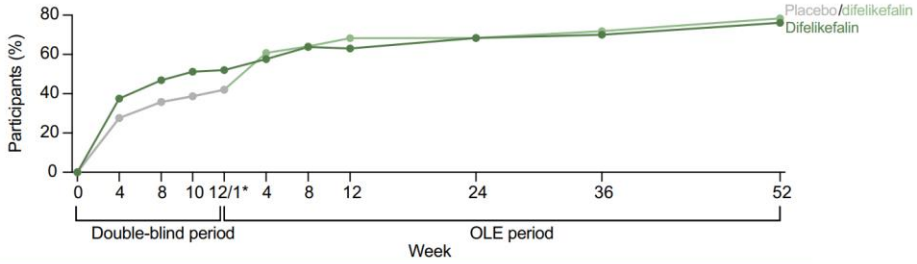
Abbreviations: CI = confidence interval; LS = least-squares.

Notes: *$P \leq 0.05$ and **$P \leq 0.001$ difelikefalin vs. placebo. Differences between placebo and difelikefalin with respect to proportions were analysed using a logistic regression model containing terms for the treatment group, baseline score, use of an anti-itch medication during the week before randomisation, presence of specific medical conditions, and geographic region. Missing values were not imputed. Clinically meaningful thresholds were determined as ≥15-point reductions in Skindex-10 and ≥5-point reductions in 5-D Itch total scores (unpublished data).

Source: Topf et al. 2022 (51).

In addition, the proportion of participants achieving a clinically meaningful 5-D Itch response (≥5-point improvement) was maintained with long-term difelikefalin treatment Figure 10.

Figure 10: Achievement of a ≥5-point improvement in 5-D Itch total score in the pooled KALM-1 and KALM-2 studies



Week	0	4	8	10	12/1*	4	8	12	24	36	52
Placebo/ difelikefalin, n/N	0/ 372	98/ 355	130/ 363	139/ 359	153/ 364	214/ 352	200/ 312	205/ 300	141/ 206	110/ 153	76/ 97
Placebo/ difelikefalin, %	0	27.6	35.8	38.7	42.0	60.8	64.1	68.3	68.4	71.9	78.4
Difelikefalin, n/N	0/ 340	122/ 325	152/ 324	166/ 324	172/ 331	179/ 311	176/ 276	167/ 265	132/ 193	98/ 140	70/ 92
Difelikefalin, %	0	37.5	46.9	51.2	52.0	57.6	63.8	63.0	68.4	70.0	76.1

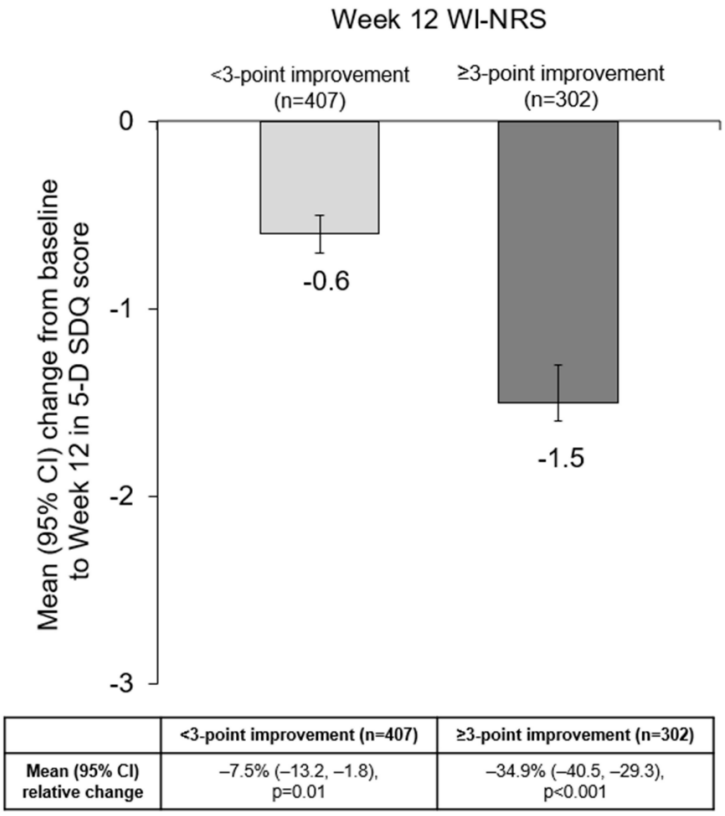
Abbreviations: OLE = open-label extension.

Notes: Data given as n and N indicate the number of participants who achieved a ≥5-point improvement in the 5-D Itch total score and the total number of participants assessed at each time point, respectively. Data as observed. *Week 12 of the double-blind period and week 1 of the open-label extension period, during which participants taking placebo during the double-blind period switched to active treatment with difelikefalin. In KALM-2, in addition to the participants who discontinued from the open-label extension period, 313 of 399 (78.4%) participants could not complete the 52-week open-label extension period because of the sponsor's decision to stop the study for reasons unrelated to safety or a lack of drug effects. A 2-week discontinuation following the end of the double-blind period of KALM-1 is not pictured in the figure.

Source: Topf et al. 2022 (51).

7.1.6 Sleep improvement

An exploratory, post-hoc analysis of sleep quality was conducted for KALM-1 and -2 to explore the impact in the reduction of pruritis severity on sleep quality based on the SDQ score (42). KALM-1 and -2 data were combined from patients receiving either difelikefalin or placebo for 12 weeks. A greater improvement in 5-D SDQ score was observed in patients with ≥3-point WI-NRS score improvement, compared to patients with <3-point WI-NRS improvement (mean [95% CI]: –1.5 [–1.6, –1.3], P<0.001 vs -0.6 [-0.7, -0.5], P<0.001 (Figure 11). This equated to a relative improvement of -34.9% (-40.5, -29.3, P<0.001) in patients with ≥3-point WI-NRS score improvement, and -7.5% (-13.2, -1.8, P=0.01) in patients with <3 point improvement. Similarly, patients with a ≥3-point improvement in WI-NRS score were more likely to have a >1 point improvement in 5-D SDQ score over time (Figure 12).



	<3-point improvement (n=407)	≥3-point improvement (n=302)
Mean (95% CI) relative change	–7.5% (–13.2, –1.8), p=0.01	–34.9% (–40.5, –29.3), p<0.001

Figure 11 Mean change in 5-D SDQ score (KALM-1 and KALM-2)*

Abbreviations: CI = confidence interval; WI-NRS = Worst Itching In-tensity Numerical Rating Scale; SDQ = sleep disability question.

* A paired t test was performed to compare the sleep score at baseline and Week 12 for each WI-NRS improvement category. All P values are exploratory and should be interpreted descriptively.

Source: Weiner et al., 2023, figure 5a (52).

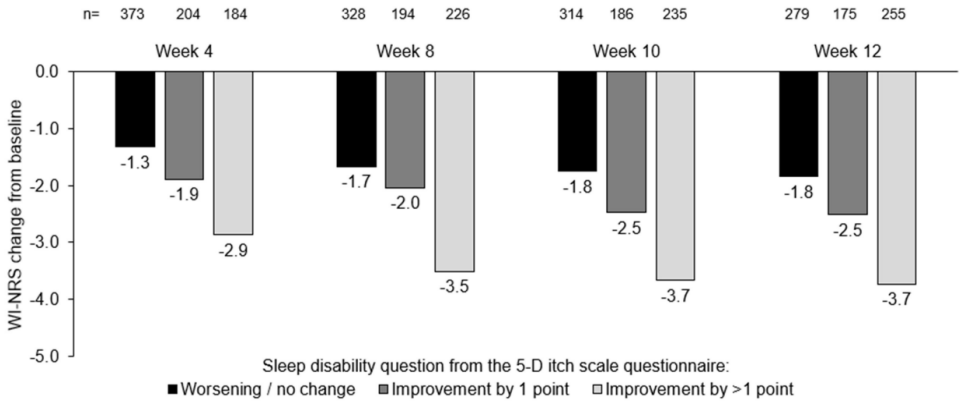


Figure 12: Change from baseline WI-NRS score by improvement in the 5-D SDQ score

Abbreviations: WI-NRS = Worst Itching In-tensity Numerical Rating Scale.

Source: Weiner et al., 2023, figure 5b (52).

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

For efficacy data related to pruritus severity in the model, a regression analyses of the confidential on-file individual patient data from three difelikefalin trials (KALM-1, KALM-2, and CLIN3105) is applied for the first 64 weeks of the model, whereas long-term extrapolation beyond the first 64 weeks is based on other sources from published literature. As the clinical trials included very few cases of death, other sources were used to model mortality for the full model time horizon.

8.1.1 Extrapolation of efficacy data

Not applicable. Beyond trial data, patients were assumed to remain in the same health state until death or transplantation.

8.1.2 Calculation of transition probabilities

8.1.2.1 Transition between pruritis severity health states for patients on haemodialysis

Difelikefalin treatment efficacy, i.e., the probability of transitioning between pruritus severity states, is based on difelikefalin trial data. For the first 64 weeks, difelikefalin transition probabilities are determined by the multinomial regression models developed using confidential on-file individual patient-level data from three difelikefalin trials (CLIN3105, KALM-1, and KALM-2. These regression models determine the transition probabilities based on the baseline patient characteristics: age, gender distribution, diabetes, haemodialysis duration, use of anti-itch medication, and pruritus severity. The resulting transition probabilities are applied to those patients who continue difelikefalin treatment. For patients who discontinue difelikefalin before week 64 or receive renal transplantation, the severity state is determined separately. Beyond the first 64 weeks, all patients are modelled to remain at the same severity as at week 64, until death or renal transplantation.

Data from the KALM-1, KALM-2, and CLIN3105 was used to inform patient characteristics, difelikefalin treatment discontinuation, use of anti-itch medication, and most importantly, the transitions between the pruritus severity states. Data included baseline patient characteristics (age, sex, diabetes, use of anti-itch medications at baseline, years of end-stage renal disease / haemodialysis / CKD-aP), and itching severity measures over time. The total number of patients in the pooled data was 1,070 (Table 24). However, since KALM-1 and KALM-2 patients were switched to difelikefalin in the open-label extensions (OLE) following these studies, these OLEs could be used to enrich the difelikefalin data by up to 424 additional patients with exposure to difelikefalin, bringing the total pooled data up to

1,494 patients. Because the CLIN3015 trial did not include a week 4 follow-up point, that trial data could not be used for regression analyses.

Table 24: Number of patients available from each analysed trial

Trial / arm	CLIN3105 PBO / DFK	KALM-1 PBO / DFK	KALM-2 PBO / DFK	KALM OLEs PBO / DFK	Total pooled PBO / DFK
Total	0 / 222	188 / 189	236 / 235	0 / 424	424 / 1070
Excluding none / mild 5-D itch scale at baseline	0 / 207	185 / 180	218 / 220	0 / 272	403 / 879
+ Week 4 included	0 / 0	164 / 160	207 / 196	0 / 210	371 / 578
+ Week 4 and 12 included	0 / 0	154 / 147	197 / 184	0 / 191	351 / 522
+ Week 12 and 48 included	0 / 0	0 / 115	0 / 23	0 / 67	0 / 205
+ Week 48 and 64 included	0 / 0	0 / 88	0 / 2	0 / 0	0 / 90

Abbreviations: DFK: Difelikefalin, OLE: Open-label extension, PBO: Placebo

In the difelikefalin trials, the baseline pruritus severity and trial eligibility were assessed with the Worst Itching Intensity Numeric Rating Scale (WI-NRS). Unfortunately, this instrument was not used beyond the first 12-weeks. In addition, the downside of WI-NRS is that it measures only the worst intensity of the itch.

Instead of WI-NRS, the more comprehensive, multidimensional measure–the 5-D itch scale (Elman et al. 2010)–was used in trial eligibility assessment to determine pruritus severity. In addition to intensity, the 5-D itch scale considers duration (how many hours a day), direction (whether getting better or worse), disability (which activities impacted), and distribution (which body parts affected) of the itch over the last two weeks.

The primary reason for using the 5-D itch scale was that it was measured up to 64 weeks in the KALM-1 and KALM-2 trials, and thus using the 5-D itch scale allowed better utilization of the available trial data. For the modelling, the 5-D itch scale values were categorized to none, mild, moderate, severe, and overwhelming using cut-off values developed by Lai et al., 2017 (69) . As the 5-D itch scale and WI-NRS do not overlap perfectly, there were a small number of patients who had none or mild pruritus at baseline, when measured with the 5-D itch scale. These patients not included in the dataset used for the regression analyses, bringing the total number of patients available for regression models to 1,030.

Four multinomial regression models were used to predict the transition probabilities for transferring between pruritus severity health states Table 25. All models were run with the largest possible dataset and most variables. Due to the small number of observations

in the worse pruritus severities, severities had to be combined for modelling. Thus, the predicted severities had to be manually separated back to the respective categories.

Table 25: Multinomial regression model specifications

	Baseline → Week 4	Week 4 → 12	Week 12 → 48	Week 48 → 64
Treatment arms	**DFK, PBO, and DFK from PBO OLE**	**DFK, PBO, and DFK from PBO OLE**	**DFK and DFK from PBO OLE**	**DFK**
N	937	873	205	90
Variables in the model				
Age (under 65 / 65 or older)	x	x	x	x
Sex (male / female)	x	x	x	x
Diabetes (Y/N)	x	x	x	x
Anti-itch meds (Y/N)	x	x	x	-
HD duration (less than 2 year / 2 years or more)	x	x	x	-
Starting pruritus severity	Moderate, severe, or overwhelming	None, mild, moderate, and severe or overwhelming	None, mild, moderate, and severe or overwhelming	None, mild, moderate, and severe or overwhelming
Ending pruritus severity	None, mild, moderate, and severe or overwhelming	None, mild, moderate, and severe or overwhelming	None, mild, moderate, and severe or overwhelming	None, mild, and moderate or more severe

DFK = difelikefalin, PBO = placebo.

Accuracy of the modelled predictions

Accuracy of the regression models' predictive capability was examined by comparing the modelled pruritus severity distribution to distribution at the last observed time point in the trial (12 weeks for placebo, 48 weeks for difelikefalin, including difelikefalin from placebo OLE), when the prediction model input variable data was set to equal those observed in the data.

As seen in Table 26, the developed multinomial regression models perform quite well as all predicted proportions are within 2 % of the proportions observed in the trial data. The regression models predict patients treated with difelikefalin to have a slightly poorer condition (fewer patients with severity 'none'), while they predict patients treated with placebo to have a slightly better condition (fewer patients with severity 'overwhelming').

Table 26: Model accuracy regression vs. observed data

Value	None	Mild	Moderate	Severe	Overwhelming
Predicted severity at week 12 in the placebo arm					
Observed in data	9.8 %	27.4 %	44.0 %	15.2 %	3.5 %
Regression models	9.8 %	27.8 %	43.7 %	13.9 %	4.8 %
Difference	0.0 %	-0.4 %	0.4 %	1.3 %	-1.3 %
Predicted severity at week 48 in the difelikefalin arm					
Observed in data	34.8 %	34.8 %	24.8 %	5.2 %	0.5 %
Regression models	36.3 %	35.2 %	23.2 %	4.8 %	0.5 %
Difference	-1.6 %	-0.4 %	1.6 %	0.4 %	0.0 %

The transition probabilities for each comparator arm are presented in Table 27 and Table 28, while the patient distributions are presented in Figure 13 and Figure 14. As stated earlier, beyond the trial data period (64 weeks for difelikefalin arm and 12 weeks for the SoC arm), all patients are modelled to remain at the same severity as at week 64, until death or renal transplantation. A scenario where all SoC patients remaining in their initial severity health state until death or transplantation (no SoC effect) was explored in scenario analysis.

Table 27: Transitions matrix for the difelikefalin arm

Difelikefalin transition matrix					
		To week 4			
From week 0	None	Mild	Moderate	Severe	Overwhelming
None	100.00 %	0.00 %	0.00 %	0.00 %	0.00 %
Mild	0.00 %	100.00 %	0.00 %	0.00 %	0.00 %
Moderate	16.20 %	30.98 %	49.14 %	3.67 %	0.00 %
Severe	5.80 %	17.93 %	52.41 %	17.89 %	5.96 %
Overwhelming	5.80 %	17.93 %	52.41 %	17.89 %	5.96 %
		To week 12			
From week 4	None	Mild	Moderate	Severe	Overwhelming
None	50.84 %	38.09 %	10.18 %	0.89 %	0.00 %
Mild	26.07 %	48.82 %	23.18 %	1.28 %	0.64 %
Moderate	8.17 %	30.72 %	55.20 %	5.32 %	0.59 %
Severe	3.31 %	7.23 %	52.10 %	21.80 %	15.57 %

Overwhelm-ing	3.31 %	7.23 %	52.10 %	21.80 %	15.57 %
			To week 48		
From week 12	None	Mild	Moderate	Severe	Overwhelm-ing
None	80.93 %	16.62 %	2.44 %	0.00 %	0.00 %
Mild	44.09 %	45.04 %	8.37 %	2.50 %	0.00 %
Moderate	21.71 %	50.78 %	21.64 %	5.87 %	0.00 %
Severe	7.02 %	22.16 %	45.18 %	19.23 %	6.41 %
Overwhelm-ing	7.02 %	22.16 %	45.18 %	19.23 %	6.41 %
			To week 64		
From week 48	None	Mild	Moderate	Severe	Overwhelm-ing
None	80.91 %	12.13 %	6.97 %	0.00 %	0.00 %
Mild	36.93 %	49.84 %	10.58 %	2.65 %	0.00 %
Moderate	11.85 %	52.31 %	31.36 %	4.48 %	0.00 %
Severe	0.00 %	0.00 %	33.33 %	66.67 %	0.00 %
Overwhelm-ing	0.00 %	0.00 %	33.33 %	66.67 %	0.00 %
			Onwards		
From week 64	None	Mild	Moderate	Severe	Overwhelm-ing
None	100.00%	0.00%	0.00%	0.00%	0.00%
Mild	0.00%	100.00%	0.00%	0.00%	0.00%
Moderate	0.00%	0.00%	100.00%	0.00%	0.00%
Severe	0.00%	0.00%	0.00%	100.00%	0.00%
Overwhelm-ing	0.00%	0.00%	0.00%	0.00%	100.00%

Table 28: Transitions matrix for the Standard of Care arm

Comparator transition matrix					
			To week 4		
From week 0	None	Mild	Moderate	Severe	Overwhelm-ing
None	100.00%	0.00%	0.00%	0.00%	0.00%
Mild	0.00%	100.00%	0.00%	0.00%	0.00%
Moderate	6.60%	21.99%	63.14%	6.30%	1.97%
Severe	1.74%	9.35%	49.45%	29.14%	10.32%
Overwhelm-ing	1.74%	9.35%	49.45%	29.14%	10.32%
			To week 12		
From week 4	None	Mild	Moderate	Severe	Overwhelm-ing
None	45.48%	41.49%	11.24%	1.79%	0.00%
Mild	22.01%	50.18%	24.15%	3.67%	0.00%
Moderate	6.44%	29.45%	53.64%	8.63%	1.85%
Severe	2.06%	5.48%	40.04%	36.20%	16.23%
Overwhelm-ing	2.06%	5.48%	40.04%	36.20%	16.23%
			Onwards		

From week 12	None	Mild	Moderate	Severe	Overwhelm-ing
None	100.00%	0.00%	0.00%	0.00%	0.00%
Mild	0.00%	100.00%	0.00%	0.00%	0.00%
Moderate	0.00%	0.00%	100.00%	0.00%	0.00%
Severe	0.00%	0.00%	0.00%	100.00%	0.00%
Overwhelm-ing	0.00%	0.00%	0.00%	0.00%	100.00%

Figure 13: Pruritus severity over the first 64 weeks at regression data points

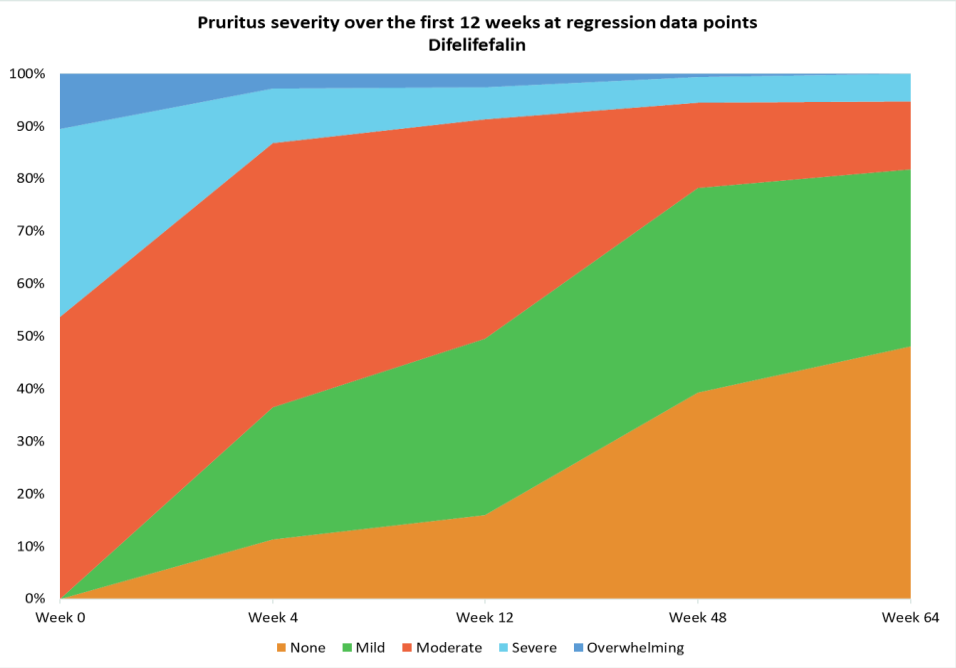
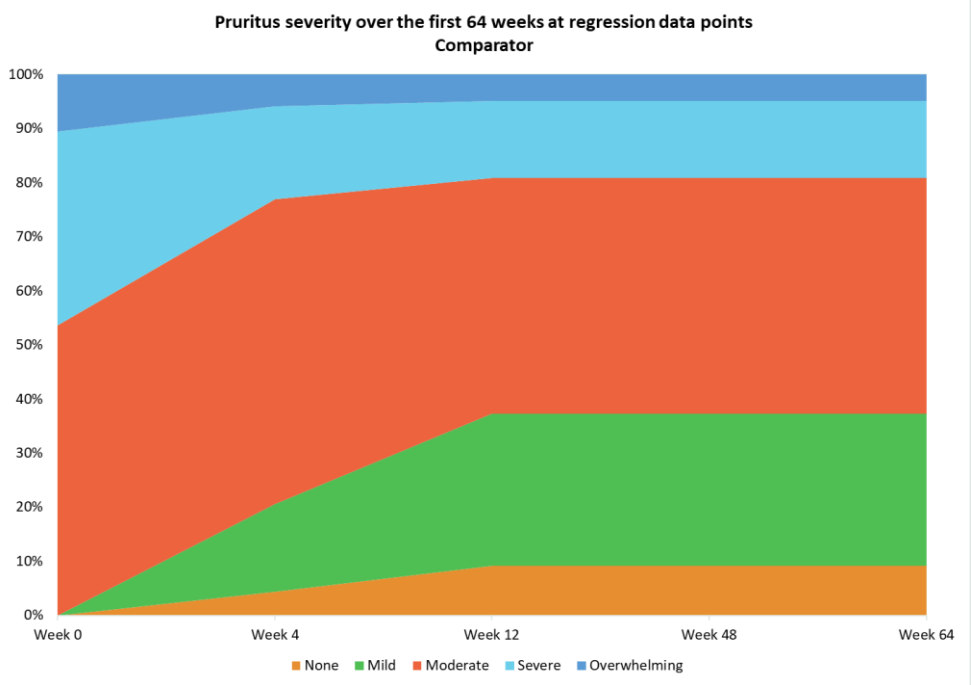


Figure 14: Pruritus severity over the first 64 weeks at regression data points



The economic model baseline characteristics are used as variables in the model. The trial-based baseline characteristics are used for the base case, while the impact of applying the characteristics of the prevalent haemodialysis population from the DNSL 2022 report is explored in scenario analysis.

The pruritus health state of patients discontinuing difelikefalin is presented in Table 29. This was based on the clinical trials with the last observation obtained.

Table 29: Pruritus severity of patients discontinuing difelikefalin treatment

Severity	Distribution for patients discontinuing at weeks 0 to 12	Distribution for patients discontinuing at weeks 12 to 64
None	6.9 %	30.5 %
Mild	7.7 %	28.1 %
Moderate	49.7 %	33.5 %
Severe	29.7 %	5.7 %
Overwhelming	6.1 %	2.1 %

Note: Pruritus severity after difelikefalin discontinuation is based on the last observed severity obtained from the trials.

The remaining transitions are based on efficacy data from other publications; thus, these transitions are presented in section 8.2.

8.2 Presentation of efficacy data from additional documentation

8.2.1.1 Transition between pruritis severity health states for transplanted patients

As some patients may still experience pruritus following renal transplantation, the study by Krajewski et al., 2021 (8) was used to model the pruritus of transplanted patients. This study was used, as no Danish studies were identified reporting pruritus for renal transplanted patients. The study found that in 56 of 76 patients (73.7%) their itch disappeared completely following transplantation. The majority of patients with persistent itch reported moderate itch (85.7%), two of them mild (9.5%), and only one person was suffering from severe itch (4.8%). As a result, in the model the transplanted patients were distributed as presented in Table 30, which were applied in the transition trace.

To understand the relevance of the Krajewski et al., 2021 (8) results in a Danish context, the proportions were presented for two Danish clinical experts, which both acknowledged that these numbers could be representative for the Danish populations. A scenario where all transplanted patients are transitioning to the no pruritus health state was explored.

Table 30: Pruritus severity distribution for transplanted patients

Severity	Calculation:	Proportion
None	56/76	73.7 %
Mild	(20/76)*0.095	2.5 %
Moderate	(20/76*0.857	22.6 %
Severe	(20/76)*0.048	1.3 %
Overwhelming	(20/76)*0.000	0.0 %

8.2.1.2 Transplantation rates

The Danish Nephrological Institute's national report (DNSL report) from 2022 (5) was used to model identify the transplantation rate for haemodialysis patients in Denmark. DNSL has existed since 1990 as a Danish nationwide database for recording the treatment of patients with chronic kidney failure who receive renal replacement therapy. In table D of the report, the first-time renal transplanted patient group is presented. The table included data from 2020 to 2022. A total of 640 (237 in 2020, 208 in 2021, and 195 in 2022) patients were reported to receive a renal transplant between 2020 and 2022, while 71.7%, 75.5% and 73.80% of these patients were treated with dialysis before the transplantation in 2020, 2021 and 2022, respectively. As it was not reported which type of dialysis the patients received before transplantation, both haemodialysis and peritoneal dialysis were included. In table C, it is reported that 2,673 prevalent patients were receiving any type of dialysis in 2020, while 2,680 and 2,655 prevalent patients received dialysis in 2021 and 2022, respectively. Based on the numbers, the annual transplantation rates were calculated for 2020, 2021 and 2022, and an weighted average was calculated, which was used in the model. The numbers and calculated rates are presented in Table 31.

Table 31: Base rates for receiving renal transplantation

	N	Annual rate	Rate per cycle
# dialysis patients 2020	2673		
# Transplanted 2020	237		
# dialysis patients transplanted 2020	170	0.0636	
# dialysis patients 2021	2680		
# Transplanted 2021	208		
# dialysis patients transplanted 2021	157	0.0586	
# dialysis patients 2022	2655		
# Transplanted 2022	195		
# dialysis patients transplanted 2022	144	0.0542	
Weighted rate		0.0591	**0.0011**

The weighted rate was adjusted according to age to account for the difference between the average age of transplantation, ~51 years of age, and the modelled baseline age of ~58 years of age. Age-specific transplantations rates were also calculated from the DNSL report. Similar to the calculations above, the number of dialysis patients and transplantations were identified. As the proportion of patients receiving a renal transplantation after dialysis treatment was not report per age group, the average proportion was used (73.59%) to calculate the estimated number of patients in each age group receiving a transplant following dialysis.

The data was fitted to a least-square function to estimate the ongoing probability of receiving a transplantation. Because the probability of receiving a transplant is much higher for patients younger than 20, the extrapolation function was fitted only to patients aged 20 years or older, and an unadjusted rate was fitted to these patients. As no patients above the age of 80 years were observed receiving a transplantation, an unadjusted rate was also fitted for these patients. The function was used to estimate the age-specific transplantation rate for patients aged 20 to 80 years. For patients younger than 20 and patients older than 80, the unadjusted rates of 0.561 and 0.000 were used, respectively. The data and the function used are presented in Table 32. The flat unadjusted transplantation rate of 0.0011 per cycle is explored in scenario analysis.

Table 32: Age dependent transplantation data and fitted function

Age group	Average age	N	n	n (adjusted)*	Rate per patient-year
17 or lower	15	21	16	12	0.5607**
18-29	23.5	164	52	38	0.2333
30-39	34.5	325	67	49	0.1517
40-49	44.5	760	111	82	0.1075
50-59	54.5	1432	178	131	0.0915
60-69	64.5	1809	163	120	0.0663

70-79	74.5	2526	53	39	0.0154
80 or older	84.5	971	0	0	0.0000**

Function: *0.00004 * age^2 + -0.00751 * age + 0.37938*

*Estimated incident transplantation patient that received dialysis before transplantation.

**For patients 17 or younger, and patient 80 or older, the unadjusted rate was applied. Data from these patients were not included in the fitted least square model.

8.2.1.3 Mortality on haemodialysis

Mortality was also estimated based on the DNSL 2022 report. There were 2,139, 2,142, and 2,119 prevalent patients on haemodialysis in 2020, 2021 and 2022, respectively. 420, 479, and 430 patients are reported dead while on haemodialysis in 2020, 2021 and 2022, respectively. Using these figures, the average annual mortality rate was 0.2083 (0.0040 per weekly model cycle) among the patients receiving haemodialysis. This is the unadjusted base mortality rate for haemodialysis patients in the base case analysis. In this base rate population 24.1% were diabetics and with an estimated average age of 63.9 years.

Table 33: Mortality rates

	N	Annual mortality rate
Total patients 2022	2119	
Died during year	430	0.203
Total patients 2021	2142	
Died during year	479	0.224
Total patients 2020	2139	
Died during year	420	0.196
Weighted rate		**20.83%**

As the baseline age of the trial was lower than what is found in Danish literature, the mortality was adjusted for age. The data from Boenink et al. 2020 (6) was used to identify age-dependent mortality in the Danish population of renal replacement therapy. The data was fitted to an exponential function in order estimate age-dependent mortality. The data and the function are presented in Table 34.

Table 34: Age dependent mortality for patients on any renal replacement therapy - Boenink et al. 2020 (6)

Age group	Average age	1 year mortality	95% CI
20-44	35	0.021	0.021-0.022
45-64	55	0.070	0.069-0.071
65-74	70	0.159	0.157-0.160
75 or older	80	0.288	0.286-0.290

Function*: 0.00281*e$^{0.05791 * age}$*

The mortality was also adjusted for diabetes. The study by Sørensen et al., 2007 (7) estimated the difference in survival of Danish end-stage renal disease patients with and

without diabetes. Using a multivariate Cox regression survival rate analysis on data from 8,421 Danish patients with ESRD from 1990 to 2005, the study reported a HR between diabetic and non-diabetic patients of 1.55 (95% CI 1.45-1.66). The HR was applied in the model and adjusted for proportion of patients with diabetes. In trial baseline characteristics 50.5% of patients had diabetes, while a weighted average was calculated as 24.1% based on numbers from DNSL 2022, however, the DNSL report only reported when diabetes was the reason for the dialysis. This was presented for the two clinical experts, which both expected the 24.1% to be an underestimation of diabetes in Danish patients. Therefore, the impact of higher diabetes proportions was explored in scenario analysis. The adjusted HR applied to the trace was $\underline{1.123}$ = $1.550^{(0.505-0.241)}$

8.2.1.4 Mortality transplanted patients

The base rate mortality was identified using the DSNL 2022 report, which reported 5-year survival for first time renal transplanted patients. 202 out of 219 patients were alive following 5 years, which was converted to a per cycle mortality rate of 0.056%. The average age of the patients being transplanted was 51.5 based on the numbers reported in DNSL 2022, which younger compared to the age of baseline characterises of the trial (63.9 years). To adjust for age-dependent differences in mortality, the data presented in Table 34 from Boenink et al. 2020 (6) was applied again.

The study by Sørensen et al., 2007 (7) was used to adjust for differences in mortality based on diabetes as HR=1.88, (95% CI 1.50–2.36) for transplantation patients. Based on numbers from the DNSL 2022 on proportion of transplanted patients that had diabetic kidney disease, a weighted average was calculated as 16.4% of transplanted patients had diabetes. However, this is still expected to be an underestimation, as the numbers only represented the reason for their renal disease. Therefore, the impact of higher diabetes proportions was explored in scenario analysis.

8.3 Modelling effects of subsequent treatments

Due to uncertainty other effects of treatments and SoC outside of what is covered in clinical trials and the limited treatment options with CKD-aP, effect of any subsequent treatments was not modelled.

8.4 Other assumptions regarding efficacy in the model

- After week 64, patients are assumed to stay in the same pruritus health state until death or transplant. However, in the model, patients are allowed to continue on difelikefalin after the 64 weeks trial data cut-off. This assumed as the SMPC does not specify that treatment should be discontinued after 64 weeks. This assumption is explored in scenario analysis, stopping difelikefalin treatment at week 64.
- When questioning Danish Clinical experts on whether they expected difference in mortality between the different pruritus severity groups, both agreed that patients with more severe pruritus were likely to have higher mortality. However, the clinical experts stated that the higher mortality was not due to the pruritus itself. Rather, they expected these patients to have more comorbidities and as

result of this also more severe pruritus. As a result, no difference in mortality between pruritus severity health states was assumed in the model. Differentiation in mortality based on pruritus severity was explored in scenario analysis.

8.5 Overview of modelled average treatment length and time in model health state

As no extrapolation of trial data to estimate key parameters as OS and PFS was used in model, Table 35 was not found applicable. Table 36 present the time on treatment for difelikefalin and also the time in each health state for both difelikefalin and SoC.

Table 35: Estimates in the model

	Modelled average	Modelled median	Observed median from relevant study
Difelikefalin	Not applicable	Not applicable	Not applicable
SoC	Not applicable	Not applicable	Not applicable

Abbreviations: SoC = Standard of Care

Table 36: Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Health state	Difelikefalin (years)	SoC (years)
Duration of treatment	2.97	Not applicable
HD None	1.40	0.37
HD Mild	1.37	1.06
HD Moderate	0.86	1.72
HD Severe	0.24	0.56
HD Overwhelming	0.03	0.19
Transplanted None	1.05	1.05
Transplanted Mild	0.04	0.04
Transplanted Moderate	0.32	0.32
Transplanted Severe	0.02	0.02
Transplanted Overwhelming	0.00	0.00

Abbreviations: HD = Haemodialysis; SoC = Standard of Care

9. Safety

9.1 Safety data from the clinical documentation

The double-blind safety population consists of randomised subjects who received at least 1 dose of double-blind study drug during the double-blind treatment period. Subjects in the double-blind safety population were analysed according to the actual treatment received. This population was used to analyse all safety endpoints collected during the double-blind phase. However, the number and proportion of patients who discontinue

treatment regardless of reason is based on the enrolled population. The results are presented in the following tables: Table 37, Table 38, Table 39, and Table 40.

The median duration of treatment during the double-blind treatment period of KALM-1 was 85.0 days (range 5 to 93 days) in the difelikefalin group and 85.0 days (range 3 to 94 days) in the placebo group. In KALM-2, the median duration of treatment during the double-blind treatment period was 85.0 days (range 3 to 90 days) in the difelikefalin group and 85.0 days (range 7 to 91 days) in the placebo group, and 19.14 weeks (range 0.4 to 53.0 weeks) in the open-label phase. In CR845-CLIN3105, the median duration of treatment was 85.0 days (range 3 to 92 days).

In KALM-1, KALM-2 and CR845-CLIN3105, adverse events were reported as treatment-emergent adverse events (TEAEs). In KALM-1 (double-blind phase), TEAEs relative to the double-blind treatment period were identified as any adverse event with an onset date after the first dose of the study drug up to the start of the discontinuation period for subjects who entered the discontinuation period or 6 days after the last dose for early termination subjects (67). KALM-2 (double-blind phase), TEAEs relative to the double-blind treatment period were identified as any adverse event with an onset date after the first dose of the study drug up to the start of the open-label period for subjects who entered the open-label period, or any adverse event with onset date 6 days after the last dose for early termination subjects (55). In CR845-CLIN3105, a TEAE was defined as an event that started any time after the first dose of study drug up until the follow-up visit or early termination (or 7 days after the last dose if no early termination visit was conducted), whichever was later (70).

Table 37 provides an overview of safety events in KALM-1 and KALM-2 (double-blind phase). Generally, the safety events where similar both within treatment groups in KALM-1 and KALM-2, respectively. However, both within KALM-1 and KALM-2 more participants in the difelikefalin arm discontinued treatment (regardless of reason and due to adverse events) than the placebo arm.

Table 37: Overview of safety events KALM-1 and KALM-2. Double-blind treatment period, double-blind safety population.**

	KALM-1 Difelikefalin (N=189)	KALM-1 Placebo (N=188)	KALM-2 Difelikefalin (N=235)	KALM-2 Placebo (N=236)
Number of adverse events¥, n	416	362	600	523
Number and proportion of patients with ≥1 adverse events¥, n (%)	130 (68.8)	117 (62.2)	160 (68.1)	145 (61.4)
Number of serious adverse events*¥, n	90	90	114	88
Number and proportion of patients with ≥ 1 serious	49 (25.9)	41 (21.8)	58 (24.7)	51 (21.6)

	KALM-1 Difelikefalin (N=189)	KALM-1 Placebo (N=188)	KALM-2 Difelikefalin (N=235)	KALM-2 Placebo (N=236)
adverse events*¥, n (%)				
Number of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 events, n	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	N/A	N/A	N/A	N/A
Number of adverse reactions£, n	21	12	52	35
Number and proportion of patients with ≥ 1 adverse reactions£, n (%)	13 (6.9)	10 (5.3)	22 (9.4)	16 (6.8)
Number and proportion of patients who had a dose reduction, n (%)	N/A	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	27 (14.3)	18 (9.6)	29 (12.3)	13 (5.5)
Number and proportion of patients who discontinue treatment due to adverse events¥, n (%)	15 (7.9)	9 (4.8)	13 (5.5)	8 (3.4)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; N/A = not applicable; TEAE = treatment-emergent adverse event.

¥ An adverse event was termed a TEAE.

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

** The double-blind safety population consists of randomised subjects who received at least 1 dose of double-blind study drug during the double-blind treatment period. Subjects in the double-blind safety population were analysed according to the actual treatment received. This population was used to analyse all safety endpoints collected during the double-blind phase. However, the *number and proportion of patients who discontinue treatment regradless of reason* is based on the enrolled population (subjects who signed informed consent).

§ CTCAE v. 5.0 must be used if available.

£ An adverse reaction was termed a treatment-related TEAE.

Source: KALM-1 double-blind CSR, 2020; table 5 and 21 (67); KALM-2 double-blind CSR, 2020; table 5 and 25 (55).

In KALM-2 (OLE phase), a TEAE was defined as an adverse event with a start date on/after the date of the first dose of study treatment in the open-label treatment period up to study follow-up visit or early termination visit (or 7 days after the last dose if no follow-up or early termination visit was conducted) (68).

Table 38 an overview of safety events in KALM-2 (OLE phase) as well as CR845-CLIN3105 is provided. Within KALM-2, there was a higher number and proportion of patients with ≥ 1 adverse reaction in the placebo/difelikefalin group than in the difelikefalin/difelikefalin group (7 (3.3%) vs. 1 (0.5%), respectively).

Table 38: Overview of safety events KALM-2, open-label extension phase, open-label safety population, and safety events of CR845-CLIN3105.**

	KALM-2 Difelikefalin/ difelikefalin (N=189)	KALM-2 Placebo/ difelikefalin (N=210)	CR845-CLIN3105 Difelikefalin (N=222)
Number of adverse events¥, n	550	705	414
Number and proportion of patients with ≥1 adverse events¥, n (%)	117 (61.9)	139 (66.2)	143 (64.4)
Number of serious adverse events*¥, n	140	187	91
Number and proportion of patients with ≥ 1 serious adverse events*¥, n (%)	61 (32.3)	69 (32.9)	45 (20.3)
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	N/A	N/A	N/A
Number of adverse reactions£, n	1	9	18
Number and proportion of patients with ≥ 1 adverse reactions£, n (%)	1 (0.5)	7 (3.3)	16 (7.2)
Number and proportion of patients who had a dose reduction, n (%)	N/A	N/A	N/A

	KALM-2 Difelikefalin/ difelikefalin (N=189)	KALM-2 Placebo/ difelikefalin (N=210)	CR845-CLIN3105 Difelikefalin (N=222)
Number and proportion of patients who discontinue treatment regardless of reason€, n (%)	187 (98.9)	207 (98.6)	25 (11.3)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	9 (4.8)	12 (5.7)	13 (5.9)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; N/A = not applicable; TEAE = treatment-emergent adverse event.

¥ An adverse event was termed a TEAE.

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

** Unless noted otherwise, the open-label safety population was used for all analyses in the OLE phase. This was defined as the group of subjects who received at least 1 dose of open-label study drug during the open-label treatment period. Subjects in the open-label safety population were analysed according to the sequence of treatments received in the double-blind treatment period and the open-label treatment period (i.e., placebo/difelikefalin and difelikefalin/difelikefalin).

§ CTCAE v. 5.0 must be used if available.

£ An adverse reaction was termed a treatment-related TEAE.

€ Of the 187 patients in the difelikefalin/difelikefalin group 146 discontinued due to sponsor stopping study early. Of tge 207 patients in the placebo/difelikefalin group 167 discontinued due to sponsor stopping study early.

Source: KALM-2 OLE CSR, 2020; table 4 and 17 (68); CR845-CLIN3105 CSR, 2020; table 4 and 19 (70).

In Table 39 the frequency of all serious adverse events with frequency of ≥ 5% recorded in KALM-1 and KALM-2 (double-blind phase) is listed.

Table 39: Serious adverse events* (KALM-1 and KALM-2 double-blind treatment period; double-blind safety population)**

Adverse events, n (%)	KALM-1 Difelikefalin (N=189)	KALM-1 Placebo (N=188)	KALM-2 Difelikefalin (N=235)	KALM-2 Placebo (N=236)
	Number (%) of patients with adverse events	**Number (%) of patients with adverse events**	**Number (%) of patients with adverse events**	**Number (%) of patients with adverse events**
Cardiac disorders	9 (4.8)	4 (2.1)	12 (5.1)	5 (2.1)
Infections and infestations	15 (7.9)	15 (8.0)	21 (8.9)	14 (5.9)
Metabolism and nutrition disorders	6 (3.2)	12 (6.4)	5 (2.1)	5 (2.1)
Respiratory, thoracic and mediastinal disorders	10 (5.3)	7 (3.7)	10 (4.3)	5 (2.1)
Vascular disorders	5 (2.6)	3 (1.6)	6 (2.6)	13 (5.5)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

** The double-blind safety population consists of randomised subjects who received at least 1 dose of double-blind study drug during the double-blind treatment period. These subjects were analysed according to the actual treatment received. This population was used to analyde all safety endpoints collected during the double-blind phase.

Source: KALM-1 DB CSR, 2020; table 26 (67); KALM-2 DB CSR, 2020; table 30 (55).

In Table 40, the frequency of all serious adverse events with frequency of ≥ 5% recorded in KALM-2 (OLE phase) is listed.

Table 40: Serious adverse events* (KALM-2 open-label extension phase; open-label safety population)**

Adverse events, n (%)	Difelikefalin/ difelikefalin (N=189), KALM-2	Placebo/ difelikefalin (N=210), KALM-2
	Number (%) of patients with adverse events	**Number (%) of patients with adverse events**
Gastrointestinal disorders	8 (4.2)	14 (6.7)
Infections and infestations	23 (12.2)	31 (14.8)
Injury, poisoning and procedural complications	8 (4.2)	13 (6.2)
Metabolism and nutrition disorders	10 (5.3)	7 (3.3)
Respiratory, thoracic and mediastinal disorders	12 (6.3)	10 (4.8)
Vascular disorders	9 (4.8)	12 (5.7)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

** Unless noted otherwise, the open-label safety population was used for all analyses in the OLE phase. This was defined as the group of subjects who received at least 1 dose of open-label study drug during the open-label treatment period. Subjects in the open-label safety population were analysed according to the sequence of treatments received in the double-blind treatment period and the open-label treatment period (i.e., placebo/difelikefalin and difelikefalin/difelikefalin).

Source: KALM-2 OLE CSR, 2020; table 24 (68).

As seen in above, the frequency of adverse events aligned between the difelikefalin arm and SoC arm. As a result, no adverse event costs were included for the sack of model parsimony was not included.

9.2 Safety data from external literature applied in the health economic model

N/A

10. Documentation of health-related quality of life (HRQoL)

Table 41: Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
5-D itch scale	KALM-1 and KALM-2 (51)	Disease-specific clinical effectiveness
Skindex-10	KALM-1 and KALM-2 (51)	Disease-specific clinical effectiveness
EQ-5D-3L	Hernandez et al., 2023 (9)	Conversion from 5D-itch scale to generic quality of life
EQ-5D-3L	Eriksson et al., 2017 (10)	Utilities used to create ratio between dialysis and transplanted patient, which can estimate utilities for transplanted patients for this submission

Abbreviations: 5-D = five dimentions; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version

The 5D-itch scale and Skindex-10 are both disease-specific clinical effectiveness HRQoL measurements. These are both defined in section 3.7 and the trial outcomes of the measures are presented in section 6 and 7, and thus these will not be presented here. Hernandez et al., 2023 (9) and Eriksson et al., 2017 (10) is presented in section 10.3

10.1 Presentation of the health-related quality of life

Not applicable. Health-related quality of life is presented in section 10.3. Mapping is presented in 10.2.1.1.

10.1.1 Study design and measuring instrument

10.1.2 Data collection

10.1.3 HRQoL results

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

10.2.1.1 Mapping

The model from Hernandez et al., 2023 (9) was used to map the trial data to generic EQ-5D-3L data. For the haemodialysis pruritus severity health states from none to severe the observed values EQ-5D values for each 5-D ich value were used to generate average health

states utilities values. For the overwhelming health states, due to too few observations, the utility value for that group could not be obtained directly. Thus, a linear extrapolation function was fitted to available results, and the EQ-5D values were estimated beyond the 20 points on the 5-D itch scale. The values are presented in Table 42. The function for the prediction is presented in Figure 15.

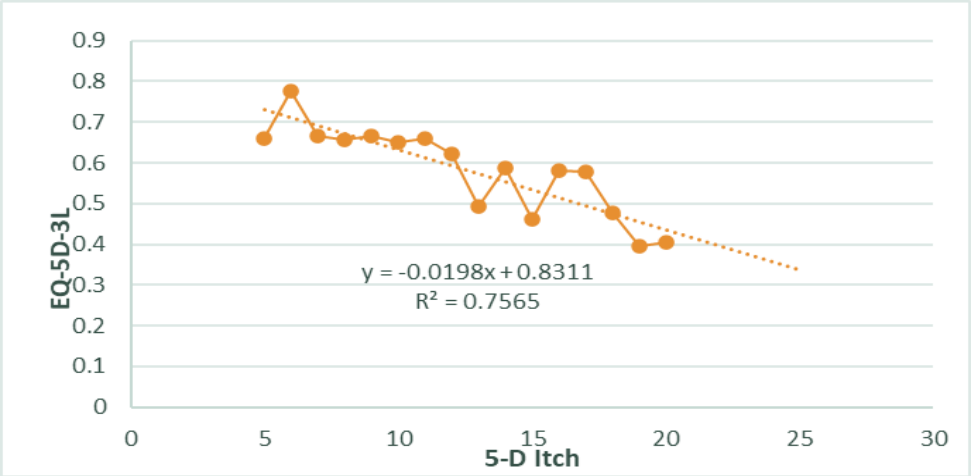
As stated earlier, the original EQ-5D-5L data from Hernandez et al., 2023 (9) is not available to the applicant, thus, it was not possible to apply Danish preference weights. The utilities were age-adjusted in the model in accordance with section 7.3 of the methods guide.

Table 42: EQ-5D values based on Hernandez et al., 2023 (9)

Categorized severity	Observed		Average by severity (used in model)
	5-D itch	EQ-5D-3L	
None	5	0.6608	0.6899
	6	0.7771	
	7	0.6654	
	8	0.6562	
Mild	9	0.6671	0.6594
	10	0.6501	
	11	0.661	
Moderate	12	0.6231	0.5536
	13	0.4917	
	14	0.5862	
	15	0.4605	
	16	0.5826	
	17	0.5772	
Severe	18	0.4761	0.4260
	19	0.3965	
	20	0.4055	
Severity	**Predicted**		**Average by severity (used in model)**
	5-D Itch	**EQ-5D**	
Overwhelming	21	0.4152	0.3756
	22	0.3954	
	23	0.3756	
	24	0.3558	
	25	0.3360	

Abbreviations: 5-D = five dimentions; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version

Figure 15: Equation for predicted EQ-5D utility weight for patients with overwhelming pruritus



Abbreviations: 5-D = five dimentions; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version

Patients who have received a renal transplant have substantially higher utility values after the transplant than they had during dialysis. Based on Eriksson et al. 2017 (10), the ratio between the utility values before and after the transplantation is approximately 1.164 using the Danish value sets (Table 43). By applying this average ratio to the utilities established for haemodialysis patients, we can obtain the estimated pruritus severity-specific utility values for renal transplant recipients. The other value sets and an average of the three are tested in scenario analyses.

Table 43: Differences in utility values before and after renal transplant observed in literature

Country	Instrument	Dialysis	Trans-plant	Ratio	Source
Nordic	EQ-5D (SE)	0.81	0.89	1.099	Eriksson et al. 2017 (10)
Nordic	EQ-5D (DK)	0.73	0.85	1.164	Eriksson et al. 2017 (10)
Nordic	EQ-5D (UK)	0.68	0.82	1.206	Eriksson et al. 2017 (10)
Average		0.74	0.853	1.156	

Abbreviations DK = Denmark; SE = Sweden; UK = United Kingdom

10.2.2 Disutility calculation

No disutilities are applied in the model.

10.2.3 HSUV results

The base case HSUV are presented in Table 44.

Table 44: Overview of health state utility values

	Results [95% CI]	Instrument	Tariff used	Comments
Haemodialysis None	0.6899 [0.5490 - 0.8148]	EQ-5D-3L	UK	Estimated based on the observed values from Hernandez et al., 2023 (9)
Haemodialysis Mild	0.6594 [0.5262 - 0.7809]	EQ-5D-3L	UK	

	Results [95% CI]	Instrument	Tariff used	Comments
Haemodialysis Moderate	0.5536 [0.4448 - 0.6598]	EQ-5D-3L	UK	
Haemodialysis Severe	0.4260 [0.3440 - 0.5101]	EQ-5D-3L	UK	
Haemodialysis Overwhelming	0.3756 [0.3038 - 0.4504]	EQ-5D-3L	UK	Estimated based on the predicted (exponential function) values from Hernandez et al., 2023(9)
Transplanted None	0.8033 [0.6283 - 0.9317]	EQ-5D-3L	UK	Estimated based on the haemodialysis values from Hernandez et al., 2023 (9) multiplied with a ratio which is based on Eriksson et al. 2017.(10)
Transplanted Mild	0.7678 [0.6048 - 0.8974]	EQ-5D-3L	UK	
Transplanted Moderate	0.6445 [0.5149 - 0.7642]	EQ-5D-3L	UK	
Transplanted Severe	0.4961 [0.3996 - 0.5927]	EQ-5D-3L	UK	
Transplanted Overwhelming	0.4374 [0.3531 - 0.5236]	EQ-5D-3L	UK	

Abbreviations: 5-D = five dimentions; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version; UK = United Kingdom

10.3 Presentation of the health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

As stated above, Hernandez et al., 2023 (9) is used to generate utility values for haemodialysis health states, while Eriksson et al., 2017 (10) is used to calculate a ratio between dialysis utility and utility of transplanted patients, which is used to generate the health state utilities for the transplanted patients of this health economic model. The studies are presented below.

10.3.1 Study design Hernandez et al., 2023 (9)

HRQoL is expected to decrease in patients with more severe CKD-aP. Existing evidence suggests that the severity of the pruritus is associated with depression, poor sleep quality, increased mortality, and reduced health-related quality of life (HRQoL) (28) (4) (32). Lower HRQoL is observed using disease specific HRQoL measures such as 5-D itch scale and Skindex-10. However, as no generic preference-based measures of health were collected in the KALM-1 or KALM-2 trials, a separate primary data collection study across UK dialysis centres was undertaken to develop a mapping algorithm relating the WI-NRS and 5-D Itch Scale to the EQ-5D-3L. The study collected EQ-5D-5L data and four pruritus-related measures (WI-NRS, 5-D itch scale, verbal rating scale and Skindex-10). Verbal rating scale and Skindex-10 were not included in the mapping study as they did not add additional information, but information was exploited for data checking and cleaning.

Inclusion criteria were patients over 18 years of age, receiving haemodialysis for at least 3 months.

10.3.2 Data collection Hernandez et al., 2023 (9)

Primary data collection was undertaken between November 2020 and June 2021 across 5 sites in England on adult patients who had been receiving haemodialysis for at least 3 months. Good Clinical Practice (GCP) -qualified research staff identified and approached patients who met the inclusion criteria while they attended the haemodialysis unit to receive their therapy. Following verbal explanation, patients read a patient information sheet, and after having the opportunity to ask questions, written consent was obtained. Data was collected using the relevant questionnaires. Researchers gave participants the option to complete the questionnaire themselves or with support. Sheffield Teaching Hospitals NHS Foundation Trust was the sponsor of the study, and ethical approval was obtained (Northwest – Greater Manchester, IRAS Reference: 285714).

The data collected was used to estimate EQ-5D-3L mapping functions from 5-D Itch scale scores, WI-NRS, and 5-D Itch scale scores and WI-NRS combined. All mapping functions included age, sex, diabetes status, and length of time on dialysis as additional conditioning variables. Despite limitations with missing observations, the 5-D Itch scale score to EQ-5D-3L mapping algorithm was considered the most appropriate option, given the paucity of published data in CKD-aP. To estimate the relationship between the CKD-aP measures (WI-NRS and 5-D itch) and the EQ-5D, the Adjusted Limited Dependent Variable Mixture Model was used.

Across the five participating centres that collectively care for 2,326 people on haemodialysis, 523 were approached to participate in the study, of whom 487 consented. EQ-5D-5L, WI-NRS and 5-D itch had data missing for 9, 1 and 24 patients, respectively. Amongst the 24 patients with a missing 5-D itch score, the majority (17) reported no itching in the last week (verbal rating scale) or in the last 24 h (WI-NRS). The 5-D itch questionnaire was fully completed by 463 out of the 487 patients. However, the sample included individuals, who apparently had not had pruritus in the past. As patients with no previous experience of itching might not accurately reflect the populations in which the utility values will be used, this group was excluded from the estimation sample. After excluding these and taking into account missing values in other variables, the final common sample size for the statistical analysis was 377.

10.3.3 HRQoL Results Hernandez et al., 2023 (9)

Two alternative EQ-5D-3L models were developed, mapping from: (i) the 5-D itch score; and (ii) the WI-NRS. A 3- and a 2-component model are selected for the mappings, including 5-D itch score and WI-NRS, respectively, in addition to age, sex, the presence of diabetes and the number of years on dialysis. The 5-D itch mapping model was able to reproduce the mean utilities in the data quite closely.

However, the predictions by WI-NRS model had systematic problems in the predictions by WI-NRS groups reflected in inferior measures of model fit and the general lack of statistical significance of the coefficients for the WI-NRS in the mapping model, suggesting that WI-NRS is not a good predictor of EQ-5D-3L in these data. A mapping including both measures of pruritus was also developed; however, this did not significantly improve the

performance of the mapping and so is not reported here. As a result, the model used was the 5-D itch scale model.

As the study was carried out to support the submission to National Institute for Health and Care Excellence (NICE), the data on EQ-5D-5L were converted into an EQ-5D-3L UK utility using the van Hout crosswalk, adhering to the NICE guidance (71). The EQ-5D-5L data is not available to the applicant and can therefore not be used to for this application.

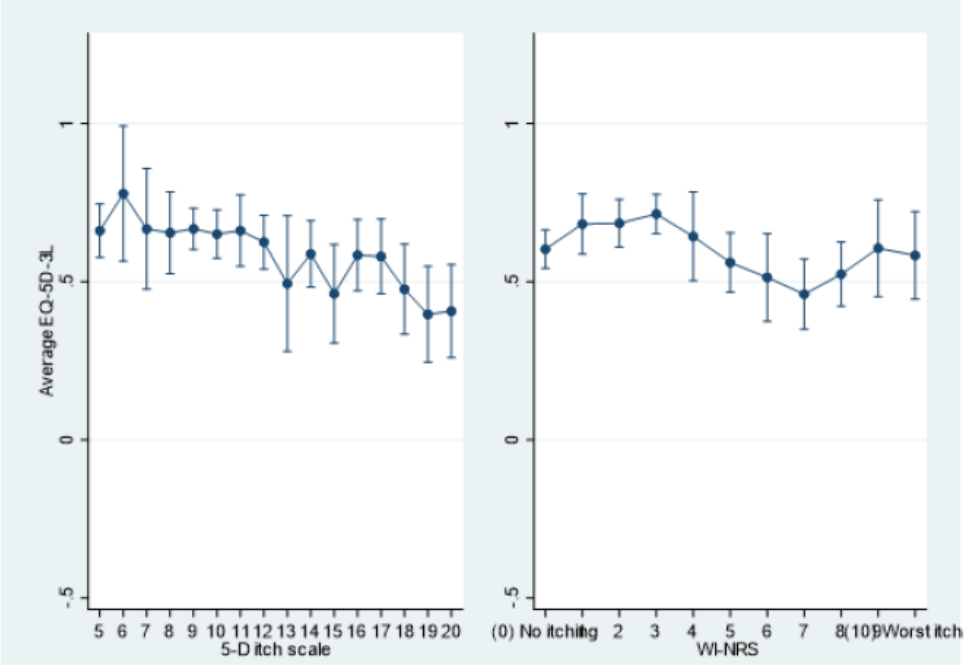
Table 45 presents summary statistics of the final sample for different groups of self-reported CKD-aP severity. There is a higher proportion of patients with diabetes among patients who had no self-reported itching the previous fortnight. Within the sample of individuals who have pruritus, the average EQ-5D-3L decreases as itching increases, but this value is slightly lower for people with no itching when compared to people with mild itch.

Table 45: Summary statistics of the final sample by self-reported CKD-aP severity.

Severity	Not present		Mild		Moderate		Severe/unbearable	
Variables	Mean/ Prop.	SD	Mean/ Prop.	SD	Mean/ Prop.	SD	Mean/ Prop.	SD
Female	*28.8%*		*27.5%*		*31.2%*		*49.3%*	
Diabetes	*40.9%*		*27.5%*		*38.5%*		*32.4%*	
Age	*65.71*	*15.43*	*65.18*	*15.73*	*65.64*	*14.67*	*61.72*	*17.57*
Years in dialysis	*3.51*	*5.32*	*4.19*	*4.74*	*4.01*	*6.05*	*4.55*	*5.79*
5-D itch score	*5.95*	*1.70*	*9.76*	*2.18*	*13.67*	*3.11*	*17.73*	*2.86*
WI-NRS score	*0.47*	*1.61*	*2.43*	*2.40*	*5.34*	*2.50*	*7.51*	*2.51*
EQ-5D-3L	*0.669*	*0.30*	*0.683*	*0.26*	*0.509*	*0.31*	*0.499*	*0.30*
Observations	*66*		*131*		*109*		*71*	

Abbreviations: 5-D = five dimentions; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version; SD = standard deviation; WI-NRS = worst itch numeric rating scale.

Figure 16: Estimated means of EQ-5D-3L and 95 % bootstrapped confidence intervals by 5-D itch index and WI-NRS (5-D itch scale 20 includes all observations in the range 20 to 25).



Abbreviations: 5-D = five dimentions; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version; WI-NRS = worst itch numeric rating scale.

Figure 16 plots the relationship between EQ-5D-3L and 5-D itch in the data; scores of 20+ are grouped together because of the low number of observations. As expected, the average EQ-5D-3L tends to decline as the 5-D itch index score goes up. The panel on the right depicts the relationship between EQ-5D-3L and WI-NRS. Unlike the 5-D itch index, the average EQ-5D-3L oscillates as WI-NRS increases and does not show a clear downward trend. The numbers were reproduced in the model to estimate the utility weights for each modelled CKD-aP pruritus severity state.

10.3.4 Study design Eriksson et al., 2017 (10)

A study involving cross-sectional patient-reported outcomes and retrospective clinical data was undertaken April– December 2014 in Denmark, Finland, Norway, and Sweden. Patients were enrolled into four mutually exclusive stages of the disease: CKD stages 1–3; CKD stages 4–5; transplant recipients; and dialysis patients. Different patient report outcomes (PROs) were collected. Patients' HRQoL was primarily assessed using the EuroQol EQ-5D-3L due to its applicability across a wide range of health conditions and common use in health economic evaluations. Additional information was obtained via the SF-12v2 instrument due to its ability to distinguish between mental and physical health, while keeping response burden to a minimum.

Summary statistics were calculated, including means and SDs for continuous variables and frequency distributions for categorical variables. EQ-5D index scores were estimated using UK, Danish and Swedish value sets.

10.3.5 Data collection Eriksson et al., 2017 (10)

Prior to recruitment of patients all staff at participating clinics received training in study procedures to ensure standardization of patient enrolment and data collection. Data were extracted from medical charts using a case report form (CRF) and complemented with self-administered questionnaires to collect PROs. Finally, the Work Productivity and Activity Impairment General Health (WPAI:GH) questionnaire was used in this study to estimate the impact of health problems on regular daily activities. Patients' HRQoL was primarily assessed using the EuroQol EQ-5D-3L due to its applicability across a wide range of health conditions and common use in health economic evaluations. The SF-12v2 instrument was also assessed due to its ability to distinguish between mental and physical health, while keeping response burden to a minimum A total of 266 patients were contacted; of these 243 (91%) provided consent to participate in the study. The majority of patients were enrolled in Denmark (n = 118), followed by Sweden (n = 58), Norway (n = 50) and Finland (n = 17). The Modification of Diet in Renal Disease (MDRD) equation was used to estimate GFR in 86% of non-dialysis patients, followed by the Lund-Malmö equation (8%) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (6%).

Dialysis patients comprised the oldest group, followed by transplant recipients and non-end-stage renal disease (ESRD) patients. Mean ages ranged from 52 years in patients with CKD stages 1–3 to 64 years in dialysis patients. Employment rates were highest in the earlier stages of the disease. No differences between the disease stages were seen in sex, body mass index and systolic blood pressure.

10.3.6 HRQoL Results Eriksson et al., 2017 (10)

Across the study population, a significant proportion of patients reported (some or extreme) problems with pain, as captured in the EQ-5D, ranging from 44% in transplant recipients to 59% in dialysis patients, presented in Table 46. Overall HRQoL, as measured by the EQ-5D and SF-12, was generally higher in transplanted patients compared with dialysis patients (Table 47).

Table 46: Problems reported in the five dimensions of EQ-5D

Problems reported on the EQ-5D, proportion (%) of patients	CKD 1–3 (*n* = 64)	CKD 4–5 (*n* = 55)	Dialysis (*n* = 61)	Transplant (*n* = 63)	P-value
Mobility	8	20	48	22	<0.0001
Self-care	2	4	18	8	0.0037
Usual activities	16	36	62	32	<0.0001
Pain/discomfort	48	47	59	44	0.2151
Anxiety/depression	30	31	41	22	0.1204

Abbreviations: CKD = chronic kidney disease; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version;

Table 47: Overall HRQoL based the four groups

HRQoL estimates, mean ± SD	CKD 1–3 (*n* = 64)	CKD 4–5 (*n* = 55)	Dialysis (*n* = 61)	Transplant (*n* = 63)	P-value
EQ-5D index (UK)	0.86±0.16	0.79±0.23	0.68±0.30	0.82±0.21	0.0036

EQ-5D index (DK)	0.87±0.14	0.82±0.18	0.73±0.22	0.85±0.16	0.0025
EQ-5D index (SE)	0.91±0.08	0.88±0.11	0.81±0.13	0.89±0.10	<0.0001

Abbreviations: CKD = chronic kidney disease; DK = Denmark; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version; SE = Sweden; UK = United Kingdoms

10.3.7 HSUV and disutility results

The final values used are presented in section 10.2.3.

11. Resource use and associated costs

11.1 Pharmaceutical costs - intervention and comparator

The pharmaceutical and other topical products are presented Table 48. The model assumes the cost of difelikefalin for the difelikefalin arm only. All other products are applied for both arms dependent on the pruritus severity health state. Wastage was not included.

Difelikefalin treatment was modelled to continue until the patient either:

- stops due to any reason before week 64,
- stops due to lack of treatment effect at week 64,
- receives renal transplantation or dies.

In the base case analysis, 13 % of the patients treated with difelikefalin discontinue treatment (for any reason) by week 12 (Fishbane et al. 2022 – Supplements). In addition, 23 % of patients stop from week 12 to week 64 based on published difelikefalin trial data (Fishbane et al. 2022 – Supplements). Pruritus severity after difelikefalin discontinuation is based on the last observed severity obtained from confidential on-file trial data. Dosing of difelikefalin and other agents against pruritus is found in section 3.5. Dosing of treatment in relation to dialysis and following transplantation is found in Appendix K.

Table 48: Pharmaceutical costs used in the model

Pharmaceutical	ATC code	Strength	Packaging size	Pack Price (DKK) (AIP)	Administration
Difelikefalin	V03AX04	50 micrograms/ml	12 vials	3,034.58	IV
Antihistamine (Hydroxyzinhydrochl.)	N05BB01	25 mg	100 tabl	21.80	Oral
Emollient (Dexem crème)	N/a	N/a	50 g	34.90	Topical
Topical corticosteriod (hydrokortison)	D07AA02	1%	30 g	83.68	Topical
Gabapentin	N02BF01	300 mg	100 tabl	14.16	Oral
Pregabalin	N02BF02	25 mg	60 tabl	11.50	Oral

ESA	B03XA01	10000	6 vials	5,700.00	IV
IV Iron	B03AC	20 mg/ml	25 ml	745.00	IV
Primary phosphate binder (calcium carbonate + vitamin D)	A12AX	400 mg	240 tabl	110.50	Oral
Second phosphate binder (sevelamer)	V03AE02	800 mg	180 tabl	1,240.00	Oral
Tacrolimus	L04AD02	2 mg	50 tabl	856.04	Oral
Mycophenolate	L04AA06	500 mg	150 tabl	475.00	Oral
Prednisolone	H02AB06	5 mg	100 tabl	38.42	Oral

11.2 Pharmaceutical costs – co-administration

All products are presented above in Table 48.

11.3 Administration costs

Most of the products included in Table 48 are administrated either orally or topically. Difelikefalin, ESA, and iron are administrated via intravenously (IV). However, as all administrations are expected to happen directly in relation to the dialysis session (after ended dialysis), further administration costs have not been applied a cost to avoid double counting. As such, the cost of drug administration is expected to be included in the DRG-tariff for the dialysis session (DKK 3,078. DRG 2023 11PR10).

11.4 Disease management costs

Based on clinical expert feedback, the relevant resources were identified. The resource use was estimated by two clinical experts, if the clinical expert did not agree on the frequency, the average of the two answers were taken to estimate the resource frequency.

Resource use for CKD-aP patients in haemodialysis are presented in Table 49, while the resource use for transplanted CKD-aP patients is presented in Table 50. Renal transplantation were applied as an one-off cost.

The two clinical experts stated that the average patient would have three dialysis visits per week, however, some patients may have more or less dialysis visits per week. The clinicians stated that patients with more severe pruritus may have more dialysis visits per week on average compared to those with less severe CKD-aP, mostly to optimise dialysis. For the none to moderate CKD-aP patients, a hospitalisation roughly every other month was estimated, which was expected to increase for the severe to overwhelming patients. The clinicians expected very few dialysis patients to have UV-light therapy, as they already use a lot of time on the hospital. General practitioner visits were estimated to every 3-4 months for dialysis patients.

The unit costs were estimated using DRG tariffs presented in Table 51.

Table 49: Resource use for disease management in CKD-aP dialysis patients per year

Annual visits	None	Mild	Moderate	Severe	Over-whelming
Dialysis visit	150.8	150.8	156	158.6	158.6
Periods of hospitalization	6	6	6	12	12
Dermatologist's office visits	0.6	0.6	1.38	4.2	4.8
UV light therapy visits	0	0	0	0.12	0.24
General practitioner visits	2.4	2.4	3	3	3

Table 50: Resource use for disease management in CKD-aP transplanted patients per year

Annual visits	None	Mild	Moderate	Severe	Over-whelming
Periods of hospitalisation	6	6	6	12	12
Dermatologist's office visits	2	2	2	2	2
General practitioner visits	1.2	1.2	3	4.8	6

Table 51: Disease management costs used in the model

Activity	Unit cost	DRG code
Dialysis visit	DKK 3,078	DRG 2023: 11PR10 Dialyse, øvrige. (DN189) Kronisk nyreinsuffi-ciens UNS. (BJFD20) Hæmodialyse ved kronisk nyresygdom
Periods of hospitalisation	DKK 35,456	DRG 2023: 11MA02 Andre primære eller sekundære medicinske nyresygdomme uden dialyse (DN189) Kronisk nyreinsufficiens UNS
Dermatologist's office visit	DKK 1,634	DRG 2023: 09MA98 MDC11 1-dagsgruppe, pat, mindst 7 år
UV light therapy visit	DKK 1,634	DRG 2023: 09MA98 MDC11 1-dagsgruppe, pat, mindst 7 år
GP-visit	DKK 154	Værdisætning af enhedsomkostninger vers. 1.7 - 0101 Konsulta-tion
Renal transplantation	DKK 271,244	DRG 2023: 11MP02 Nyretransplantation

11.5 Costs associated with management of adverse events

As seen in section 9, the frequency of adverse events aligned between the difelikefalin arm and SoC arm. As a result, no adverse event costs were included for the sack of model parsimony was not included.

11.6 Subsequent treatment costs

Not applicable. Subsequent treatment costs were not modelled separately. Following difelikefalin discontinuation, patients in the difelikefalin arm will be treated with SoC only.

11.7 Patient costs

Patient time was estimated via clinical expert feedback and assumption. Time use is presented in Table 52. Based on the unit cost catalogue, each patient hour was costed by DKK 203. For each hospital visit, a transport cost of DKK 149.20 was applied, calculated based on the unit cost catalogue (DKK 3.73 per km for 40 km per visit).

Table 52: Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Dialysis	4 hours
Difelikefalin administration	10 minutes
Hospitalisation	24 hours
Other outpatient visits	30 minutes

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

Table 53: Base case overview

Feature	Description
Comparator	Standard of care (+placebo)
Type of model	Markov model
Time horizon	40 years (lifetime)
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life applied with EQ-5D-3D. This is based on a mapping of 5-D itch scale trial data to EQ-5D-3L used in the model.
Costs included	Pharmaceutical costs Hospital costs Patient costs
Dosage of difelikefalin	One vial, three times a week after dialysis.

Feature	Description
Average time on treatment difelikefalin	2.97 years
Average time in model health state	
Haemodialysis	Difelikefalin: 3.90 SoC: 3.90
Transplanted	Difelikefalin: 1.43. SoC: 1.43
Baseline characteristics	Mean age: 63.86 Male: 63.6% Diabetes: 50.6% Over 2 years of dialysis: 26.8% Over 65 years: 30.2% None and mild pruritus: 0% Moderate: 53.7% Severe: 35.8% Overwhelming: 10.5%

Abbreviations: CKD = chronic kidney disease; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version; SoC = Standard of Care.

12.1.1 Base case results

Base case results are presented in Table 54.

Table 54: Base case results, discounted estimates

	DIFELIKEFALIN	Standard of Care	DIFFERENCE
Total costs	**DKK 3,822,763**	**DKK 3,846,787**	**-DKK 24,024**
Difelikefalin	**DKK 107,447**	**DKK 0**	**DKK 107,447**
On Haemodialysis	**DKK 3,359,762**	**DKK 3,491,232**	**-DKK 131,470**
- Treatments related to pruritus	DKK 11,736	DKK 16,480	-DKK 4,744
- Treatments related to CKD or HD	DKK 213,254	DKK 218,613	-DKK 5,359
- Haemodialysis and outpatient visits	DKK 1,664,501	DKK 1,687,149	-DKK 22,648
- Other specialised care	DKK 814,650	DKK 910,771	-DKK 96,122
- Patient time and transport cost	DKK 655,620	DKK 658,218	-DKK 2,598
Renal transplantation	**DKK 36,977**	**DKK 36,977**	**DKK 0**
After renal transplant	**DKK 318,578**	**DKK 318,578**	**DKK 0**
- Medications	DKK 55,206	DKK 55,206	DKK 0
- Specialised care	DKK 230,316	DKK 230,316	DKK 0
- Patient time and transport cost	DKK 33,055	DKK 33,055	DKK 0

	DIFELIKEFALIN	Standard of Care	DIFFERENCE
Total life years	**4.598**	**4.598**	**0.000**
- On haemodialysis	3.546	3.546	0.000
- After renal transplant	1.052	1.052	0.000
Total QALYs	**3.035**	**2.817**	**0.218**
- On haemodialysis	2.232	2.015	0.218
- After renal transplant	0.802	0.802	0.000
Incremental cost per QALY gained (ICER)		Difelikefalin is dominating	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Deterministic one-way was conducted for all relevant parameters. The ten most influential parameters are presented in a tornado diagram in Figure 17, with a negative ICER representing a dominating outcome. As seen, the biggest uncertainty of the model is the resource use, including dialysis visits and hospitalisation. The reason for this is that dialysis is a large cost driver, and as more patients in the difelikefalin arm are placed in the none and mild pruritus severity compared with the SoC arm, while on the other hand, more SoC patients are placed in moderate and severe pruritus severity group. Thus, it seems logical that a change in number of dialysis visits for a single pruritus severity health state, results in larger deviations in the cost-effectiveness result. Based on the clinical expert feedback we received, it seems highly unlikely that a single pruritus severity group would deviate largely from others in terms of numbers of dialysis visits per year. To explore the impact of number of dialysis visits further, a scenario was conducted in which the number of dialysis visits for each pruritus severity health state was simultaneously changed to the lower bound values. The same scenario was conducted with the upper bound values. Other influential parameters include severity at discontinuation and utility of haemodialysis patients; however, these parameters did not cross the y-axis, meaning that difelikefalin is dominating using both the upper and lower bound values for these parameters.

In Table 55, different relevant scenarios are presented. Only two scenarios resulted in a non-dominant incremental result. The application of differentiation in survival based on pruritus' severity via HRs identified in Sukul et., 2021,(29) resulted in additional life years and QALYs in the difelikefalin (incremental QALYs 0.218/0.266 – base case/scenario). However, this also resulted in significant additional cost incurred in the difelikefalin arm due to addition resource use, resulting in an ICER of DKK 213,201 per QALY. The data from Sukul et al., 2021 (29) was not applied in the base case, as it is not Danish specific and Danish clinical expert found it implausible that survival would change by treating the pruritus alone (see section 8.4). The scenario where all patients are discontinued on difelikefalin after 64 weeks (equal to longest trial period) and patients transitioned to the same pruritus severity distributions as the SoC arm resulted in an ICER of DKK 323,944 per QALY. Difelikefalin remained dominant in the other scenarios.

Figure 17: Tornado diagram presenting the ten most influential parameters

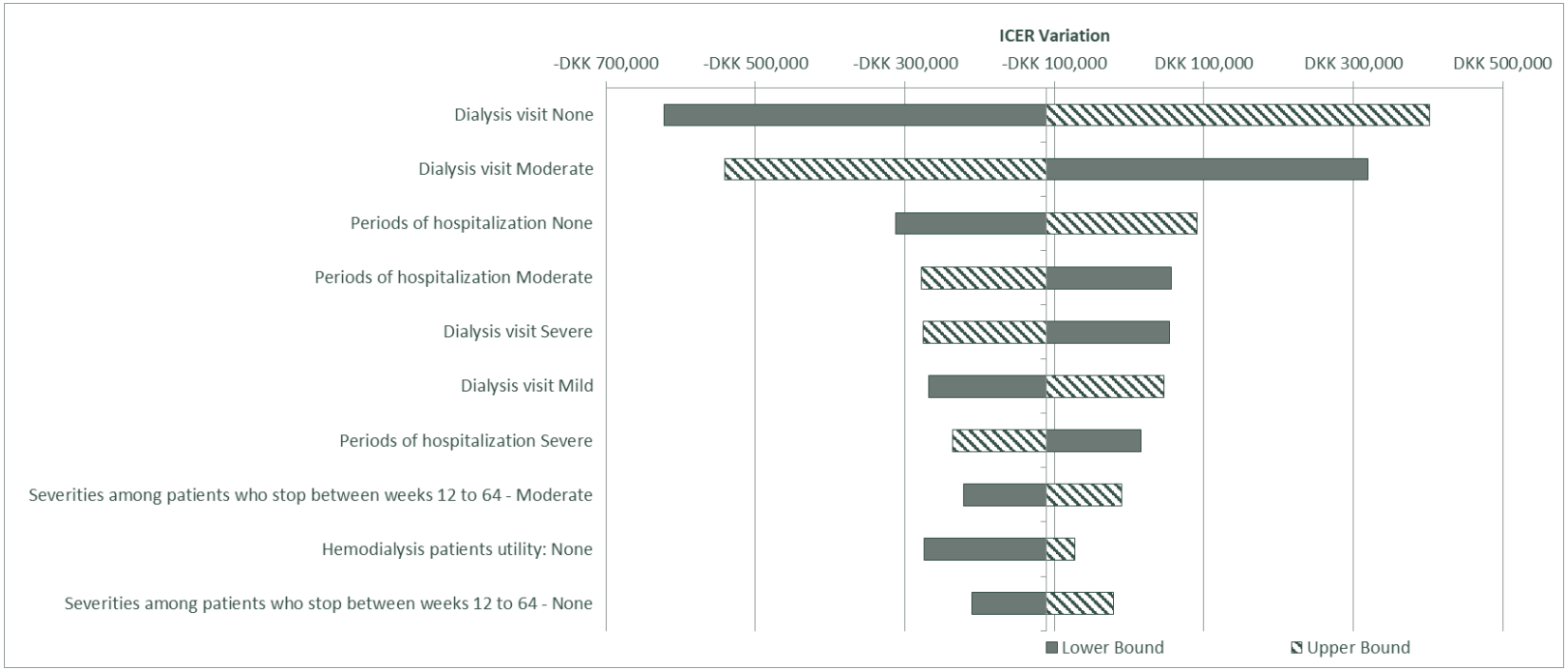


Table 55: Scenario one-way sensitivity analyses results

	Change QALYs	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case		Base case	-DKK 24,024	0.218	Difelikefalin dominates

	Change QALYs	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Danish baseline characteristics	-2%	Result applicable with Danish characteristics based on DNSL report (5)	-DKK 24,687	0.214	Difelikefalin dominates
No efficacy with SoC	128%	Real-world scenario patients would not experience placebo effect	-DKK 310,918	0.498	Difelikefalin dominates
All patients start in overwhelming pruritis	18%	Check cost-effectiveness for overwhelming patients	-DKK 78,532	0.258	Difelikefalin dominates
All patients start in severe pruritus	22%	Check cost-effectiveness for severe patients	-DKK 85,255	0.265	Difelikefalin dominates
HRs applied to differentiate mortality between pruritus severity health states	22%	HRs from Sukul et al., 2021(29) supplementary table 3 model 4	DKK 56,749	0.266	DKK 213,201
All transplanted patients transition to no pruritus*	0%	Range of impact on the base case results	-DKK 24,024	0.218	Difelikefalin dominates
Unadjusted transplantation rate applied (0.0011 per cycle)	-6%	Range of impact on the base case results	-DKK 20,282	0.204	Difelikefalin dominates
Unadjusted mortality rate HD (0.004 per cycle)	4%	Range of impact on the base case results	-DKK 23,317	0.226	Difelikefalin dominates
Set diabetes proportions for HD mortality risks equal to baseline characteristics (adjusted HR=1)	8%	Test model robustness in terms of diabetes impact	-DKK 28,870	0.235	Difelikefalin dominates

	Change QALYs	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Set diabetes proportions for transplanted mortality risks equal to baseline characteristics (adjusted HR=1)*	0%	Test model robustness in terms of diabetes impact	-DKK 24,024	0.218	Difelikefalin dominates
Stop difelikefalin treatment at 64 weeks – patients stay in same health state	0%	Patients only treated for the time trial data was collected	-DKK 92,144	0.218	Difelikefalin dominates
Stop difelikefalin treatment at 64 weeks – patients transition to same health state distribution as SoC	-77%	Patients only treated for the time trial data was collected	DKK 16,472	0.051	DKK 323,944
Transplanted patient utility based on ratio from Swedish value set*	0%	Range of impact on the base case results	-DKK 24,024	0.218	Difelikefalin dominates
Transplanted patient utility based on ratio from United Kingdom value set*	0%	Range of impact on the base case results	-DKK 24,024	0.218	Difelikefalin dominates
Transplanted patient utility based on ratio from average of the 3 value sets*	0%	Range of impact on the base case results	-DKK 24,024	0.218	Difelikefalin dominates
Number of dialysis visits: lower bound for all five health states	0%	Dialysis visits most impactful parameters in one-way analysis	-DKK 21,785	0.218	Difelikefalin dominates
Number of dialysis visits: upper bound for all five health states	0%	Dialysis visits most impactful parameters in one-way analysis	-DKK 26,263	0.218	Difelikefalin dominates
Only rely on efficacy data from the placebo-controlled duration, i.e. week 0-12	-52%	DMC request	-DKK 3,943	0.105	Difelikefalin dominates

	Change QALYs	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Function used for modelling renal transplant rates by age: 3rd degree polynomial	-3%	To further explore the sensitivity related to the choice of function.	-DKK 22,515	0.212	Difelikefalin dominates
Function used for modelling renal transplant rates by age: Logarithmic	>1%	To further explore the sensitivity related to the choice of function.	-DKK 23,786	0.217	Difelikefalin dominates

*These incremental results of these scenarios are equal to the incremental results of the base case due to the underlying assumption that there is no difference in mortality, transplant rates and distribution of patients in pruritus severity health states following transplantation. As a result, the scenarios impacted both arms equally.

Abbreviations: HD = Haemodialysis; HR = Hazard ratio; SoC = Standard of Care

12.2.2 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) was conducted to assess the overall parameter uncertain. All model parameter with uncertainty were included. In general, gamma distribution was selected for cost input, beta for proportions, and log normal for ratios. Normal distribution was selected if no reason to believe that data significantly deviated from a normal distribution pattern. A PSA scatter plot of 2,000 iterations is presented in Figure 18, with a cost-effectiveness acceptability curve presented in Figure 19.

The mean PSA results indicated that difelikefalin dominates SoC. Mean incremental cost was -DKK 17,269 and mean incremental QALYs was 0.208. This aligns with the deterministic results.

Figure 18: Cost-effectiveness plane

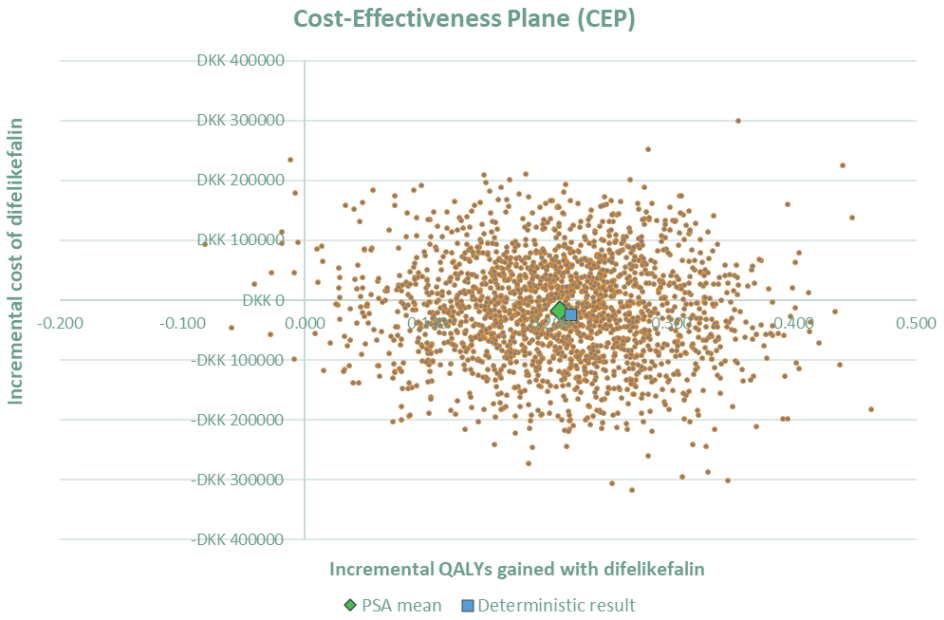
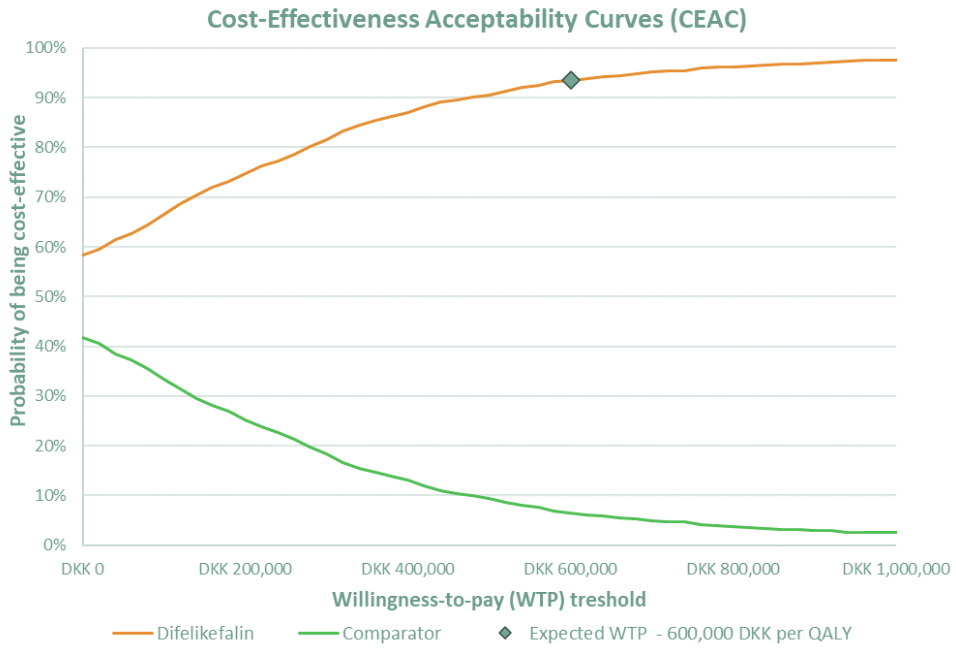
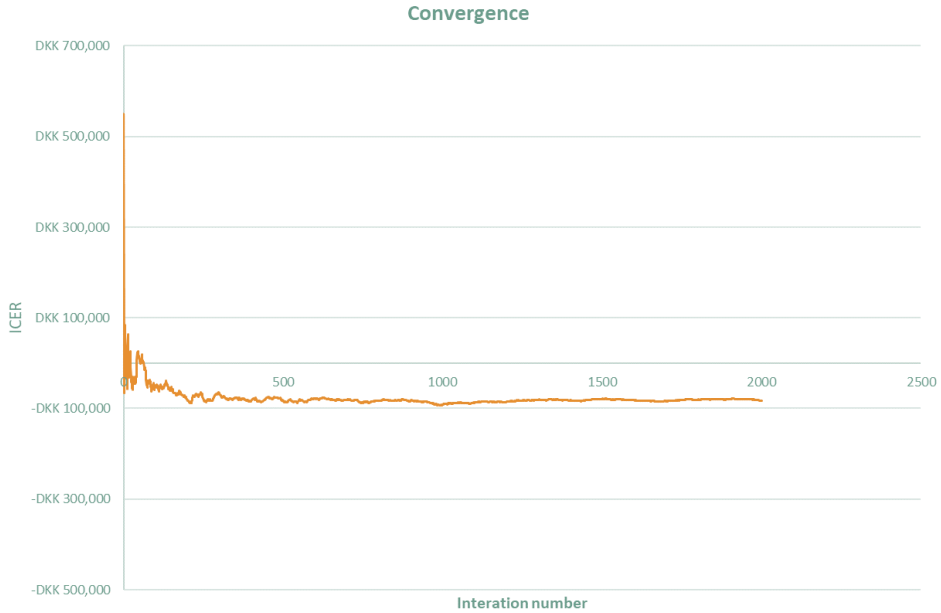


Figure 19: Cost-effectiveness acceptability curve



The 2,000 iterations were based on the convergence test (Figure 20), indicting the ICER stabilising around DKK -100,000. The full set of parameters included in the model, including details of distributional forms, are presented in Appendix G.

Figure 20: Convergence test of probabilistic sensitivity analysis



13. Budget impact analysis

Number of patients (including assumptions of market share)

Based on the DNSL 2022 report, the average number of prevalent HD patients between 2018 and 2022 was 2,153 patients, while the average number of incident patients was 415. Of these 92.11% were on treated in-centre. Based on clinical expert feedback, approximately 30% of these patients have moderate-to-severe pruritus. As a result, the model applied 595 prevalent eligible patients at the start point and 115 incident eligible patients for each year. As seen in Table 2, this results in 710 patients in the first year and 115 patients in the remaining years.

As clinicians indicated that they expect to try gabapentinoids alone before using difelikefalin, the difelikefalin market share in the first year was set to 15% increasing with 5% for each year. Number of patients starting treatment each year is presented in Table 56.

Table 56: Number of new patients expected to be treated over the next five-year period if difelikefalin is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Difelikefalin	106	23	29	35	40
Standard of care	604	92	86	81	75
			Non-recommendation		
Difelikefalin	0	0	0	0	0
Standard of care	710	115	115	115	115

Budget impact

The budget impact is informed by comparing the costs for the Danish healthcare system per year over five years in the scenario where difelikefalin is recommended as standard treatment and the scenario where difelikefalin is not recommended as standard treatment. The total budget impact per year is the difference between the two scenarios.

The budget impact estimated in Table 57 is based on non-discounted cost outputs (2023 DKK) from the cost-effectiveness model for five years, and the assumed eligible patients described above, as well as the assumed uptake of difelikefalin for the treatment of eligible CKD patients with moderate-to-severe pruritus patients described above. The total budget impact over five years is DKK -1,522,709

Table 57: Expected budget impact of recommending difelikefalin for CKD patients with moderate-to-severe pruritus

	Year 1	Year 2	Year 3	Year 4	Year 5
If difelikefalin is recommended (DKK)	542,497,779	511,903,695	496,227,455	481,949,560	469,061,819
If difelikefalin is NOT recommended (DKK)	541,587,589	512,453,772	496,855,328	482,565,672	469,700,656
Budget impact of the recommendation (DKK)	**910,189**	**- 550,077**	**- 627,872**	**- 616,112**	**- 638,837**

14. List of experts

The clinicians consulted during this application comprise of:

- Lene Boesby (Ph.d. Cheflæge Afdeling for nyresygdomme, Rigshospitalet). Was employed at Sjællands Universitetshospital, Region Sjælland during time of conversation
- Krista Dybtved Kjærgaard (Afdelingslæge ved dialyseklinikken Regionshospital Horsens, Aarhus Universitetshospital)

15. References

1. European Medicines Agency. Kapruvia : EPAR - Product Information. 2022 25-07-2022.

2. European Medicines Agency. Kapruvia. Difelikefalin 2022 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/kapruvia.

3. Danish Medicines Agency. Medicinpriser.dk 2023 [updated 16-10-2023. Available from: https://medicinpriser.dk.

4. Pisoni RL, Wikström B, Elder SJ, Akizawa T, Asano Y, Keen ML, et al. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2006;21(12):3495-505.

5. Dansk Nefrologisk Selskabs Landsregister. Landsdækkende database for patienter med kronisk nyresvigt: Årsrapport for 2022 - 1. januar til 31. december 2022. 2022.

6. Boenink R, Stel VS, Waldum-Grevbo BE, Collart F, Kerschbaum J, Heaf JG, et al. Data from the ERA-EDTA Registry were examined for trends in excess mortality in European adults on kidney replacement therapy. Kidney Int. 2020;98(4):999-1008.

7. Sørensen VR, Mathiesen ER, Heaf J, Feldt-Rasmussen B. Improved survival rate in patients with diabetes and end-stage renal disease in Denmark. Diabetologia. 2007;50(5):922-9.

8. Krajewski PK, Olczyk P, Krajewska M, Krajewski W, Szepietowski JC. Clinical Characteristics of Itch in Renal Transplant Recipients. Front Med (Lausanne). 2021;7:615334.

9. Hernandez Alava M, Sasso A, Hnynn Si PE, Gittus M, Powell R, Dunn L, et al. Relationship Between Standardized Measures of Chronic Kidney Disease-associated Pruritus Intensity and Health-related Quality of Life Measured with the EQ-5D Questionnaire: A Mapping Study. Acta Derm Venereol. 2023;103:adv11604.

10. Eriksson D, Karlsson L, Eklund O, Dieperink H, Honkanen E, Melin J, et al. Health-related quality of life across all stages of autosomal dominant polycystic kidney disease. Nephrol Dial Transplant. 2017;32(12):2106-11.

11. Crews DC, Bello AK, Saadi G. Burden, access, and disparities in kidney disease. Brazilian Journal of Medical and Biological Research. 2019;52.

12. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements. 2013;3:1-150.

13. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl (2011). 2017;7(1):1-59.

14. Abbasi MA, Chertow GM, Hall YN. End-stage renal disease. BMJ Clin Evid. 2010;2010.

15. Grundmann S, Ständer S. Chronic pruritus: clinics and treatment. Ann Dermatol. 2011;23(1):1-11.

16. Gutzmer R, Mommert S, Gschwandtner M, Zwingmann K, Stark H, Werfel T. The histamine H4 receptor is functionally expressed on T(H)2 cells. J Allergy Clin Immunol. 2009;123(3):619-25.

17. Mettang T, Kremer AE. Uremic pruritus. Kidney Int. 2015;87(4):685-91.

18. Makar M, Smyth B, Brennan F. Chronic Kidney Disease-Associated Pruritus: A Review. Kidney Blood Press Res. 2021;46(6):659-69.

19. Papoiu AD, Emerson NM, Patel TS, Kraft RA, Valdes-Rodriguez R, Nattkemper LA, et al. Voxel-based morphometry and arterial spin labeling fMRI reveal neuropathic and neuroplastic features of brain processing of itch in end-stage renal disease. J Neurophysiol. 2014;112(7):1729-38.

20. Kimmel M, Alscher DM, Dunst R, Braun N, Machleidt C, Kiefer T, et al. The role of micro-inflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. Nephrol Dial Transplant. 2006;21(3):749-55.

21. Narita I, Alchi B, Omori K, Sato F, Ajiro J, Saga D, et al. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. Kidney Int. 2006;69(9):1626-32.

22. Phan NQ, Lotts T, Antal A, Bernhard JD, Ständer S. Systemic kappa opioid receptor agonists in the treatment of chronic pruritus: a literature review. Acta Derm Venereol. 2012;92(5):555-60.

23. Mettang T, Pauli-Magnus C, Alscher DM. Uraemic pruritus--new perspectives and insights from recent trials. Nephrol Dial Transplant. 2002;17(9):1558-63.

24. Verduzco HA, Shirazian S. CKD-Associated Pruritus: New Insights Into Diagnosis, Pathogenesis, and Management. Kidney Int Rep. 2020;5(9):1387-402.

25. . !!! INVALID CITATION !!! (14, 18).

26. . !!! INVALID CITATION !!! (19).

27. Block GA, Evenepoel, P., Fishbane, S., Budden, J. J., Morin, I., Menzaghi, F., Wen, W. and Lerma, E. V. Correlation of serum phosphate with pruritus severity and response to difelikefalin. American Society of Nephrology Kidney Week; 3-6 November 2022; Orlando, FL. 2022.

28. Rayner HC, Larkina M, Wang M, Graham-Brown M, van der Veer SN, Ecder T, et al. International Comparisons of Prevalence, Awareness, and Treatment of Pruritus in People on Hemodialysis. Clin J Am Soc Nephrol. 2017;12(12):2000-7.

29. Sukul N, Karaboyas A, Csomor PA, Schaufler T, Wen W, Menzaghi F, et al. Self-reported Pruritus and Clinical, Dialysis-Related, and Patient-Reported Outcomes in Hemodialysis Patients. Kidney Med. 2021;3(1):42-53.e1.

30. Sukul N, Zhao J, Pisoni R, Walpen S, Schaufler T, Asgari E, et al. MO901: Longitudinal Pruritus Assessment in Hemodialysis Patients: 1-Year Course of Symptoms and Associations With Clinical and Patient-Reported Outcomes. Nephrology Dialysis Transplantation. 2022;37(Supplement_3).

31. Kimata N, Fuller DS, Saito A, Akizawa T, Fukuhara S, Pisoni RL, et al. Pruritus in hemodialysis patients: Results from the Japanese Dialysis Outcomes and Practice Patterns Study (JDOPPS). Hemodial Int. 2014;18(3):657-67.

32. Poku E, Fotheringham, J., Thokala, P., Harnan, S., Wong, R. and Hernandez, M. 'The impact of chronic kidney disease-associated pruritus (CKD-aP) on health-related quality of

life (HRQoL) in haemodialysis patients: a systematic review'. CRD42020175035. PROSPERO. 2020.

33. Hays R, Kallich, J., Mapes, D., Coons, S. and Carter, W. . Kidney Disease Quality of Life instrument™ - 36 items (KDQOL-36™ Survey). 2000.

34. Ware JE, Kosinski, M. and Keller, S. D. . SF-12: How to score the SF-12 physical and mental health summary scales. The Health Institute, New England Medical Center. 1995(2nd edn.).

35. Ramakrishnan K, Bond TC, Claxton A, Sood VC, Kootsikas M, Agnese W, Sibbel S. Clinical characteristics and outcomes of end-stage renal disease patients with self-reported pruritus symptoms. Int J Nephrol Renovasc Dis. 2013;7:1-12.

36. van der Willik EM, Lengton R, Hemmelder MH, Hoogeveen EK, Bart HAJ, van Ittersum FJ, et al. Itching in dialysis patients: impact on health-related quality of life and interactions with sleep problems and psychological symptoms-results from the RENINE/PROMs registry. Nephrol Dial Transplant. 2022;37(9):1731-41.

37. Karaboyas A, Pisoni, R., Rayner, H., Guebre-Egziabher, F., Csomor, P., Schaufler, T., Wen, W., Menzhagi, F., Hasegawa, T., Chen, Y., Al-Ghamdi, S. and Sukul, N. . Pruritus and patient- reported outcomes: associations between the Skindex-10 and PROs in hemodialysis patients. American Society of Nephrology Kidney Week; Washington DC: American Society of Nephrology; 2019.

38. CSL Vifor. Danish Clinical Expert Interviews [Data on file]. 2023.

39. Rossi GM, Corradini M, Blanco V, Mattei S, Fiaccadori E, Vaglio A, Manenti L. Randomized trial of two after-dialysis gabapentin regimens for severe uremic pruritus in hemodialysis patients. Intern Emerg Med. 2019;14(8):1341-6.

40. Nofal E, Farag F, Nofal A, Eldesouky F, Alkot R, Abdelkhalik Z. Gabapentin: A promising therapy for uremic pruritus in hemodialysis patients: A randomized-controlled trial and review of literature. J Dermatolog Treat. 2016;27(6):515-9.

41. Naini AE, Harandi AA, Khanbabapour S, Shahidi S, Seirafiyan S, Mohseni M. Gabapentin: a promising drug for the treatment of uremic pruritus. Saudi J Kidney Dis Transpl. 2007;18(3):378-81.

42. Gunal AI, Ozalp G, Yoldas TK, Gunal SY, Kirciman E, Celiker H. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. Nephrol Dial Transplant. 2004;19(12):3137-9.

43. Cheikh Hassan HI, Brennan F, Collett G, Josland EA, Brown MA. Efficacy and safety of gabapentin for uremic pruritus and restless legs syndrome in conservatively managed patients with chronic kidney disease. J Pain Symptom Manage. 2015;49(4):782-9.

44. Rayner H, Baharani J, Smith S, Suresh V, Dasgupta I. Uraemic pruritus: relief of itching by gabapentin and pregabalin. Nephron Clin Pract. 2012;122(3-4):75-9.

45. Ishida JH, McCulloch CE, Steinman MA, Grimes BA, Johansen KL. Gabapentin and Pregabalin Use and Association with Adverse Outcomes among Hemodialysis Patients. J Am Soc Nephrol. 2018;29(7):1970-8.

46. Aperis G, Paliouras C, Zervos A, Arvanitis A, Alivanis P. The use of pregabalin in the treatment of uraemic pruritus in haemodialysis patients. J Ren Care. 2010;36(4):180-5.

47. Solak Y, Biyik Z, Atalay H, Gaipov A, Guney F, Turk S, et al. Pregabalin versus gabapentin in the treatment of neuropathic pruritus in maintenance haemodialysis patients: a prospective, crossover study. Nephrology (Carlton). 2012;17(8):710-7.

48. Committee for Medicinal Products for Human Use. Summary of positive opinion for Kapruvia: European Medicines Agency; 2022 [updated 24-02-2022. Available from: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-kapruvia_en.pdf.

49. Agarwal R, Burton J, Gallieni M, Kalantar-Zadeh K, Mayer G, Pollock C, Szepietowski JC. Alleviating symptoms in patients undergoing long-term hemodialysis: a focus on chronic kidney disease-associated pruritus. Clin Kidney J. 2022;16(1):30-40.

50. Fishbane S, Wen W, Munera C, Lin R, Bagal S, McCafferty K, et al. Safety and Tolerability of Difelikefalin for the Treatment of Moderate to Severe Pruritus in Hemodialysis Patients: Pooled Analysis From the Phase 3 Clinical Trial Program. Kidney Med. 2022;4(8):100513.

51. Topf J, Wooldridge T, McCafferty K, Schömig M, Csiky B, Zwiech R, et al. Efficacy of Difelikefalin for the Treatment of Moderate to Severe Pruritus in Hemodialysis Patients: Pooled Analysis of KALM-1 and KALM-2 Phase 3 Studies. Kidney Med. 2022;4(8):100512.

52. Weiner DE, Schaufler T, McCafferty K, Kalantar-Zadeh K, Germain M, Ruessmann D, et al. Difelikefalin improves itch-related sleep disruption in patients undergoing haemodialysis. Nephrol Dial Transplant. 2023.

53. Mathur VS, Lindberg J, Germain M, Block G, Tumlin J, Smith M, et al. A longitudinal study of uremic pruritus in hemodialysis patients. Clin J Am Soc Nephrol. 2010;5(8):1410-9.

54. Phan NQ, Blome C, Fritz F, Gerss J, Reich A, Ebata T, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. Acta Derm Venereol. 2012;92(5):502-7.

55. Cara Therapeutics. Clinical Study Report for the Double-Blind Phase of KALM-2. Difelikefalin (IV CR845). A Multicenter, Double-Blind, Randomized, Placebo Controlled Study to Evaluate the Safety and Efficacy of Intravenous CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus, with a 52 Week Open-Label Extension. [Data on file]. 2020 06 Oct 2020.

56. F. M, editor Clinically meaningful reduction of itch and improvement in multiple quality of life measures in hemodialysis patients with moderate-to-severe pruritus following treatment with difelikefalin. Presented at the 27th Annual Congress of the European Academy of Dermatology and Venereology; September 12–16, 2018; Paris.

57. Kimball AB, Naegeli AN, Edson-Heredia E, Lin CY, Gaich C, Nikaï E, et al. Psychometric properties of the Itch Numeric Rating Scale in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2016;175(1):157-62.

58. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. Br J Dermatol. 2010;162(3):587-93.

59. Medicinrådet D. Medicinrådets metodevejledning for vurdering af nye lægemidler. 2021.

60. Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F. A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus. N Engl J Med. 2020;382(3):222-32.

61. Weiner DE, Vervloet MG, Walpen S, Schaufler T, Munera C, Menzaghi F, et al. Safety and Effectiveness of Difelikefalin in Patients With Moderate-to-Severe Pruritus Undergoing Hemodialysis: An Open-Label, Multicenter Study. Kidney Med. 2022;4(10):100542.

62. ClinicalTrials.gov. A Study to Evaluate the Safety and Efficacy of CR845 in Hemodialysis Patients With Moderate-to-Severe Pruritus (KALM-1). NCT03422653. 2018 [updated 26-04-2022. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03422653?term=kalm1&draw=2&rank=1.

63. ClinicalTrials.gov. CR845-CLIN3103: A Global Study to Evaluate the Safety and Efficacy of CR845 in Hemodialysis Patients With Moderate-to-Severe Pruritus (KALM-2). NCT03636269 2018 [updated 26-04-2022. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03636269?term=kalm2&draw=2&rank=1.

64. ClinicalTrials.gov. CR845-CLIN3105: A Study to Evaluate the Safety and Effectiveness of CR845 in Hemodialysis Patients With Moderate-to-Severe Pruritus 2019 [updated 15-10-2021. Available from: https://classic.clinicaltrials.gov/ct2/show/study/NCT03998163?term=NCT03998163&draw=2&rank=1.

65. van Laarhoven AIM, van der Sman-Mauriks IM, Donders ART, Pronk MC, van de Kerkhof PCM, Evers AWM. Placebo effects on itch: a meta-analysis of clinical trials of patients with dermatological conditions. J Invest Dermatol. 2015;135(5):1234-43.

66. Medicinrådet D. Medicinrådets anbefaling vedr. dupilumab til moderat til svær prurigo nodularis. medicinrådet.dk; 2023.

67. Cara Therapeutics. Clinical Study Report for the Double-Blind Phase of KALM-1. Difelikefalin (IV CR845). A Multicenter, Double-Blind, Randomized, Placebo Controlled Study to Evaluate the Safety and Efficacy of Intravenous CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus, with a 52 Week Open-Label Extension . [Data on file]. 2020 13 Jan 2020.

68. Cara Therapeutics. Clinical Study Report for the Open-label Extension Phase of KALM-2. Difelikefalin (IV CR845). A Multicenter, Double-Blind, Randomized, Placebo Controlled Study to Evaluate the Safety and Efficacy of Intravenous CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus, with a 52 Week Open-label Extension. [Data on file]. 2020 12 Nov 2020.

69. Lai JW, Chen HC, Chou CY, Yen HR, Li TC, Sun MF, et al. Transformation of 5-D itch scale and numerical rating scale in chronic hemodialysis patients. BMC Nephrol. 2017;18(1):56.

70. Cara Therapeutics. Clinical Study Report for Difelikefalin (IV CR845). An Open-Label, Multicenter, Study to Evaluate the Safety and Effectiveness of Intravenous CR845 in Hemodialysis Patients With Moderate-to-Severe Pruritus. Protocol Number CR845-CLIN3105. 2020.

71. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.

72. Nordjylland R. PRI - Kronisk Nyresvigt Kalk/fosfor-balance og relaterede emner 2023 [Available from: https://pri.rn.dk/Sider/10980.aspx.

73. Nordjylland R. PRI - Nyretransplantation Immunosuppression 2023 [Available from: https://pri.rn.dk/Sider/16430.aspx.

Appendix A. Main characteristics of studies included

Table 58: Main characteristic of KALM-1

Trial name: KALM-1	NCT number: NCT03422653
Objective	To evaluate the safety and efficacy of IV difelikefalin at a dose of 0.5 mcg/kg administered after each dialysis session.
Publications – title, author, journal, year	Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F; KALM-1 Trial Investigators. A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus. N Engl J Med. 2020 Jan 16;382(3):222-232. doi: 10.1056/NEJMoa1912770. Epub 2019 Nov 8. PMID: 31702883 (60) Fishbane S, Wen W, Munera C, Lin R, Bagal S, McCafferty K, Menzaghi F, Goncalves J, Safety and Tolerability of Difelikefalin for the Treatment of Moderate-to-Severe Pruritus in Hemodialysis Patients: Pooled Analysis From the Phase 3 Clinical Trial Program, Kidney Medicine (2022), doi: https://doi.org/10.1016/j.xkme.2022.100513 (50) Topf J, Wooldridge T, McCafferty K, Schömig M, Csiky B, Zwiech R, Wen W, Bhaduri S, Munera C, Lin R, Jebara A, Cirulli J, Menzaghi F, Efficacy of Difelikefalin for the Treatment of Moderate-to-Severe Pruritus in Hemodialysis Patients: Pooled Analysis of KALM-1 and KALM-2 Phase 3 Studies, Kidney Medicine (2022), doi: https://doi.org/10.1016/j.xkme.2022.100512 (51)
Study type and design	Double-blinded randomised placebo-controlled phase III study including a 12-week double-blind phase and a 52-week open-label extension phase. Enrolled patients were randomly assigned 1:1 using an interactive Web-response system and stratified according to baseline use of concomitant antipruritic medications and history of prespecified medical conditions.
Sample size (n)	378

Main inclusion criteria	To be eligible for inclusion into the double-blind phase of the study, a patient must meet the following criteria:
	• Has ESRD and has been on haemodialysis 3 times/week for at least 3 months prior to the start of screening;
	• Has at least 2 single-pool Kt/V measurements ≥1.2, or at least 2 urea reduction ratio measurements ≥65%, or 1 single pool Kt/V measurement ≥1.2 and 1 urea reduction ratio measurement ≥65% on different dialysis days during the 3 months period prior to screening;
	• Prior to randomisation:
	  ○ Has completed WI-NRS worksheets up to 8 days prior to 1st dose;
	  ○ Has a mean baseline WI-NRS indicative of moderate to severe uremic pruritus.
	• To be eligible for inclusion into the open-label extension phase of the study, each patient will have to fulfil the additional key following criteria at the time of entry into the open-label extension phase:

Trial name: KALM-1	NCT number: NCT03422653
	○ Has received at least 30 doses of the planned 36 doses of study drug during the double-blind phase of this study; ○ Continues to meet inclusion criteria. In addition, patients must be 18 years and older
Main exclusion criteria	A patient will be excluded from the double-blind phase of the study if any of the following criteria are met: • Known noncompliance with dialysis treatment that in the opinion of the investigator would impede completion or validity of the study; • Scheduled to receive a kidney transplant during the study; • New or change of treatment received for itch including antihistamines and corticosteroids (oral, IV, or topical) within 14 days prior to screening; • Received another investigational drug within 30 days prior to the start of screening or is planning to participate in another clinical study while enrolled in this study; • Has pruritus only during the dialysis session (by patient report); • Is receiving ongoing ultraviolet B and anticipates receiving such treatment during the study; • Participated in a previous clinical study with difelikefalin. • A patient will be excluded from the open-label extension phase of the study if any of the additional key following criteria are met at the time of entry into the open-label extension phase: ○ Completed the double-blind phase of this study but exhibited adverse events during the course of the treatment period that may preclude continued exposure to the study drug; ○ Was noncompliant with protocol procedures during the double-blind phase of this study which is indicative of an inability to follow protocol procedures.
Intervention	Difelikefalin (IV administration), 0.5 mcg/kg after each dialysis session (3 times/week). N = 189.
Comparator(s)	Placebo (IV administration), after each dialysis session (3 times/week). N = 188
Follow-up time	12 weeks of active treatment.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was proportion of participants achieving a ≥3-point improvement (reduction) in the weekly mean of daily 24-hour WI-NRS scores (week 12). Secondary endpoints include itch-related QoL (change from baseline in 5-D itch scale score, week 12), itch-related QoL (change from baseline in total Skindex-10 scale score, week 12), and proportion of participants

Trial name: KALM-1	NCT number: NCT03422653
	achieving a ≥4-point improvement (reduction) in the weekly mean of daily 24-hour WI-NRS scores (week 12).
Method of analysis	All the efficacy analyses were conducted in the ITT population, which was defined as all the patients who underwent randomisation. In the primary analysis, missing weekly mean WI-NRS scores were estimated with the use of multiple imputation under a missing-at-random assumption. The difference between the study arms was analysed using a logistic-regression model containing terms for trial group, baseline WI-NRS score, baseline use of antipruritic medication, and history of prespecified medical conditions. The final P value was calculated with the use of the Cui–Hung–Wang weighted test statistic. The changes in scores on the 5-D and Skindex-10 scales at week 12 were analysed with the use of an ANCOVA model, with trial group as a fixed effect and baseline score and stratification factors as covariates. The percentage of patients who had a decrease of at least 4 points from baseline to week 12 in the weekly mean WI-NRS score was analysed with the use of the method described for the primary outcome.
Subgroup analyses	The primary efficacy endpoint was analyzed separately for interim analysis and post-interim analysis subjects, and by stratification factor, study region, and dialysis type. A descriptive analysis of the change in WI-NRS from baseline at Week 12 and by study site was also conducted, along with an analysis of the proportion of subjects achieving a ≥3-point improvement
Other relevant information	N/A

Abbreviations: ANCOVA = analysis of covariance; ESRD = end-stage renal disease; ITT = intention-to-treat; IV = intravenous; N/A = not applicable; QoL = quality of life; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Sources: ClinicalTrials.gov, 2018 (62); Fishbane et al., 2020 (60)

Table 59: Main characteristic of KALM-2

Trial name: KALM-2	NCT number: NCT03636269
Objective	To evaluate the safety and efficacy of IV difelikefalin at a dose of 0.5 mcg/kg administered after each dialysis session.
Publications – title, author, journal, year	Fishbane S, Wen W, Munera C, Lin R, Bagal S, McCafferty K, Menzaghi F, Goncalves J, Safety and Tolerability of Difelikefalin for the Treatment of Moderate-to-Severe Pruritus in Hemodialysis Patients: Pooled Analysis From the Phase 3 Clinical Trial Program, Kidney Medicine (2022), doi: https://doi.org/10.1016/j.xkme.2022.100513 (50) Topf J, Wooldridge T, McCafferty K, Schömig M, Csiky B, Zwiech R, Wen W, Bhaduri S, Munera C, Lin R, Jebara A, Cirulli J, Menzaghi F, Efficacy of Difelikefalin for the Treatment of Moderate-to-Severe Pruritus in Hemodialysis Patients: Pooled Analysis of KALM-1 and KALM-2 Phase 3 Studies, Kidney Medicine (2022), doi: https://doi.org/10.1016/j.xkme.2022.100512 (51)
Study type and design	Double-blinded randomised placebo-controlled phase III study including a 12-week double-blind phase and a 52-week open-label extension phase. Enrolled patients were randomly assigned 1:1. Participants were

Trial name: KALM-2	NCT number: NCT03636269
	stratified according to use of concomitant anti-itch medications (yes or no) and by the presence or absence of specific medical conditions (i.e., history of fall or fracture [related to fall]; confusional state, mental status change, altered mental status, or disorientation; gait disturbance or movement disorder) during the run-in period. The participants, care providers, and investigators were masked.
Sample size (n)	473
Main inclusion criteria	To be eligible for inclusion into the double-blind phase of the study, a patient must meet the following criteria: • Has ESRD and has been on haemodialysis 3 times per week for at least 3 months prior to the start of screening; • Has at least 2 single-pool Kt/V measurements ≥1.2, or at least 2 urea reduction ratio measurements ≥65%, or 1 single pool Kt/V measurement ≥1.2 and 1 urea reduction ratio measurement ≥65% on different dialysis days during the 3 months period prior to screening; • Prior to randomisation: ○ Has completed WI-NRS worksheets up to 8 days prior to 1st dose; ○ Has a mean baseline WI-NRS indicative of moderate to severe uremic pruritus. • To be eligible for inclusion into the open-label extension Phase of the study, each patient will have to fulfil the additional key following criteria at the time of entry into the open-label extension phase: ○ Has received at least 30 doses of the planned 36 doses of study drug during the double-blind phase of this study; ○ Continues to meet inclusion criteria. In addition, patients must be 18 years and older.
Main exclusion criteria	A patient will be excluded from the double-blind phase of the study if any of the following criteria are met: • Known noncompliance with dialysis treatment that in the opinion of the investigator would impede completion or validity of the study; • Scheduled to receive a kidney transplant during the study; • New or change of treatment received for itch including antihistamines and corticosteroids (oral, IV, or topical) within 14 days prior to screening; • Received another investigational drug within 30 days prior to the start of screening or is planning to participate in another clinical study while enrolled in this study; • Has pruritus only during the dialysis session (by patient report); • Is receiving ongoing ultraviolet B and anticipates receiving such treatment during the study; • Participated in a previous clinical study with difelikefalin.

Trial name: KALM-2	NCT number: NCT03636269
	• A patient will be excluded from the open-label extension phase of the study if any of the additional key following criteria are met at the time of entry into the open-label extension phase: ○ Completed the double-blind phase of this study but exhibited adverse events during the course of the treatment period that may preclude continued exposure to the study drug; ○ Was noncompliant with protocol procedures during the double-blind phase of this study which is indicative of an inability to follow protocol procedures.
Intervention	Difelikefalin (IV administration), 0.5 mcg/kg after each dialysis session (3 times/week). N = 235.
Comparator(s)	Placebo (IV administration), after each dialysis session (3 times/week). N = 236.
Follow-up time	12 weeks of active treatment.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was proportion of participants achieving a ≥3-point improvement (reduction) in the weekly mean of daily 24-hour WI-NRS scores (week 12). Secondary endpoints include proportion of participants achieving a ≥4-point improvement (reduction) in the weekly mean of daily 24-hour WI-NRS scores (week 12), itch-related QoL (change from baseline in total Skindex-10 scale score, week 12), and itch-related QoL (change from baseline in 5-D itch scale score, week 12).
Method of analysis	Efficacy analyses were conducted in ITT population consisting of all randomised participants. In the primary analyses, *P* values were adjusted to account for planned interim analysis for sample size re-estimation. For the primary and secondary categorical endpoints, estimated proportions, OR, and *P* value are based on a logistic regression model with terms for treatment group, baseline WI-NRS score, region, use of anti-itch medication during the week prior to randomization, and the presence of specific medical conditions. Continuous endpoints were analysed by ANCOVA with treatment group as a fixed effect, and baseline score, region, and randomisation stratification as covariates. Missing data were imputed using multiple imputation under missing at random assumption.
Subgroup analyses	The primary efficacy endpoint was analyzed separately for interim analysis and post-interim analysis subjects, and by stratification factor, study region, and dialysis type. A descriptive analysis of the change in WI-NRS from baseline at Week 12 and by study site was also conducted, along with an analysis of the proportion of subjects achieving a ≥3-point improvement
Other relevant information	N/A

Abbreviations: ANCOVA = analysis of covariance; ESRD = end-stage renal disease; ITT = intention-to-treat; IV = intravenous; N/A = not applicable; OR = odds ratio; QoL = quality of life; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Sources: ClinicalTrials.gov, 2018 (63); Topf et al., 2022 (51).

Appendix B. Efficacy results per study

Results per study

Table 60: Results per KALM-1

Results of KALM-1 (NCT03422653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients achieving a ≥3-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12	Difelikefalin	189	82/157 (52.2)[Ω]	N/A	N/A	N/A	RR: 1.72	1.32–2.24	<0.001	Estimated percent, OR and P value used a logistic regression model with terms for treatment group, baseline WI-NRS score, use of anti-itch medication during the week prior to randomisation, and the presence of specific medical conditions. Missing values were imputed using multiple imputation under missing-at-random missing data assumption for interim subjects and post-interim subjects separately. P value is based on the Cui, Hung, Wang procedure. The	(60, 67)
	Placebo	189	51/165 (30.9)[Ω]								
Proportion of patients achieving a ≥3-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12	Difelikefalin	189	51.0* (42.9–58.9)	N/A	N/A	N/A	OR: 2.72	1.72–4.30	<0.001		(60, 67)
	Placebo	189	27.6* (20.2–36.6)								
Proportion of patients	Difelikefalin	189	64/157 (40.8)[Ω]	N/A	N/A	N/A	RR: 1.99	1.43–2.78	<0.001		(60, 67)

achieving a ≥4-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12	Placebo	189	35/165 (21.2)Ω							estimates only include scores on-treatment.	
Proportion of patients achieving a ≥4-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12	Difelikefalin	189	38.9* (29.8–48.7)	N/A	N/A	N/A	OR: 2.89	1.75–4.76	<0.001		(60, 67)
	Placebo	189	18.0* (12.1–26.0)								
LS mean change from baseline at week 12 in 5-D itch scale total score	Difelikefalin	189	–5.0 (-5.7, -4.4)	-1.3	-2.0, -0.5	<0.001	N/A	N/A	N/A	The change from baseline in total 5-D Itch Scale score at the end of week 12 was investigated using ANCOVA with fixed effects for treatment, with baseline score and the randomisation stratification variables as covariates. Missing values were imputed using multiple imputation under missing-at-random missing data assumption.	(67)
	Placebo	189	–3.7 (-4.4, -3.1)								

LS mean change from baseline at week 12 in Skindex-10 scale total score	Difelikefalin	189	–17.2 (-19.6, -14.7)	-5.1	-8.0, -2.3	<0.001	N/A	N/A	N/A	The change from baseline in total Skindex-10 scale score at the end of week 12 was investigated using ANCOVA with fixed effects for treatment, with baseline score and the randomisation stratification variables as covariates. Missing values were imputed using multiple imputation under missing-at-random missing data assumption.	(67)
	Placebo	189	–12.0 (-14.5, -9.6)								

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; RR = relative risk; LS = least-squares; N/A = not applicable; OR = odds ratio; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Note: The primary and secondary outcomes were evaluated using a prespecified hierarchical statistical testing procedure; the P value for each outcome was considered inferential if the preceding end point in the sequential testing procedure was statistically significant at a two-sided 0.05 significance level. ΩObserved, no./total no. (%). *LS mean in percentage.

Source: Fishbane et al. 2020; table S7 (60); KALM-1 double-blind CSR, 2020; table 13, 15, 16 and 17 (67),.

Table 61: Results per KALM-2

Results of KALM-2 (NCT03636269)											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients achieving a	Difelikefalin	237	95 (49.7) Ω	N/A	N/A	N/A	OR: 1.61	1.08–2.41	0.020	Combined analysis used the separate interim and	(55)

≥3-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12	Placebo	236	77 (37.2) Ω							post-interim results to generate an adjusted overall estimate and P value using the Cui, Hung, Wang methodology.	
Proportion of patients achieving a ≥3-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12	Difelikefalin	237	54.0* (43.9–63.9)	N/A	N/A	N/A	N/A	N/A	N/A	Estimated percentage, OR and P value used a logistic regression model with terms for treatment group, baseline WI-NRS score, region, use of anti-itch medication during the week prior to randomisation, and the presence of specific medical conditions. Missing values were imputed using multiple imputation under missing-at-random missing data assumption for interim subjects and post-interim subjects separately.	(55)
	Placebo	236	42.2* (32.5–52.5)								
Proportion of patients achieving a ≥4-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12	Difelikefalin	237	72 (37.7) Ω	N/A	N/A	N/A	OR: 1.77	1.14–2.74	0.010		(55)
	Placebo	236	52 (25.1) Ω								
Proportion of patients achieving a ≥4-point improvement in the weekly mean of the daily 24-hour WI-NRS scores at week 12	Difelikefalin	237	41.2 (33.0–50.0)	N/A	N/A	N/A	N/A	N/A	N/A		(55)
	Placebo	236	28.4 (21.3–36.7)								
LS mean change from baseline at week 12	Difelikefalin	237	–16.6 (-19.3, -14.0)	-1.8	-4.3, 0.8	0.171	N/A	N/A	N/A	Change from baseline in total Skindex 10 Scale score at the end of week 12	(55)

in Skindex-10 scale total score	Placebo	236	-14.8 (-17.4, -12.2)						for the ITT population were based on ANCOVA with fixed effects for treatment, with baseline score and the randomisation stratification variables as covariates. Missing values were imputed using multiple imputation under missing-at-random missing data assumption.	
LS mean change from baseline at week 12 in 5-D itch scale total score	Difelikefalin	237	–4.9 (-5.6, -4.2)	-1.1	-1.7, -0.4	0.002	N/A	N/A	Change from baseline in total 5-D Itch Scale score at the end of week 12 for the ITT population were based on ANCOVA with fixed effects for treatment, with baseline score and the randomisation stratification variables as covariates. Missing values were imputed using multiple imputation under missing-at-random missing data assumption..	(55)
	Placebo	236	–3.8 (-4.5, -3.1)							

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ITT = intention-to-treat; LH = Lawrence, Hung; LS = least-squares; N/A = not applicable; OR = odds ratio; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Note: Secondary efficacy endpoints were analysed in a hierarchical testing order. If an endpoint did not reach statistical significance, then each subsequent endpoint was not considered significant. ΩThe value in the parentheses is as percentage. Counts and percentages were based on non-missing data. *LS mean in percentage.

Source: KALM-2 double-blind CSR, 2020; table 13, 16, 20 and 21 (55).

Appendix C. Comparative analysis of efficacy

C.1 Methodology

The comparative analysis included in this submission is a pooled analysis of KALM-1 and KALM-2 evaluating difelikefalin's efficacy and the itch-related QoL overall and in subgroups (51). Pooled data from the KALM-1 and KALM-2 studies was analysed to obtain a combined estimate of the treatment effects of difelikefalin in HD participants with moderate to severe pruritus, including QoL endpoints.

Efficacy analyses were conducted in the ITT population from the pooled KALM-1 and KALM-2 studies, which consisted of all randomised participants. Differences between placebo and difelikefalin were analysed using a logistic regression model containing terms for the treatment group, baseline WI-NRS score, use of an anti-itch medication during the week before randomisation, presence of specific medical conditions, and geographic region. For the analysis of the proportions of participants who achieved ≥3-point or ≥4-point reductions in the weekly mean WI-NRS scores, missing weekly WI-NRS scores were imputed by multiple imputation under a missing-at-random assumption. Participants who reported <4 daily WI-NRS scores at week 12 or who discontinued treatment early were considered non-responders in the analysis of the complete WI-NRS response. Proportions of participants achieving a ≥5-point improvement in the 5-D Itch total score and a ≥15-point improvement in the Skindex-10 total score were analysed without imputation for missing values. Proportions of participants achieving a ≥5-point improvement in 5-D Itch total score are reported for the pooled population during the placebo-controlled, double-blind period (12 weeks) and the open-label extension period (up to 52 weeks) (51).

Continuous efficacy endpoints were analysed by a mixed model for repeated measures, with terms for treatment, visit, treatment-by-visit interaction, baseline score, use of an anti-itch medication during the week before randomisation, the presence of specific medical conditions, and geographic region. An unstructured covariance structure was applied to model the within-participant errors. Missing values were not imputed. The mean improvements from baseline in 5-D Itch total score are reported for the pooled population during the placebo-controlled, double-blind period (12 weeks) and the open-label extension period (up to 52 weeks) (51).

The subgroup analyses of ≥3-point and ≥4-point reductions from baseline in the weekly mean WI-NRS scores were performed using the same methodology as that employed for the full ITT population (51).

C.2 Results

Results from the main analyses are presented in Table 62.

Table 62: Comparative analysis of studies comparing difelikefalin to placebo for patients with moderate-to-severe pruritus

				Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**		
≥3-point reduction in WI-NRS scores, week 12	Difelikefalin	426	51.1%	OR: 1.93	1.44-2.57	< 0.001	Logistic regression with multiple imputation under a missing-at-random assumption.	No
	Placebo	425	35.2%					
≥4-point reduction in WI-NRS scores, week 12	Difelikefalin	426	38.7% (32.8%- 45.0%)*	N/A	N/A	< 0.001	Logistic regression with multiple imputation under a missing-at-random assumption.	No
	Placebo	425	23.4% (18.7%-28.8%)*					
≥15-point improve-ments in Skindex-10 total scores, week 12	Difelikefalin	426	55.5%	N/A	N/A	< 0.001	No imputation for missing values.	No
	Placebo	425	40.5%					
≥5-point improvements in 5-D Itch total scores, week 12	Difelikefalin	426	52.1%	N/A	N/A	0.01	No imputation for missing values.	Yes (5-D scores were used in the model)
	Placebo	425	42.3%					
LS mean change from baseline to week 12 in Skindex-10 total scores	Difelikefalin	426	−16.9 (−18.6 to −15.2)	N/A	N/A	0.001	Mixed model for repeated measures. An unstructured covariance structure was applied to model the within-participant errors. Missing values were not imputed.	No
	Placebo	425	−13.5 (−15.1 to −11.8)					

				Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**		
LS mean change from baseline to week 12 in 5-D Itch total scores	Difelikefalin	426	−4.9 (−5.4 to −4.5)	N/A	N/A	< 0.001	Mixed model for repeated measures. An unstructured covariance structure was applied to model the within-participant errors. Missing values were not imputed.	Yes (5-D scores were used in the model)
	Placebo	425	−3.7 (−4.1 to −3.3)					

Abbreviations: CI = confidence interval; LS = least squares; N/A = not applicable; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Notes: *LS mean.

Source: Topf et al. 2022 (51).

Subgroup analyses of the primary outcome, ≥3-point reduction in the weekly mean WI-NRS score at week 12, are presented in Figure 21. Similar numbers of participants in the difelikefalin and placebo groups were included in each subgroup based on age, race, geographic region, use of an anti-itch medication, the presence of specific medical conditions, and use of gabapentin or pregabalin. When achievement of ≥3-point reductions in the weekly mean WI-NRS scores at week 12 was evaluated in these subgroups, improvements in itch intensity favoured difelikefalin vs. placebo in all subgroups except for the group of participants who reported their race as “other” (i.e., not White or Black or African American; including those who identified as American Indian or Alaska native [n = 13], Asian [n = 45], native Hawaiian or other Pacific Islander [n = 10], unknown [n = 3], and other [n = 14]). Similar findings were observed in subgroup analyses that evaluated achievement of a ≥4-point reduction in the weekly mean WI-NRS score at week 12 Figure 22.

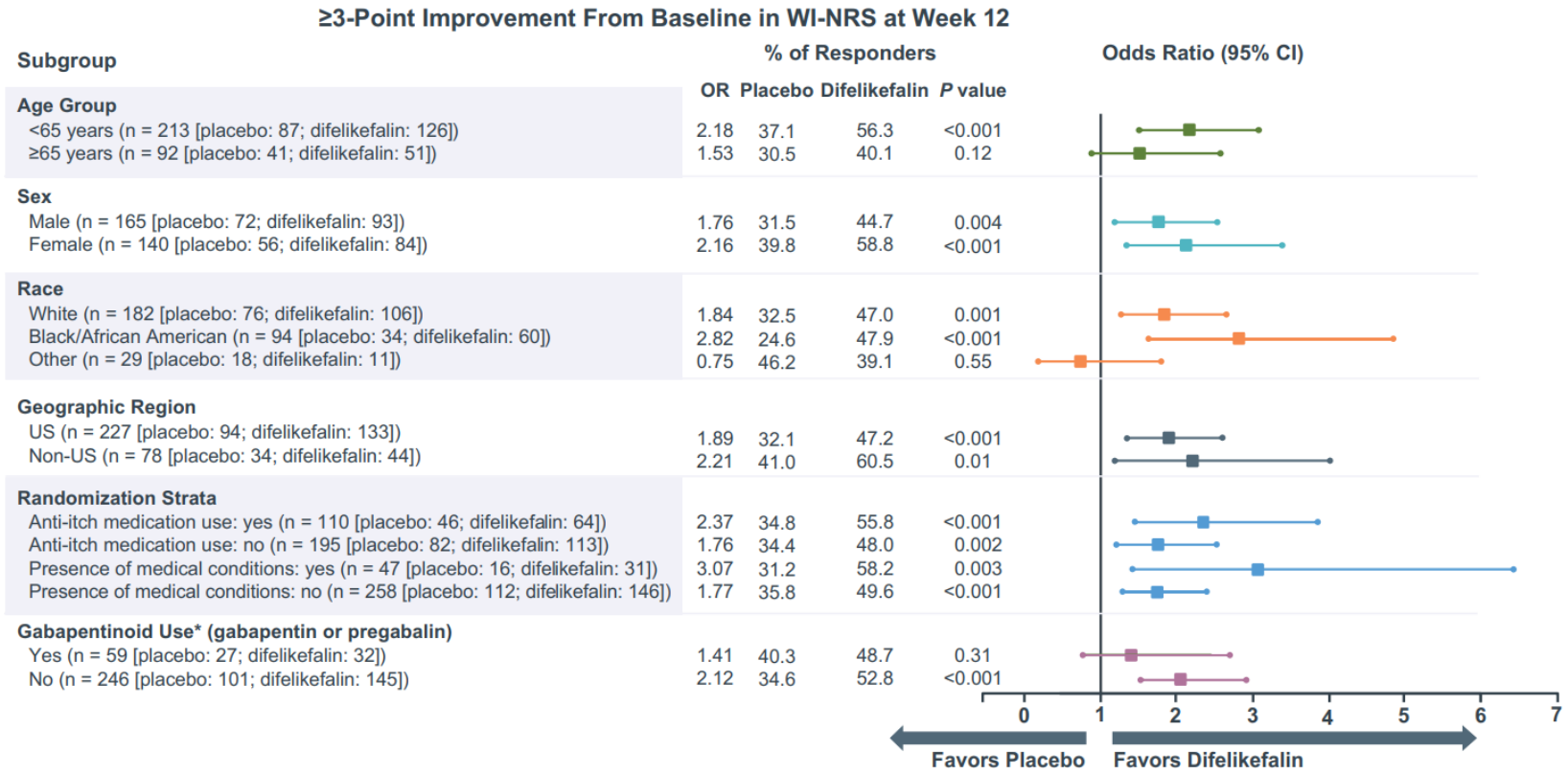


Figure 21 Subgroup analyses for ≥3-point WI-NRS responses at week 12

Abbreviations: CI = confidence interval; OR = odds ratio; US = United States; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Notes: *Prior gabapentinoid use values include participants who used gabapentin or pregabalin for any condition, including itch. Differences between placebo and difelikefalin with respect to proportions were analysed using a logistic regression model containing terms for the treatment group, baseline WI-NRS score, use of an anti-itch medication during the week before randomisation, presence of specific medical conditions, and geographic region. Missing weekly WI-NRS scores were imputed by multiple imputation under a missing-at-random assumption.

Source: Topf et al. 2022 (51).

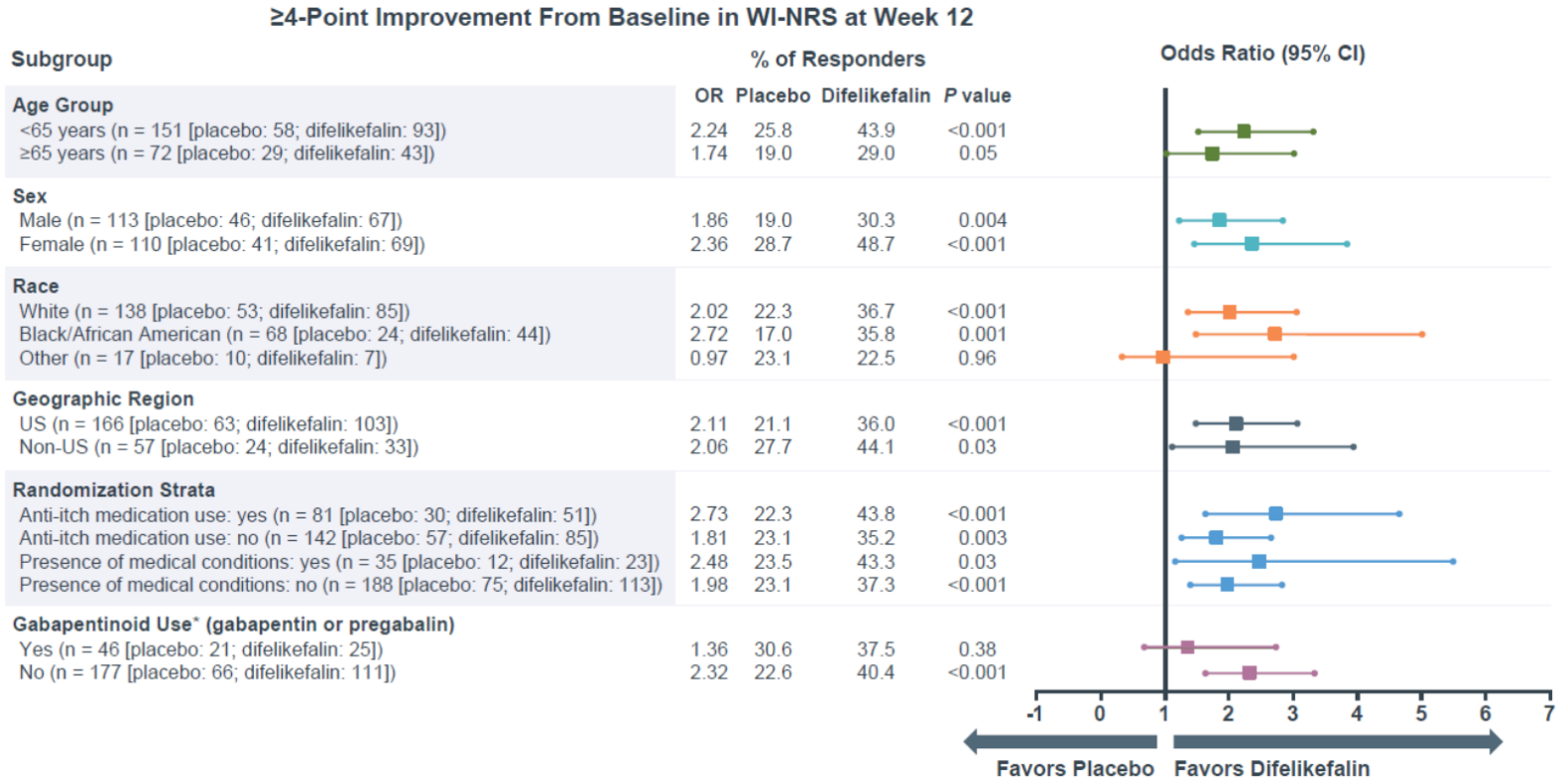


Figure 22 Subgroup analyses for ≥4-point WI-NRS responses at week 12

Abbreviations: CI = confidence interval; OR = odds ratio; US = United States; WI-NRS = Worst Itching Intensity Numerical Rating Scale.

Notes: *Prior gabapentinoid use values include participants who used gabapentin or pregabalin for any condition, including itch. Differences between placebo and difelikefalin with respect to proportions were analysed using a logistic regression model containing terms for the treatment group, baseline WI-NRS score, use of an anti-itch medication during the week before randomisation, presence of specific medical conditions, and region/study. Missing weekly WI-NRS scores were imputed by multiple imputation under a missing-at-random assumption.

Source: Topf et al. 2022 (51).

Appendix D. Extrapolation

D.1 Extrapolation of [effect measure 1]

Not applicable.

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

Appendix E. Serious adverse events

Table 63: Serious adverse events in KALM-1 (double-blind phase, double-blind safety population)

Adverse events, n (%)	Difelikefalin (N=189)	Placebo (N=188)
	Number (%) of patients with adverse events	Number (%) of patients with adverse events
Subjects with any event	49 (25.9)	41 (21.8)
Cardiac disorders	9 (4.8)	4 (2.1)

Adverse events, n (%)	Difelikefalin (N=189)	Placebo (N=188)
Atrial fibrillation	2 (1.1)	1 (0.5)
Angina pectoris	2 (1.1)	0
Bradycardia	0	2 (1.1)
Gastrointestinal disorders	8 (4.2)	8 (4.3)
Diarrhoea	2 (1.1)	1 (0.5)
Gastrointestinal haemorrhage	2 (1.1)	0
General disorders and administration site conditions	5 (2.6)	3 (1.6)
Chest pain	1 (0.5)	3 (1.6)
Asthenia	2 (1.1)	0
Hepatobiliary disorders	2 (1.1)	0
Cholelithiasis	2 (1.1)	0
Infections and infestations	15 (7.9)	15 (8.0)
Pneumonia	3 (1.6)	5 (2.7)
Sepsis	3 (1.6)	4 (2.1)
Septic shock	1 (0.5)	3 (1.6)
Investigations	1 (0.5)	4 (2.1)
Troponin increased	0	2 (1.1)
Metabolism and nutrition disorders	6 (3.2)	12 (6.4)
Hyperkalaemia	4 (2.1)	4 (2.1)
Fluid overload	2 (1.1)	4 (2.1)
Hyperglycaemia	1 (0.5)	2 (1.1)
Hypoglycaemia	0	2 (1.1)

Adverse events, n (%)	Difelikefalin (N=189)	Placebo (N=188)
Nervous system disorders	4 (2.1)	4 (2.1)
Metabolic encephalopathy	1 (0.5)	2 (1.1)
Psychiatric disorders	3 (1.6)	2 (1.1)
Mental status changes	2 (1.1)	2 (1.1)
Respiratory, thoracic and mediastinal disorders	10 (5.3)	7 (3.7)
Chronic obstructive pulmonary disease	3 (1.6)	1 (0.5)
Acute respiratory failure	1 (0.5)	2 (1.1)
Hypoxia	1 (0.5)	2 (1.1)
Respiratory failure	2 (1.1)	0
Vascular disorders	5 (2.6)	3 (1.6)
Hypotension	3 (1.6)	2 (1.1)

Notes: The double-blind safety population consists of randomised subjects who received at least 1 dose of double-blind study drug during the double-blind treatment period. These subjects were analysed according to the actual treatment received. This population was used to analyde all safety endpoints collected during the double-blind phase.

Source: KALM-1 DB CSR, 2020; table 26 (67).

Table 64: Serious adverse events in KALM-2 (double-blind phase, double-blind safety population)

Adverse events, n (%)	Difelikefalin (N=235)	Placebo (N=236)
	Number (%) of patients with adverse events	Number (%) of patients with adverse events
Subjects with any event	58 (24.7)	51 (21.6)
Blood and lymphatic system disorders	2 (0.9)	4 (1.7)
Anaemia	2 (0.9)	4 (1.7)
Cardiac disorders	12 (5.1)	5 (2.1)
Bradycardia	2 (0.9)	1 (0.4)
Cardiac failure congestive	1 (0.4)	2 (0.8)
Acute myocardial infarction	2 (0.9)	0
Cardiac failure	2 (0.9)	0
Gastrointestinal disorders	7 (3.0)	6 (2.5)
Diarrhoea	1 (0.4)	2 (0.8)
Gastrointestinal haemorrhage	2 (0.9)	1 (0.4)
Abdominal pain	2 (0.9)	0
General disorders and administration site conditions	10 (4.3)	1 (0.4)
Chest pain	8 (3.4)	1 (0.4)
Pyrexia	2 (0.9)	0
Infections and infestations	21 (8.9)	14 (5.9)
Sepsis	3 (1.3)	3 (1.3)
Cellulitis	2 (0.9)	1 (0.4)
Device related infection	2 (0.9)	1 (0.4)
Osteomyelitis	2 (0.9)	1 (0.4)
Urinary tract infection	2 (0.9)	1 (0.4)
Bronchitis	0	2 (0.8)

Adverse events, n (%)	Difelikefalin (N=235)	Placebo (N=236)
Influenza	2 (0.9)	0
Pneumonia	2 (0.9)	0
Injury, poisoning, and procedural complications	7 (3.0)	10 (4.2)
Arteriovenous fistula thrombosis	0	3 (1.3)
Fall	2 (0.9)	1 (0.4)
Vascular access malfunction	1 (0.4)	2 (0.8)
Metabolism and nutrition disorders	5 (2.1)	5 (2.1)
Hyperkalaemia	4 (1.7)	3 (1.3)
Fluid overload	0	2 (0.8)
Psychiatric disorders	4 (1.7)	0
Mental status changes	3 (1.3)	0
Respiratory, thoracic, and mediastinal disorders	10 (4.3)	5 (2.1)
Dyspnoea	4 (1.7)	2 (0.8)
Chronic obstructive pulmonary disease	2 (0.9)	1 (0.4)
Respiratory failure	2 (0.9)	0
Vascular disorders	6 (2.6)	13 (5.5)
Hypotension	0	5 (2.1)
Peripheral ischaemia	3 (1.3)	1 (0.4)
Deep vein thrombosis	2 (0.9)	1 (0.4)
Hypertension	0	3 (1.3)
Hypertensive crisis	0	2 (0.8)

The double-blind safety population consists of randomised subjects who received at least 1 dose of double-blind study drug during the double-blind treatment period. These subjects were analysed according to the actual treatment received. This population was used to analyde all safety endpoints collected during the double-blind phase.

Source: KALM-2 DB CSR, 2020; table 30 (55).

Table 65: Serious adverse events in KALM-2 (OLE phase, open-label safety population)

Adverse events, n (%)	Difelikefalin/difelikefalin (N=189)	Placebo/difelikefalin (N=210)
	Number (%) of patients with AEs	Number (%) of patients with AEs
Subjects with any event	61 (32.3)	69 (32.9)
Blood and lymphatic system disorders	4 (2.1)	2 (1.0)
Anaemia	4 (2.1)	2 (1.0)
Cardiac disorders	9 (4.8)	9 (4.3)
Acute myocardial infarction	3 (1.6)	2 (1.0)
Gastrointestinal disorders	8 (4.2)	14 (6.7)
Gastrointestinal haemorrhage	1 (0.5)	3 (1.4)
General disorders and administration site conditions	8 (4.2)	9 (4.3)
Chest pain	6 (3.2)	4 (1.9)
Asthenia	1 (0.5)	4 (1.9)
Infections and infestations	23 (12.2)	31 (14.8)
Pneumonia	11 (5.8)	11 (5.2)
Sepsis	8 (4.2)	6 (2.9)
Device related infection	1 (0.5)	3 (1.4)
Septic shock	3 (1.6)	1 (0.5)
Injury, poisoning and procedural complications	8 (4.2)	13 (6.2)
Arteriovenous fistula site complication	1 (0.5)	5 (2.4)
Arteriovenous fistula thrombosis	2 (1.1)	3 (1.4)
Metabolism and nutrition disorders	10 (5.3)	7 (3.3)
Fluid overload	5 (2.6)	1 (0.5)
Hyperkalaemia	2 (1.1)	2 (1.0)
Psychiatric disorders	3 (1.6)	4 (1.9)

Adverse events, n (%)	Difelikefalin/difelikefalin (N=189)	Placebo/difelikefalin (N=210)
Mental status changes	3 (1.6)	2 (1.0)
Respiratory, thoracic and mediastinal disorders	12 (6.3)	10 (4.8)
Respiratory failure	3 (1.6)	4 (1.9)
Chronic obstructive pulmonary disease	1 (0.5)	4 (1.9)
Dyspnoea	4 (2.1)	1 (0.5)
Vascular disorders	9 (4.8)	12 (5.7)
Hypotension	3 (1.6)	2 (1.0)

Abbreviations: AEs = adverse evets

Unless noted otherwise, the open-label safety population was used for all analyses in the OLE phase. This was defined as the group of subjects who received at least 1 dose of open-label study drug during the open-label treatment period. Subjects in the open-label safety population were analysed according to the sequence of treatments received in the double-blind treatment period and the open-label treatment period (i.e., placebo/difelikefalin and difelikefalin/difelikefalin), and all sequences pooled.

Source: KALM-2 OLE CSR, 2020; table 24 (68).

Appendix F. Health-related quality of life

All data is presented in the main submission. Please see section 10.

Appendix G. Probabilistic sensitivity analyses

[Show in Table 66 which data/assumptions (point estimate, and lower and upper bound) form the basis for the selected probability distributions used in the probabilistic analysis.]

Table 66: Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Baseline				
age	58.70	57.77	59.63	Normal
Proportion male	0.60	0.56	0.63	Beta
Proportion with diabetes	0.51	0.47	0.54	Beta
Proportion of patients with 2 years or less of haemodialysis	0.27	0.24	0.30	Beta
Proportion of patients older than 65 years	0.30	0.27	0.33	Beta
Baseline pruritus severity: None	0.00	0.00	0.00	No distribution
Baseline pruritus severity: Mild	0.00	0.00	0.00	No distribution
Baseline pruritus severity: Moderate	0.54	0.43	0.64	Beta
Baseline pruritus severity: Severe	0.36	0.29	0.43	Beta
Baseline pruritus severity: Overwhelming	0.11	0.09	0.13	Beta
Difelikefalin treatment discontinuation				
Probability of discontinuing difelikefalin treatment (any reason) - From week 0 to 12	0.13	0.10	0.15	Beta
Probability of discontinuing difelikefalin treatment (any reason) - From week 12 to 64	0.23	0.20	0.27	Beta
Severities among patients who stop between weeks 0 to 12 - None	0.07	0.06	0.08	Beta
Severities among patients who stop between weeks 0 to 12 - Mild	0.08	0.06	0.09	Beta
Severities among patients who stop between weeks 0 to 12 - Moderate	0.50	0.40	0.59	Beta
Severities among patients who stop between weeks 0 to 12 - Severe	0.30	0.24	0.36	Beta
Severities among patients who stop between weeks 0 to 12 - Overwhelming	0.06	0.05	0.07	Beta
Severities among patients who stop between weeks 12 to 64 - None	0.31	0.25	0.37	Beta

Severities among patients who stop between weeks 12 to 64 - Mild	0.28	0.23	0.34	Beta
Severities among patients who stop between weeks 12 to 64 - Moderate	0.34	0.27	0.40	Beta
Severities among patients who stop between weeks 12 to 64 - Severe	0.06	0.05	0.07	Beta
Severities among patients who stop between weeks 12 to 64 - Overwhelming	0.02	0.02	0.03	Beta
stopDFK64on	2.00	2.00	2.00	No distribution
Stop difelikefalin at week 64 due to lack of treatment effect - None at week 64	0.00	0.00	0.00	Normal
Stop difelikefalin at week 64 due to lack of treatment effect - Mild at week 64	0.00	0.00	0.00	Normal
Stop difelikefalin at week 64 due to lack of treatment effect - Moderate at week 64	0.53	0.29	0.77	Normal
Stop difelikefalin at week 64 due to lack of treatment effect - Severe at week 64	0.53	0.29	0.77	Normal
Stop difelikefalin at week 64 due to lack of treatment effect - Overwhelming at week 64	1.00	1.00	1.00	Normal
Proportion of patients receiving various treatment for pruritus				
% using anti-itch medication at baseline by pruritus severity: None	0.00	0.00	0.00	No distribution
% using anti-itch medication at baseline by pruritus severity: Mild	0.30	0.24	0.36	Beta
% using anti-itch medication at baseline by pruritus severity: Moderate	0.32	0.05	0.71	Beta
% using anti-itch medication at baseline by pruritus severity: Severe	0.41	0.09	0.78	Beta
% using anti-itch medication at baseline by pruritus severity: Overwhelming	0.51	0.16	0.86	Beta
% using antihistamine at baseline by pruritus severity: None	0.00	0.00	0.00	No distribution
% using antihistamine at baseline by pruritus severity: Mild	0.30	0.24	0.36	Beta
% using antihistamine at baseline by pruritus severity: Moderate	0.32	0.26	0.39	Beta
% using antihistamine at baseline by pruritus severity: Severe	0.41	0.33	0.49	Beta
% using antihistamine at baseline by pruritus severity: Overwhelming	0.51	0.41	0.61	Beta
% using topical corticosteroid at baseline by pruritus severity: None	0.00	0.00	0.00	No distribution
% using topical corticosteroid at baseline by pruritus severity: Mild	0.02	0.01	0.02	Beta

% using topical corticosteroid at baseline by pruritus severity: Moderate	0.02	0.02	0.02	Beta
% using topical corticosteroid at baseline by pruritus severity: Severe	0.02	0.02	0.03	Beta
% using topical corticosteroid at baseline by pruritus severity: Overwhelming	0.03	0.02	0.04	Beta
% using emollient at baseline by pruritus severity: None	0.00	0.00	0.00	No distribution
% using emollient at baseline by pruritus severity: Mild	1.00	1.00	1.00	No distribution
% using emollient at baseline by pruritus severity: Moderate	1.00	1.00	1.00	No distribution
% using emollient at baseline by pruritus severity: Severe	1.00	1.00	1.00	No distribution
% using emollient at baseline by pruritus severity: Overwhelming	1.00	1.00	1.00	No distribution
% using gabapentin at baseline by pruritus severity: None	0.00	0.00	0.00	No distribution
% using gabapentin at baseline by pruritus severity: Mild	0.10	0.08	0.12	Beta
% using gabapentin at baseline by pruritus severity: Moderate	0.10	0.08	0.12	Beta
% using gabapentin at baseline by pruritus severity: Severe	0.10	0.08	0.12	Beta
% using gabapentin at baseline by pruritus severity: Overwhelming	0.10	0.08	0.12	Beta
% using pregabalin at baseline by pruritus severity: None	0.00	0.00	0.00	No distribution
% using pregabalin at baseline by pruritus severity: Mild	0.10	0.08	0.12	Beta
% using pregabalin at baseline by pruritus severity: Moderate	0.10	0.08	0.12	Beta
% using pregabalin at baseline by pruritus severity: Severe	0.10	0.08	0.12	Beta
% using pregabalin at baseline by pruritus severity: Overwhelming	0.10	0.08	0.12	Beta
Dosage of antihistamine by pruritus severity: None	25.00	25.00	25.00	No distribution
Dosage of antihistamine by pruritus severity: Mild	25.00	25.00	25.00	No distribution
Dosage of antihistamine by pruritus severity: Moderate	25.00	25.00	25.00	No distribution
Dosage of antihistamine by pruritus severity: Severe	25.00	25.00	25.00	No distribution
Dosage of antihistamine by pruritus severity: Overwhelming	25.00	25.00	25.00	No distribution

Dosage of topical corticosteroid by pruritus severity: None	3.00	3.00	3.00	No distribution
Dosage of topical corticosteroid by pruritus severity: Mild	3.00	3.00	3.00	No distribution
Dosage of topical corticosteroid by pruritus severity: Moderate	3.00	3.00	3.00	No distribution
Dosage of topical corticosteroid by pruritus severity: Severe	3.00	3.00	3.00	No distribution
Dosage of topical corticosteroid by pruritus severity: Overwhelming	3.00	3.00	3.00	No distribution
Dosage of emollient by pruritus severity: None	5.00	5.00	5.00	No distribution
Dosage of emollient by pruritus severity: Mild	5.00	5.00	5.00	No distribution
Dosage of emollient by pruritus severity: Moderate	5.00	5.00	5.00	No distribution
Dosage of emollient by pruritus severity: Severe	5.00	5.00	5.00	No distribution
Dosage of emollient by pruritus severity: Overwhelming	5.00	5.00	5.00	No distribution
Dosage of gabapentin by pruritus severity: None	300.00	300.00	300.00	No distribution
Dosage of gabapentin by pruritus severity: Mild	300.00	300.00	300.00	No distribution
Dosage of gabapentin by pruritus severity: Moderate	300.00	300.00	300.00	No distribution
Dosage of gabapentin by pruritus severity: Severe	300.00	300.00	300.00	No distribution
Dosage of gabapentin/ by pruritus severity: Overwhelming	300.00	300.00	300.00	No distribution
Dosage of pregabalin by pruritus severity: None	25.00	25.00	25.00	No distribution
Dosage of pregabalin by pruritus severity: Mild	25.00	25.00	25.00	No distribution
Dosage of pregabalin by pruritus severity: Moderate	25.00	25.00	25.00	No distribution
Dosage of pregabalin by pruritus severity: Severe	25.00	25.00	25.00	No distribution
Dosage of pregabalin by pruritus severity: Overwhelming	25.00	25.00	25.00	No distribution
% treated, pruritus severence none: ESA	0.89	0.89	0.90	Beta
% treated, pruritus severence none: IV Iron	0.73	0.72	0.74	Beta
% treated, pruritus severence none: Primary phosphate binder	0.76	0.76	0.77	Beta

% treated, pruritus severence none: Second phosphate binder	0.08	0.08	0.09	Beta
% treated, pruritus severence mild: ESA	0.89	0.89	0.90	Beta
% treated, pruritus severence mild: IV Iron	0.73	0.72	0.73	Beta
% treated, pruritus severence mild: Primary phosphate binder	0.79	0.78	0.79	Beta
% treated, pruritus severence mild: Second phosphate binder	0.09	0.08	0.09	Beta
% treated, pruritus severence moderate:ESA	0.89	0.89	0.90	Beta
% treated, pruritus severence moderate:IV Iron	0.73	0.72	0.73	Beta
% treated, pruritus severence moderate:Primary phosphate binder	0.81	0.80	0.81	Beta
% treated, pruritus severence moderate:Second phosphate binder	0.10	0.09	0.10	Beta
% treated, pruritus severence severe:ESA	0.89	0.89	0.90	Beta
% treated, pruritus severence severe:IV Iron	0.74	0.73	0.74	Beta
% treated, pruritus severence severe:Primary phosphate binder	0.81	0.80	0.82	Beta
% treated, pruritus severence severe:Second phosphate binder	0.10	0.10	0.11	Beta
% treated, pruritus severence overwhelming:ESA	0.90	0.89	0.90	Beta
% treated, pruritus severence overwhelming:IV Iron	0.73	0.73	0.74	Beta
% treated, pruritus severence overwhelming:Primary phosphate binder	0.82	0.81	0.82	Beta
% treated, pruritus severence overwhelming:Second phosphate binder	0.10	0.10	0.11	Beta
Dosage, pruritus severence none: ESA	53397.1	53397.1	53397.1	No distribution
Dosage, pruritus severence mild: IV Iron	237.2	237.2	237.2	No distribution
Dosage, pruritus severence mild: Primary phosphate binder	1200.0	1200.0	1200.0	No distribution
Dosage, pruritus severence mild: Second phosphate binder	2400.0	2400.0	2400.0	No distribution
Dosage, pruritus severence mild: ESA	55061.4	55061.4	55061.4	No distribution
Dosage, pruritus severence moderate:IV Iron	236.4	236.4	236.4	No distribution
Dosage, pruritus severence moderate:Primary phosphate binder	1200.0	1200.0	1200.0	No distribution
Dosage, pruritus severence moderate:Second phosphate binder	2400.0	2400.0	2400.0	No distribution
Dosage, pruritus severence moderate:ESA	56200.3	56200.3	56200.3	No distribution

Dosage, pruritus severence severe:IV Iron	238.1	238.1	238.1	No distribution
Dosage, pruritus severence severe:Primary phosphate binder	1200.0	1200.0	1200.0	No distribution
Dosage, pruritus severence severe:Second phosphate binder	2400.0	2400.0	2400.0	No distribution
Dosage, pruritus severence severe:ESA	59394.1	59394.1	59394.1	No distribution
Dosage, pruritus severence overwhelming:IV Iron	241.3	241.3	241.3	No distribution
Dosage, pruritus severence overwhelming:Primary phosphate binder	1200.0	1200.0	1200.0	No distribution
Dosage, pruritus severence overwhelming:Second phosphate binder	2400.0	2400.0	2400.0	No distribution
Dosage, pruritus severence overwhelming:ESA	63405.4	63405.4	63405.4	No distribution
Dosage, pruritus severence overwhelming:IV Iron	247.6	247.6	247.6	No distribution
Dosage, pruritus severence overwhelming:Primary phosphate binder	1200.0	1200.0	1200.0	No distribution
Dosage, pruritus severence overwhelming:Second phosphate binder	2400.0	2400.0	2400.0	No distribution
Costs & resource use				
Difelikefalin Cost per vial	252.88	252.88	252.88	No distribution
Difelikefalin Discount / tendering	0.00	0.00	0.00	No distribution
Difelikefalin Administrations per cycle (week)	3.00	3.00	3.00	No distribution
ESA Strength	10000.00	10000.00	10000.00	No distribution
IV Iron Strength	20.00	20.00	20.00	No distribution
Primary phosphate binder (calcium carbonate + vitamin D) Strength	400.00	400.00	400.00	No distribution
Second phosphate binder (sevelamer) Strength	800.00	800.00	800.00	No distribution
ESA Cost per package	5700.00	5700.00	5700.00	No distribution
IV Iron Cost per package	745.00	745.00	745.00	No distribution
Primary phosphate binder (calcium carbonate + vitamin D) Cost per package	110.50	110.50	110.50	No distribution
Second phosphate binder (sevelamer) Cost per package	1240.00	1240.00	1240.00	No distribution

ESA Package size	6.00	6.00	6.00	No distribution
IV Iron Package size	25.00	25.00	25.00	No distribution
Primary phosphate binder (calcium carbonate + vitamin D) Package size	240.00	240.00	240.00	No distribution
Second phosphate binder (sevelamer) Package size	180.00	180.00	180.00	No distribution
Antihistamine Strength	25.00	25.00	25.00	No distribution
Topical corticosteroid Strength	1.00	1.00	1.00	No distribution
Emollient Strength	1.00	1.00	1.00	No distribution
Gabapentin Strength	300.00	300.00	300.00	No distribution
Pregabalin Strength	25.00	25.00	25.00	No distribution
Antihistamine Cost per package	21.80	21.80	21.80	No distribution
Topical corticosteroid Cost per package	34.90	34.90	34.90	No distribution
Emollient Cost per package	83.68	83.68	83.68	No distribution
Gabapentin Cost per package	14.16	14.16	14.16	No distribution
Pregabalin Cost per package	11.50	11.50	11.50	No distribution
Antihistamine Package size	100.00	100.00	100.00	No distribution
Topical corticosteroid Package size	50.00	50.00	50.00	No distribution
Emollient Package size	30.00	30.00	30.00	No distribution
Gabapentin Package size	100.00	100.00	100.00	No distribution
Pregabalin Package size	60.00	60.00	60.00	No distribution
Unit Cost Dialysis visit	3078.00	2504.38	3709.88	Gamma
Unit Cost Periods of hospitalization	35456.00	28848.42	42734.74	Gamma
Unit Cost Dermatologist's office visits	1634.00	1329.49	1969.44	Gamma
Unit Cost UV light therapy visits	1634.00	1329.49	1969.44	Gamma
Unit Cost General practitioner visits	153.61	124.98	185.14	Gamma

Dialysis visit None	150.80	121.24	180.36	Normal
Periods of hospitalization None	6.00	4.82	7.18	Normal
Dermatologist's office visits None	0.60	0.48	0.72	Normal
UV light therapy visits None	0.00	0.00	0.00	No distribution
General practitioner visits None	2.40	1.93	2.87	Normal
Dialysis visit Mild	150.80	121.24	180.36	Normal
Periods of hospitalization Mild	6.00	4.82	7.18	Normal
Dermatologist's office visits Mild	0.60	0.48	0.72	Normal
UV light therapy visits Mild	0.00	0.00	0.00	No distribution
General practitioner visits Mild	2.40	1.93	2.87	Normal
Dialysis visit Moderate	156.00	125.42	186.58	Normal
Periods of hospitalization Moderate	6.00	4.82	7.18	Normal
Dermatologist's office visits Moderate	1.38	1.11	1.65	Normal
UV light therapy visits Moderate	0.00	0.00	0.00	No distribution
General practitioner visits Moderate	3.00	2.41	3.59	Normal
Dialysis visit Severe	158.60	127.51	189.69	Normal
Periods of hospitalization Severe	12.00	9.65	14.35	Normal
Dermatologist's office visits Severe	4.20	3.38	5.02	Normal
UV light therapy visits Severe	0.12	0.10	0.14	Normal
General practitioner visits Severe	3.00	2.41	3.59	Normal
Dialysis visit Overwhelming	158.60	127.51	189.69	Normal
Periods of hospitalization Overwhelming	12.00	9.65	14.35	Normal
Dermatologist's office visits Overwhelming	4.80	3.86	5.74	Normal
UV light therapy visits Overwhelming	0.24	0.19	0.29	Normal
General practitioner visits Overwhelming	3.00	2.41	3.59	Normal
Renal transplant mean cost: Once off	271244.00	220694.94	326927.54	Gamma
Cost medication renal transplant	52480.6	42700.3	63254.3	Gamma
Periods of hospitalization Renal transplant patients None	6.00	4.82	7.18	Normal
Dermatologist's office visits Renal transplant patients None	2.00	1.61	2.39	Normal
General practitioner visits Renal transplant patients None	1.20	0.96	1.44	Normal
Periods of hospitalization Renal transplant patients Mild	6.00	4.82	7.18	Normal

Dermatologist's office visits Renal transplant patients Mild	2.00	1.61	2.39	Normal
General practitioner visits Renal transplant patients Mild	1.20	0.96	1.44	Normal
Periods of hospitalization Renal transplant patients Moderate	6.00	4.82	7.18	Normal
Dermatologist's office visits Renal transplant patients Moderate	2.00	1.61	2.39	Normal
General practitioner visits Renal transplant patients Moderate	3.00	2.41	3.59	Normal
Periods of hospitalization Renal transplant patients Severe	12.00	9.65	14.35	Normal
Dermatologist's office visits Renal transplant patients Severe	2.00	1.61	2.39	Normal
General practitioner visits Renal transplant patients Severe	4.80	3.86	5.74	Normal
Periods of hospitalization Renal transplant patients Overwhelming	12.00	9.65	14.35	Normal
Dermatologist's office visits Renal transplant patients Overwhelming	2.00	1.61	2.39	Normal
General practitioner visits Renal transplant patients Overwhelming	6.00	4.82	7.18	Normal
Cost per patient hour	203.00	165.17	244.67	Gamma
Transport cost per visit	149.20	121.40	179.83	Gamma
Time use per visit Dialysis visit	4.00	3.22	4.78	Normal
Time use per visit Difelikefalin administration	0.17	0.13	0.20	Normal
Time use per visit Hospitalisation	24.00	19.30	28.70	Normal
Time use per visit Other outpatient visits	0.50	0.40	0.60	Normal
Utilities				
Hemodialysis patients utility: None	0.69	0.55	0.81	Beta
Hemodialysis patients utility: Mild	0.66	0.53	0.78	Beta
Hemodialysis patients utility: Moderate	0.55	0.44	0.66	Beta
Hemodialysis patients utility: Severe	0.43	0.34	0.51	Beta
Hemodialysis patients utility: Overwhelming	0.38	0.30	0.45	Beta
Utility ratio: RTR vs HD multiple	1.16	1.16	1.16	No distribution
Renal transplant recipients utility: None	0.80	0.63	0.93	Beta
Renal transplant recipients utility: Mild	0.77	0.60	0.90	Beta
Renal transplant recipients utility: Moderate	0.64	0.51	0.76	Beta
Renal transplant recipients utility: Severe	0.50	0.40	0.59	Beta
Renal transplant recipients utility: Overwhelming	0.44	0.35	0.52	Beta
Renal transplants				

Annual transplant rate	0.06	0.05	0.07	Beta
Rate per age group: Younger than 20	0.56	0.45	0.67	Beta
Rate per age group: 20-34	0.23	0.19	0.28	Beta
Rate per age group: 35-44	0.15	0.12	0.18	Beta
Rate per age group: 45-54	0.11	0.09	0.13	Beta
Rate per age group: 55-64	0.09	0.07	0.11	Beta
Rate per age group: 65-74	0.07	0.05	0.08	Beta
Rate per age group: Older than 75	0.02	0.01	0.02	Beta
Pruritus severity after the transplant: None	0.74	0.58	0.87	Beta
Pruritus severity after the transplant: Mild	0.03	0.02	0.03	Beta
Pruritus severity after the transplant: Moderate	0.23	0.18	0.27	Beta
Pruritus severity after the transplant: Severe	0.01	0.01	0.02	Beta
Pruritus severity after the transplant: Overwhelming	0.00	0.00	0.00	No distribution
Mortality				
Patients receiving renal replacement therapy - Annual mortality rate	0.21	0.20	0.22	Beta
Central hemodialysis patient characteristics mortality risks Rate ratio (RR) Diabetes	1.55	1.45	1.66	Lognormal
Average age Age distribution - Patients receiving central hemodialysis (2020)	63.86	63.45	64.27	Normal
Transplanted mortality rate 5-year mortality	0.08	0.05	0.11	Beta
Renal transplant patient characteristics mortality risks Rate ratio (RR) Diabetes	1.88	1.50	2.36	Lognormal
Average age Age distribution - Patients who have received renal transplant (2020)	51.48	41.39	61.57	Normal
Survival and mortality among patients on any renal replacement therapy by age group - 20-44	0.02	0.02	0.02	Beta
Survival and mortality among patients on any renal replacement therapy by age group - 45-64	0.07	0.07	0.07	Beta
Survival and mortality among patients on any renal replacement therapy by age group - 65-74	0.16	0.16	0.16	Beta
Survival and mortality among patients on any renal replacement therapy by age group - 75 or older	0.29	0.29	0.29	Beta
Hazard ratios for pruritus severity - Hemodialysis patients - None	1.00	0.82	1.21	Lognormal
Hazard ratios for pruritus severity - Hemodialysis patients - Mild	1.00	0.82	1.21	Lognormal
Hazard ratios for pruritus severity - Hemodialysis patients - Moderate	1.00	0.82	1.21	Lognormal
Hazard ratios for pruritus severity - Hemodialysis patients - Severe	1.00	0.82	1.21	Lognormal

Hazard ratios for pruritus severity - Hemodialysis patients - Overwhelming	1.00	0.82	1.21	Lognor-mal
Hazard ratios for pruritus severity - transplanted patients - None	1.00	0.82	1.21	Lognor-mal
Hazard ratios for pruritus severity - transplanted patients - Mild	1.00	0.82	1.21	Lognor-mal
Hazard ratios for pruritus severity - transplanted patients - Moderate	1.00	0.82	1.21	Lognor-mal
Hazard ratios for pruritus severity - transplanted patients - Severe	1.00	0.82	1.21	Lognor-mal
Hazard ratios for pruritus severity - transplanted patients - Overwhelming	1.00	0.82	1.21	Lognor-mal

Appendix H. Literature searches for the clinical assessment

Not applicable

Appendix I. Literature searches for health-related quality of life

Not applicable

Appendix J. Literature searchers for input to the health economic model

Not applicable

Appendix K. Treatment proportions and dosing of SoC

The proportions and dosing for treatment related to dialysis are presented in Table 67. All transplanted patients are expected to receive immunosuppressive treatments. The expected doses are presented in Table 68.

Table 67: Proportions and dosing for treatment related to dialysis

Proportions	None	Mild	Moderate	Severe	Overwhelming
ESA	89.16%	89.16%	89.21%	89.49%	89.81%
IV Iron	72.80%	72.69%	72.69%	73.71%	73.22%
Primary phosphate binder (calcium carbonate + vitamin D)	76.33%	78.64%	80.51%	80.94%	81.74%
Second phosphate binder (sevelamer)	8.11%	8.58%	9.93%	10.46%	10.28%
Source: Ramakrishnan et al. 2013, Table 7 (patient-months with use) (35)					
Treatment dosing	**None**	**Mild**	**Moderate**	**Severe**	**Overwhelming**
ESA (monthly dose)[1]	53397.13 IU	55061.39 IU	56200.29 IU	59394.10 IU	63405.41 IU
IV Iron (monthly dose)[1]	237.19 mg	236.42 mg	238.10 mg	241.30 mg	247.62 mg
Primary phosphate binder (daily dose)[2]	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg
Second phosphate binder (daily dose)[2]	2400 mg	2400 mg	2400 mg	2400 mg	2400 mg
Sources: 1) Ramakrishnan et al. 2013, Table 7 (35). 2) Region Nordjyllands Kronisk Nyresvigt – Kalk/fosfor-balance og relaterede emner (3 units per day for both) (72)					

Table 68: Dosing for transplanted patients

Treatment	Daily dose
Tacrolimus	17 mg
Mycophenolate	1000 mg
Prednisolone	5 mg

Sources: Drug dosing for Tacrolimus 0.2 mg per Kg based SMPC. Average patient weight based on KALM-1 and 2 studies (Topf et al. 2022) (51)
Drug dosing for mycophenolate 500mg 2 time daily based on Region Nordjylland - Nyretransplantation – Immunosuppression (73)
Drug dosing for prednisoline 5mg daily based on Region Nordjylland - Nyretransplantation – Immunosuppression (73)

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