Medicinrådet

# Bilag til Medicinrådets anbefaling vedr. maribavir til behandling af refraktær CMV-infektion (med eller uden resistens)

*Hos patienter, der har modtaget en hæmatopoietisk stamcelletransplantation eller en organtransplantation*

*Vers. 1.0*

# Bilagsoversigt

1. Ansøgers notat til Rådet vedr. maribavir
2. Forhandlingsnotat fra Amgros vedr. maribavir
3. Ansøgers endelige ansøgning vedr. maribavir

Takeda Pharma A/S takker for et rigtig godt samarbejde med sekretariatet. Vi har nøje gennemgået vurderingsrapporten og vil gerne præcisere fire væsentlige elementer for at nuancere beslutningsgrundlaget:

1. Studiets design og specifikt at det er ublindet
2. Studiepopulation versus den danske population
3. Vurderingen af bivirkninger
4. Dokumentation for QALY-gevinst

**1. Studiedesign og effekt:**

SOLSTICE-studiet er et globalt multicenter, aktivt kontrolleret, randomiseret, head-to-head fase 3 studie, der inkluderer alle de lægemidler, som anvendes i dansk klinisk praksis til behandling af R/R CMV. På trods af heterogeniteten og kompleksiteten i patientpopulationen er SOLSTICE-studiet det største studie, der til dato er udført for patienter med R/R CMV.

I vurderingsrapporten nævnes det, at der kan være bias forbundet med, at studiet er ublindet. Vi ønsker, at påpege, at både FDA og EMA var involverede i designet af studiet og fandt, at et ublindet studiedesign var mest hensigtsmæssigt. Dette skyldtes bl.a. de inkluderede lægemidlers meget forskellige bivirkningsprofiler samt administrationsformer. Af etiske hensyn skal lægemidlernes meget forskellige bivirkningsprofiler kunne inkluderes i behandlingsvalget i komparatorarmen.

Selvom studiet var ublindet, blev patienterne randomiseret. Det åbne studiedesign tillod den behandlende læge at tilpasse behandlingen til den individuelle patient. Vi mener, at dette korrekt afspejler dansk klinisk praksis, hvor behandlingen skal tilpasses den individuelle patient for at opnå optimal effekt. Begge behandlingsarme, både maribavir og IAT, blev evalueret under de samme forhold i studiet.

**2. Studiepopulation vs. dansk population:**

I vurderingsrapporten italesættes potentielle forskelle mellem behandlingslængden i den danske R/R CMV-population og patientpopulationen som indgår i SOLSTICE-studiet.

IAT-behandling gives i længere tid i dansk klinisk praksis end i SOLSTICE-studiet "[...] *hvilket kan betyde, at der er færre patienter, som opnår respons af behandlingen, end i dansk klinisk praksis*" (Vurderingsrapporten s. 5). Jævnfør figur 4 i maribavir ansøgningen udgik kun 13.7% af patienterne i IAT-armen grundet manglende effekt, mens størstedelen udgik på grund af bivirkninger (30.8%). Derfor mener vi ikke, at Medicinrådets konklusion i vurderingsrapporten er retvisende.

Vurderingsrapporten berører også, at tiden fra transplantation til opdaget R/R CMV-infektion er længere i SOLSTICE-studiet end i dansk klinisk praksis. Det nævnes, at refraktær CMV-infektion i Danmark opdages ca. 110-150 dage efter transplantationen er foretaget. Dette er korrekt for de stamcelletransplanterede patienter, men ikke for de organtransplanterede patienter (ca. 60% af patienterne i SOLSTICE-studiet), idet tiden fra transplantation er væsentlig længere for de organtransplanteret patienter. Jf. Takedas samtaler med danske eksperter forventes tiden fra transplantation til opdaget CMV-infektion at være >200 dage for organtransplanterede patienter.

Vi mener således ikke, at de usikkerheder, som er fremhævet i Medicinrådets vurderingsrapport vedr. studiedesign og populationsforskelle, medfører, at resultaterne fra SOLSTICE-studiet bliver biased eller på anden måde ikke er direkte henførbare til en dansk patientpopulation. Vi er derfor ikke enige i Medicinrådets vurdering af, at maribavirs effekt ikke er påviseligt bedre end komparatorerne.

### 3. Bivirkninger:

Vi mener, at bivirkningsprofilerne ved de enkelte lægemidler er af særlig stor betydning for den pågældende patientgruppe. De bør derfor også tillægges betragtelig værdi i vurderingen.

Medicinrådet anerkender, at nogle af komparatorerne i dansk klinisk praksis har flere bivirkninger, end der er påvist for den gennemsnitlige patientgruppe i SOLSTICE-studiet (neutropeni og nyrepåvirkning). Alligevel ekskluderes bivirkningsomkostningerne til akut nyreskade og neutropeni i vurderingen (tabel 3-2 s. 54 i vurderingsrapporten).

For at mindske bivirkningsrisiko, behandlingssvigt eller behandlingsskift ender behandlingen af R/R CMV med komparatorerne ofte i dosisreduktion og indlæggelse. Disse faktorer kan føre til suboptimal behandling, hvorfor vi mener, at maribavir repræsenterer en mere effektiv behandling for patienter med R/R CMV, samtidig med at omkostningerne forbundet med komplikationer og suboptimal behandling minimeres. Resultaterne fra SOLSTICE viser dette:

- Hændelsesraten for alvorlige uønskede hændelser er ens for maribavir og IAT-armen på trods af, at den gennemsnitlige behandlingstid for maribavir er 16,5 dage længere sammenlignet med IAT-armen.
- Ift. alvorlige uønskede hændelser, som vurderes at være forårsaget af behandlingen, er forekomsten 5,1% i maribavir-armen sammenlignet med 14,7% i IAT-armen, selv med den længere behandlingsvarighed.
- Kun 6,4% af patienterne fra maribavir-armen udgik fra SOLSTICE-studiet på grund af bivirkninger, og patienter, som udgik fra studiet grundet *treatment-emergent adverse events* var 13,2% i maribavir-armen og 31,9% i IAT-armen.

### 4. QALY som effekt mål:

Sammenlignet med IAT-behandling er der en lille, men ikke ubetydelig QALY-gevinst ved maribavir. Vi er forstående overfor Medicinrådets vurdering af, at forskellen mellem de to behandlinger ift. QALY kan være svær at kvantificere. Vi ønsker at understrege, at patienter, som modtager behandling for CMV-infektion eller sygdom, er multisyge patienter. Patienternes underliggende sygdom, som har ført til transplantation, må forventeligt fylde mere i patientens bevidsthed, end CMV-infektionen, som i mange patienters tilfælde aldrig vil føre til symptomer. Vi mener, maribavir skal vurderes på sine kliniske egenskaber i form af CMV-clearence rate og bivirkningsprofil, som er signifikant bedre end lægemidlerne, som på nuværende tidspunkt bliver anvendt i dansk klinisk praksis. Det vil være fejlbehæftet at konkludere, at maribavir ikke bidrager med klinisk relevant og bedre effekt end sine komparatorer.

Vi ser frem til resultatet af rådsmødet d. 21. juni 2023.

Med venlig hilsen Takeda

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

24.05.2023
MGK/CAF

# Forhandlingsnotat

| | |
|---|---|
| Dato for behandling i Medicinrådet | 21.06.2023 |
| Leverandør | Takeda |
| Lægemiddel | Livtencity (maribavir) |
| Ansøgt indikation | Behandling af infektion og/eller sygdom med cytomegalovirus (CMV), der er refraktær (med eller uden resistens) mod en eller flere tidligere behandlinger, herunder ganciclovir, valganciclovir, cidofovir eller foscarnet hos voksne patienter, som har gennemgået en hæmatopoietisk stamcelletransplantation (HSCT) eller organtransplantation (SOT). |
| Nyt lægemiddel / indikationsudvidelse | Nyt lægemiddel |

## Prisinformation

Amgros har forhandlet følgende pris på Livtencity (maribavir):

*Tabel 1: Forhandlingsresultat*

| Lægemiddel | Styrke | Pakningsstørrelse | AIP (DKK) | Forhandlet SAIP (DKK) | Rabatprocent ift. AIP |
|---|---|---|---|---|---|
| Livtencity | 200 mg | 56 stk. | 83.881,69 | [redacted] | [redacted] |

Prisen er ikke betinget af Medicinrådets anbefaling.

## Aftaleforhold

[redacted]

## Konkurrencesituationen

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler inkluderet i Medicinrådets vurderingsrapport. Udregningerne er lavet for 7,5 ugers behandling, som er den gennemsnitlige behandlingslængde jf. Medicinrådets vurderingsrapport.

[redacted]

*Tabel 2: Sammenligning af lægemiddeludgifter pr. patient*

| Lægemiddel | Styrke | Pakningsstørrelse | Dosering | Pris pr. pakning (SAIP, DKK) | Lægemiddeludgift for 7,5 ugers behandling (SAIP, DKK) |
|---|---|---|---|---|---|
| Livtencity | 200 mg | 56 stk. | 800 mg PO dagligt | [redacted] | [redacted] |
| Ganciclovir | 500 mg | 5 stk. | 6 mg/kg* IV én gang dagligt, 5 gange om ugen | [redacted] | [redacted] |
| Valganciclovir | 450 mg | 60 stk. | 900 mg PO dagligt | [redacted] | [redacted] |
| Foscarnet | 24 mg/ml | 250 ml. | 60 mg/kg IV* 2 gange dagligt | [redacted] | [redacted] |
| Cidofovir | 75 mg/ml | 5 ml. | 5 mg/kg IV hver 2. uge | [redacted] | [redacted] |

*gennemsnitsvægt på 74,8 kg

## Status fra andre lande

*Tabel 3: Status fra andre lande*

| Land | Status | Link |
|---|---|---|
| **Norge** | Under vurdering | Link til status |
| **Sverige** | Ikke anbefalet | Link til anbefaling |
| **England** | Anbefalet | Link til anbefaling |

## Konklusion

[redacted]

Medicinrådet

# Application for the assessment of clinically added value of maribavir (Livtencity®) for treatment of refractory and/or resistant cytomegalovirus infection after solid organ- or allogeneic hematopoietic stem cell transplantation



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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| Color scheme for text highlighting | |
|---|---|
| **Color of highlighted text** | **Definition of highlighted text** |
| | **Confidential information** |



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# 1. Basic information

| Contact information | |
|---|---|
| **Name** | **Sigurd Hilborg** |
| Title | Value Demonstration Lead |
| Phone number | +4560944922 |
| E-mail | sigurd.hilborg@takeda.com |
| **Name** | **Birgitte Strøyer** |
| Title | Market Access Lead |
| Phone number | +4520805868 |
| E-mail | birgitte.stroyer@takeda.com |
| **Name** | **Mehmet Coskun** |
| Title | Medical Advisor |
| Phone number | +4523493015 |
| E-mail | mehmet.coskun@takeda.com |



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| Overview of the pharmaceutical | |
|---|---|
| **Proprietary name** | Livtencity® |
| **Generic name** | Maribavir |
| **Marketing authorization holder in Denmark** | Takeda Pharma A/S |
| **ATC code** | J05AX10 |
| **Pharmacotherapeutic group** | Antivirale midler til systemisk brug; direkte virkende antivirale midler. |
| **Active substance(s)** | Maribavir |
| **Pharmaceutical form(s)** | Tablet 200 mg, oral administration |
| **Mechanism of action** | Anti-viral behandling. Hæmmer cytomegolovirus (CMV) UL97 proteinkinase, hvilket fører til hæmning af virus DNA-replikation, indkapsling og udskillelse af modne capsider fra nukleus. |
| **Dosage regimen** | 800 mg per dag |
| **Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)** | Maribavir er indiceret til behandling af infektion og/eller sygdom med CMV, der er refraktær (med eller uden resistens) over for en eller flere tidligere behandlinger, herunder ganciclovir, valganciclovir, cidofovir eller foscarnet, hos voksne patienter, som har gennemgået en hæmatopoietisk stamcelletransplantation (HSCT) eller organtransplantation (SOT). |
| **Other approved therapeutic indications** | Der er ingen andre godkendte indikationer |
| **Will dispensing be restricted to hospitals?** | Udleveringstilladelsen er BEGR |
| **Combination therapy and/or co-medication** | Monoterapi |
| **Packaging – types, sizes/number of units, and concentrations** | 56 stk af 200 mg filmovertrukne tabletter |
| **Orphan drug designation** | EMA har tildelt Maribavir orphan drug-status |

## 2. Abbreviations

| | |
|---|---|
| aCMV | Asymptomatic CMV |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| AIC | Akaike information criterion |
| ANC | Absolute neutrophil count |
| BIC | Akaike information criterion |



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| | |
|---|---|
| BID | Twice daily |
| CI | Confidence interval |
| CMH | Cochran-Mantel-Haenszel |
| CMV | Cytomegalovirus |
| csCMV | Clinically significant cytomegalovirus |
| CSR | Clinical study report |
| DBD | Donor after brain death |
| DCD | Donor after circulatory death |
| DNA | Deoxyribonucleic acid |
| DSA | Deterministic sensitivity analysis |
| EAC | Endpoint Adjudication Committee |
| EMA | European Medicines Agency |
| FDA | Food and drug administration |
| GvHD | Graft-versus-host disease |
| HIV | Human immunodeficiency virus |
| HR | Hazard ratio |
| HSCT | Hematopoietic stem cell transplant |
| HSUV | Health state utility value |
| IAT | Investigator-assigned treatment |
| ICER | Incremental cost effectiveness ratio |
| IPCW | Inverse probability of censoring weighted |
| IPD | Individual patient data |
| IQR | Interquartile range |
| ITT | Intention-to-treat |
| IU | International unit |
| IV | Intravenous |
| KM | Kaplan-Meier |
| LLOQ | Lower limit of quantification |
| LOS | Length of stay |
| n-csCMV | Non-clinically significant cytomegalovirus |
| NHS | National Health Service |
| NR | Not reported |
| OR | Odds ratio |
| OTUS | Outcomes, treatment patterns and healthcare resource utilization studies |
| PCR | Polymerase chain reaction |
| PO | Peroral |
| PSA | Probabilistic sensitivity analysis |
| QALY | Quality-adjusted life year |
| R/R | Refractory with or without resistance |
| RCT | Randomized controlled trial |
| SAE | Serious adverse event |
| sCMV | Symptomatic CMV |
| SD | Standard deviation |
| SE | Standard error |
| SLR | Systematic literature review |
| SOT | Solid organ transplant |
| TEAE | Treatment emergent adverse events |
| TST | Time since transplant |



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# 3. Tables and Figures

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# 4. Summary

## 4.1 Indication and population covered in this application

Maribavir is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that is refractory (with or without resistance) to one or more prior therapies, including valganciclovir, ganciclovir, foscarnet, or cidofovir in adult patients who have undergone a hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT).

This indication received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 15 September 2022 and maribavir has been granted Orphan Drug Designation by the European Commission (1). The European Commission has granted marketing authorization on 11th of November 2022.

The focus of this submission is maribavir for the treatment of SOT and HSCT recipients with CMV-infection and/or disease that are refractory with or without resistance to existing anti-CMV treatment.

## 4.2 Disease overview

Generally, CMV manifests as an asymptomatic CMV infection before progressing to symptomatic CMV disease (presenting as fever in combination with either neutropenia, thrombocytopenia or bone marrow suppression); however, patients can experience severe outcomes when not treated or are resistant or refractory to treatment. Transplant patients, who are required to have immunosuppression for transplantation, are vulnerable to both reactivation of the patient's own latent CMV infection, and/or a latent CMV infection transferred from the transplant donor to the recipient. When CMV infects an end-organ in SOT patients, it causes tissue injury that results in organ dysfunction and leads to tissue invasive diseases such as CMV pneumonia, gastrointestinal CMV disease, CMV central nervous system disease, and CMV retinitis. CMV infection after allogeneic HSCT can also lead to tissue invasive disease (e.g. oesophagitis, gastroenteritis, hepatitis, retinitis, pneumonia or encephalitis). The direct effects of tissue invasive disease or CMV syndrome are accompanied by indirect effects, including increased incidence of concurrent bacterial and/or fungal infections, potential graft-versus-host disease (GvHD), graft rejection post-transplantation and increased risk of mortality. CMV infection/disease is associated with poor overall clinical transplant outcomes, including greater risk of opportunistic co-infections, transplant rejection/failure, and mortality. Moreover, with conventional anti-CMV therapies around 4-5% of SOT and HSCT patients become treatment refractory or develop drug-resistant (Refractory/Resistant; R/R) infection/disease.

## 4.3 Current management and unmet need

CMV infections that are R/R to currently available antivirals are a major cause of morbidity and mortality among SOT and allogeneic HSCT recipients. For the treatment of patients with R/R CMV post-transplant (SOT and HSCT), the currently used options include ganciclovir, valganciclovir, foscarnet, or cidofovir. Retreatment with initial or another antiviral can be used, depending on safety profile. However, none of these antivirals are indicated for treatment of R/R post-transplant CMV infection/disease and are thus used off-label in Denmark. Moreover, these commonly used anti-CMV products are associated with drug-induced neutropenia (ganciclovir and valganciclovir) and drug-induced nephrotoxicity (foscarnet and cidofovir) which can lead to poor outcomes and mortality. Drug-induced toxicities often lead to treatment discontinuation, treatment switching, or dose adjustment. These factors may lead to sub-optimal dosing and the risk of developing R/R CMV infection/disease which is associated with increased risk of treatment failure, graft rejection, and mortality.

## 4.4 Maribavir

Maribavir is an orally administered formulation of benzimidazole riboside anti-CMV agent with a novel mechanism of action targeting the UL97 protein kinase and its natural substrates. The recommended dosage of maribavir is 400 mg (2 x 200 mg) twice daily for 8 weeks. Maribavir is the first treatment option for patients with post-transplant CMV infection/disease who is refractory with or without resistance to prior treatment. Maribavir's high level of specificity and activity against CMV reducing unintended off-target effects contributing to a favorable safety profile. The oral characteristic of Maribavir enable it to be prescribed at the hospital and then brought home by the patient to be consumed outside of the hospital.

### 4.4.1 Clinical evidence

The efficacy and safety profile of maribavir in patients with R/R CMV has been demonstrated in the pivotal randomized phase 3 SOLSTICE trial (2). In SOLSTICE maribavir had superior efficacy in clearing CMV and was well tolerated, providing a convenient oral treatment against post-transplant patients with R/R CMV infection/disease.

- More than twice as many transplant patients with R/R CMV infection/disease treated with maribavir achieved the primary endpoint of CMV viremia clearance at week 8, compared to patients treated with conventional ganciclovir, valganciclovir, foscarnet, or cidofovir (investigator-assigned treatment (IAT) (maribavir: 55.7% vs IAT: 23.9%; p<0.001).
- CMV viremia clearance and symptom control with maribavir at the end of week 8 was maintained through to week 16 (maribavir: 18.7% vs IAT: 10.3%; p=0.013) and meant the key secondary endpoint was also achieved.
- The rate of CMV recurrence requiring treatment was substantially lower in the maribavir group (34/131; 26.0%) in comparison with the IAT group (10/28; 35.7%).
- More than 3 times as many transplant patients with confirmed resistant CMV infection at baseline receiving maribavir achieved CMV viremia clearance compared to IAT (maribavir: 62.8% vs IAT: 20.3%; p<0.001).
- Maribavir had a favorable safety profile and was generally well-tolerated compared to IAT in patients with refractory or resistant CMV with a low rate of discontinuation due to treatment-emergent adverse events (TEAEs); maribavir: 13.2% vs IAT: 31.9%, and a lower incidence of treatment-related TEAEs leading to discontinuation (maribavir 4.7% vs IAT 23.3%), with no new safety signals identified.
- The most common TEAEs of maribavir included dysgeusia, nausea, diarrhea, and vomiting, while neutropenia was the most frequently reported TEAE in the IAT group (maribavir: 9.4%; IAT: 22.4%). There were no difference in all-cause mortality between the two treatment groups (maribavir: 11.5% and IAT: 11.1%).
- Finally, maribavir showed significantly reduced treatment-limiting toxicities, with almost 15 fold fewer treatment-related neutropenia recorded with maribavir, compared to ganciclovir/valganciclovir (maribavir: 1.7% vs ganciclovir/valganciclovir: 25.0%), and 16 fold fewer treatment-related renal disorders with maribavir compared to foscarnet (1.7% vs 27.7%, respectively).

### 4.4.2 Economic evidence

In patients with CMV, maribavir demonstrated a statistically significant and clinically relevant improvement in CMV clearance compared with IAT, which is also reflected in the economic model showing maribavir as a cost-effective alternative to current anti-CMV treatments. In the base case, for the intention-to-treat (ITT) population (SOT and HSCT combined), the deterministic incremental cost-effectiveness ratio (ICER) was [redacted] with higher incremental costs [redacted]), higher incremental quality-adjusted life years (QALYs) ([redacted]) and life years ([redacted]). Further, the probabilistic sensitivity analysis showed that the majority of iterations fell in the north-east quadrant indicating maribavir provides more QALYs at a higher cost than IAT. In conclusion, the economic model described in this report has translated the important clinical value drivers for maribavir into a robust economic model showing cost-effectiveness compared to IAT.

## 4.5 Conclusion

Maribavir shows superior efficacy and safety compared to currently used anti-CMV treatments in Denmark. Maribavir is the only therapy indicated for treatment of refractory with or without resistance post-transplant CMV infection. Maribavir will provide clinicians with a new and novel treatment option for patients with post-transplant CMV infection/disease.

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

## 5.1 The medical condition and patient population

***Patofysiologien ved CMV virus***



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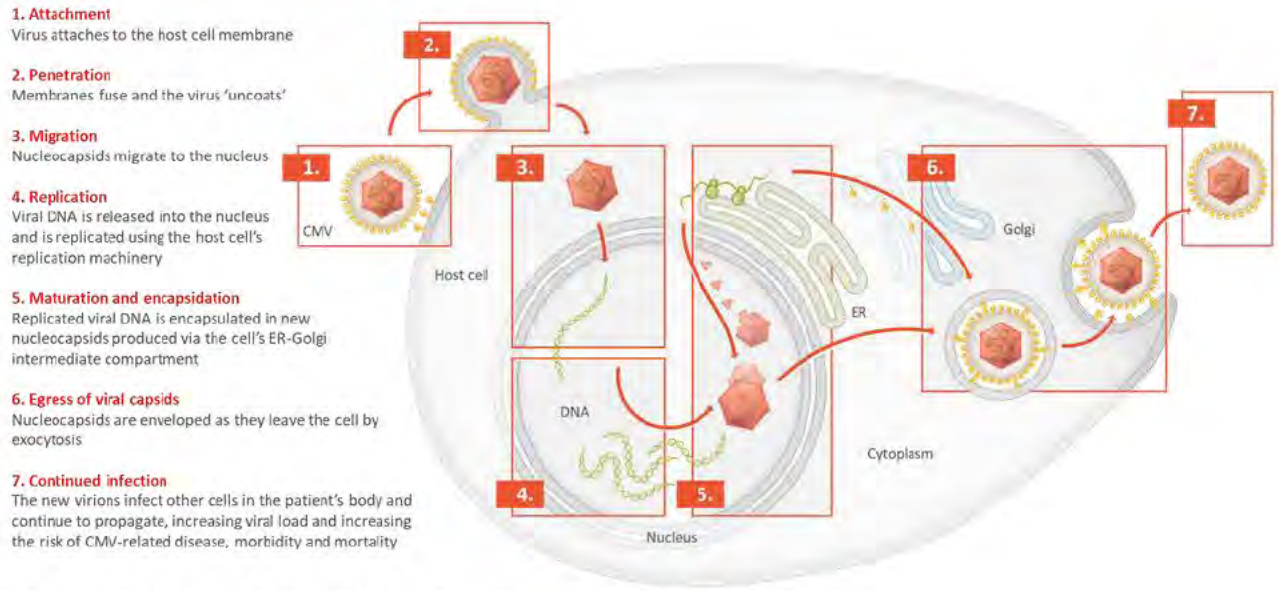
Cytomegalovirus (herefter CMV) er en dobbeltstrenget DNA-virus, der er en del af herpesvirus-familien. Virussens reproduktion afhænger af dens evne til at overtage værtsceller og lave kopier af sig selv. Livscyklussen for CMV i humane værtsceller er illustreret i Figur 1 herunder.

**Figur 1: CMV-livscyklus i humant værtscelle**




**Forkortelser: CMV, cytomegalovirus; DNA, deoxyribonucleic acid; ER, endoplasmic reticulum**
**Ref. Crough T et al. 2009 (3)**

Cirka 80% af alle danskere omkring 30 årsalderen er CMV seropositive, og har dermed virus i kroppen (4). For individer med et normalt fungerende immunsystem fremkommer CMV-infektion asymptomatisk eller mild og kan beskrives som latent (5). Svækkes immunforsvaret kan virussen reaktiveres (CMV-reaktivering), hvilket er tilfældet for mange stamcelle- og organtransplanterede patienter, der som led i deres transplantation har modtaget immunsupprimerende behandling for at forhindre organafstødning. Patienterne er derfor sårbare overfor både reaktivering af patientens egen latente CMV-infektion og/eller en latent CMV-infektion, der overføres fra transplantatdonoren til modtageren. CMV-reaktivering forløber oftest uden symptomer (CMV-viræmi uden kliniske tegn på virussygdom), men kan i nogle tilfælde udvikle sig til egentlig CMV-sygdom (CMV-viræmi og samtidig kliniske tegn på CMV-virussygdom), der kan give alvorlige kliniske symptomer fra de organer, der påvirkes. Foruden organ påvirkning har CMV-reaktivering også vist sig at være indirekte forbundet med øget risiko for komplikationer i form af bakterielle eller virale infektioner, graft-versus-host sygdom (GvHD) og organafstødning efter transplantation. Ultimativt kan disse komplikationer forårsage død (5–9). Nedenstående tabel (Tabel 1) viser en opgørelse over de typiske direkte effekter og symptomer samt de indirekte kliniske effekter af CMV-infektion i transplanterede patienter. Adskillige studier indikerer at CMV-niveau er associeret med øget risiko for transplantationsrelateret død for både organtransplantation (SOT) og hæmatopoietisk stamcelletransplantation (HSCT) (10–12). For transplanteret patienter med CMV sygdom (13,14) er risikoen for CMV relateret død forøget med 2-4 gange sammenlignet med patienter uden CMV sygdom og forøges med forhøjet CMV infektion (15,16). CMV-infektioner som er behandlingsrefraktære med eller uden resistens (herefter R/R) til eksisterende anti-CMV behandling er en afgørende årsag til sygelighed og død blandt SOT og HSCT patienter. I Tabel 2 er definitionen af CMV manifestationer beskrevet.

**Tabel 1: Direkte og indirekte effekter af CMV-infektion**

| | Direkte effekter og symptomer | Indirekte effekter |
|---|---|---|
| SOT | Feber og mononukleose-lignende symptomer<br>Neutropeni og trombocytopeni<br>Pneumonitis | Immunsuppression forårsager andre opportunistiske infektioner (svampe, bakteriel og vira), hvilket fører til vævsskadende sygdom |



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| | | |
|---|---|---|
| | Mave-tarmsygdom<br>Hepatitis<br>Pankreatitis<br>Retinitis og uveitis | Onkogenese<br>CMV-associeret transplantationsdysfunktion, afstødning og organsvigt<br>Død |
| HSCT | Det samme som for SOT, men hvor de klinisk vigtige symptomer er pneumoni, gastroenteritis og retinitis | Opportunistiske infektioner (svampe, bakteriel og vira)<br>CMV-associeret transplantationsdysfunktion, afstødning og organsvigt<br>GvHD<br>Død |

Forkortelser: GvHD, graft-versus-host sygdom; HSCT, hematopoietic stem cell transplantation, på dansk hæmatopoietisk stamcelletransplantation; SOT, solid organ transplantation, på dansk organtransplantation.
Ref. (5–8)

**Tabel 2: Beskrivelse af CMV manifestationer**

| Terminologi | Definition |
|---|---|
| **CMV-infektion** | Tilstedeværelse af målbart CMV-niveau. CMV-infektion kan være asymptomatisk. |
| **CMV-sygdom** | Symptomatisk CMV-infektion. CMV-sygdom kan klassificeres som CMV-syndrome eller invasiv CMV-sygdom med organmanifestationer |
| **CMV-syndrom** | For SOT patienter er CMV-syndrom defineret som feber (>38 °C) i mindst 2 dage indenfor en 4-dags periode, målbart CMV i blodet og enten neutropeni eller trombocytopeni.<br>For allogen HSCT patienter er definitionen af CMV-syndrome bredere og er defineret som en kombination af feber og knoglemarsvssuppression |
| **Invasiv CMV-sygdom med organmanifestationer** | En kombination af målbart CMV eller CMV-syndrom samt en organmanifestation (f.eks. CMV pneumoni, CMV gastrointestinal sygdom, CMV leverbetændelse, CMV nyrebetændelse, CMV blærebetændelse, CMV myokarditis, CMV retinitis) |

Forkortelser: CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; SOT, solid organ transplantation (17,18).

***Patientpopulation og antallet af patienter i Danmark***

Den relevante patientgruppe til behandling med maribavir er transplanterede SOT- eller allogen HSCT-patienter med CMV-infektion og/eller -sygdom, som er R/R overfor en eller flere lægemidler anvendt som nuværende standardbehandling. CMV-infektioner, der er R/R overfor aktuelt tilgængelige antivirale lægemidler, er en væsentlig årsag til morbiditet og dødelighed blandt SOT- og allogene HSCT-modtagere. Definitionen på behandlingsrefraktær er i nærværende ansøgning defineret som en CMV-infektion med dokumenteret manglende opnåelse af >1 $\log_{10}$ fald i CMV DNA-niveau i fuldblod eller plasma efter en 14-dages eller længere behandlingsperiode (2). Denne definition gælder for den aktuelle CMV-infektion og det senest administrerede anti-CMV-lægemiddel. Den refraktære CMV kan være ledsaget af resistens. Ligeledes defineres resistens som dokumentation på 1 eller flere CMV genetiske mutationer forbundet med resistens mod anti-CMV-lægemidler (2). Tabel 3 herunder viser resultatet af en intern systematisk litteratursøgning som er blevet anvendt til, at estimere incidensen for R/R CMV-infektion i forbindelse med denne ansøgning (19). Et vægtet gennemsnit af incidensen i de inkluderede studier i litteratursøgningen er anvendt til at beregne incidensen relativt til studiernes populationsstørrelser. Der findes ikke officielle og tilgængelige tal på, hvor mange R/R CMV-patienter, der findes i Danmark, og Takeda Pharma A/S har derfor som led i denne ansøgning afholdt et advisory board, hvor 5 danske speciallæger fra 5 forskellige specialer deltog (både speciallæger indenfor SOT, HSCT og infektionsmedicinske specialister var repræsenteret). Alle de medvirkende læger behandler CMV efter transplantation som en del af deres daglige virke. Diskussionerne fra advisory boardet er yderligere blevet underbygget af samtaler med 8 danske speciallæger, som ikke kunne deltage på advisory boardet, men som gerne ville dele information. Ingen af de omtalte læger har ønsket at nævnes med navn i denne ansøgning.

Incidens raterne præsenteret i Tabel 3 er baseret på litteratursøgningen. Incidens raterne er blevet vurderet af lægerne som deltog på det danske advisory board. På advisory boardet blev lægerne adspurgt om, hvor mange R/R CMV



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patienter de ser årligt. Jf. lægernes input er resultatet af litteraturstudiet overestimeret ift. dansk praksis. Dette forklares hovedsageligt af, at Rigshospitalet anvender MATCH-programmet. MATCH-programmet er en prospektiv transplantationsdatabase, hvis formål er at fungere som et kvalitetssikrings- og sikkerhedsværktøj til vurdering af risikoen for at udvikle virusinfektioner blandt transplanterede patienter. Ifølge de deltagende læger på advisory boardet har MATCH-programmet reduceret risikoen og dermed incidens raten for R/R CMV betydeligt. MATCH-programmet er udviklet på Rigshospitalet og anvendes kun på Rigshospitalet. Årsagen til, at MATCH-programmet ikke er udbredt til resten af verden, skyldes begrænsningerne ved deling af personfølsomt data, og derfor har MATCH-programmet ikke haft nogen indvirkning på den internationale incidens rate af CMV. Yderligere gav lægerne den information, at der i dansk klinisk praksis ikke som standard foretages gentest for at identificere genvarianter og dermed mulig resistens overfor CMV behandling. I dansk klinisk praksis differentieres der derfor ikke mellem behandlingsrefraktær CMV og resistent CMV, ligesom der gøres i litteratursøgningen. Tabel 4 og Tabel 5, som opgør antallet af R/R CMV patienter i Danmark i absolutte tal, indeholder dermed både en samlet incidens rate for R/R CMV patienter baseret på litteraturstudiet og en korrigeret incidens rate for R/R CMV patienter baseret på indsigt fra danske læger. Det samlede antal R/R CMV patienter er derfor baseret på indsigt fra danske læger og nedskrevet med 50%, og vil danne grundlag for incidens raten refereret fremadrettet i denne ansøgning.

**Tabel 3: Incidens rate for R/R CMV**

| Transplantations type | Incidens af bekræftet CMV 1. linje CMV behandling | Incidens af refraktær CMV 2. linje CMV behandling | Incidens af resistent CMV 2. linje CMV behandling |
|---|---|---|---|
| SOT | ≈34% (29 studier) | ≈20%* (2 studier) | ≈5% (12 studier) |
| HSCT | ≈33% (28 studier) | ≈23%* (4 studier) | ≈4% (8 studier) |

Forkortelser: HSCT, hematopoietic stem cell transplantation; SOT, solid organ transplantation
*Nogle patienter med refraktær CMV vil muligvis have haft resistens
Kilde: Takeda updated epidemiological estimates 2021 (20) is listed under supplementary documentation. Pooled estimates are based on a systematic review of published literature covering the period of 01 January 2015 through 28 July 2020 (19). Geographic scope of the literature review included both the United States and Europe. Weighted mean estimates account for sample sizes of the relevant publications.

Tabel 4 og Tabel 5 herunder viser, hvor mange danske patienter der modtog hhv. SOT eller allogen HSCT i de forgangne 5 år. Det totale antal SOT-patienter i Danmark er baseret på de nyeste tal fra transplantationstabeller (2017 til 2021) fra Scandiatransplant.org (21). Der eksisterer ingen officielt tilgængelig database, som angiver antallet af HSCT-patienter i Danmark om året. Det totale antal allogen HSCT-patienter er derfor baseret på tal fra Cancer.dk, som har opgjort antallet af danske patienter som modtog HSCT i 2021 (22). Da der ikke findes data, for hvor mange HSCT der er foretaget de senest 5 år, har Takeda Pharma A/S adspurgt danske læger, om antallet fra 2021 er repræsentativt for de forgangene 5 år, eller om der forekommer stor variation i antallet af stamcelletransplanteret om året. Lægerne bekræftede, at tallet for 2021 er repræsentativt og der ikke forekommer stor variation fra år til år. Antallet af HSCT-patienter pr. år holdes derfor konstant på 131 patienter pr. år både ex ante og ex post i denne opgørelse.

**Tabel 4: Incidens for R/R CMV SOT-patienter i Danmark over de seneste 5 år**

| År | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|
| Totalt antal SOT patienter i Danmark | 383 | 335 | 406 | 412 | 352 |
| Incidens af CMV 1. linje behandling | 130 (383*34%) | 114 | 138 | 140 | 120 |
| Incidens af refraktær CMV 2. linje behandling | 26 (130*20%) | 23 | 28 | 28 | 24 |



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| År | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|
| Incidens af resistent CMV 2. linje behandling | 7 (130*5%) | 6 | 7 | 7 | 6 |
| Samlet incidens R/R CMV 2. linje behandling baseret på lit. studie | 33 (26+7) | 28 | 35 | 35 | 30 |
| Samlet incidens R/R CMV 2. linje behandling baseret på input fra danske læger | 16 (33*0,5) | 14 | 17 | 18 | 15 |

Forkortelser: CMV, cytomegalovirus; R/R, refraktær/resistent; SOT, solid organ transplantation
I kolonnen for år 2017 er vist eksempler på hvordan incidens raterne er beregnet. Patientantallet er angivet i hele tal.

**Tabel 5: Incidens for R/R CMV allogen HSCT-patienter i Danmark over de seneste 5 år**

| År | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|
| Totalt antal HSCT patienter i Danmark | 131 | 131 | 131 | 131 | 131 |
| Incidens af CMV 1. linje behandling | 43 (131*33%) | 43 | 43 | 43 | 43 |
| Incidens af refraktær CMV 2. linje behandling | 10 (43*23%) | 10 | 10 | 10 | 10 |
| Incidens af resistent CMV 2. linje behandling baseret på lit. studie | 2 (43*4%) | 2 | 2 | 2 | 2 |
| Samlet incidens R/R CMV 2. linje behandling | 12 (10+2) | 12 | 12 | 12 | 12 |
| Samlet incidens R/R CMV 2. linje behandling baseret på input fra danske læger | 6 (12*0,5) | 6 | 6 | 6 | 6 |

Forkortelser: CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; R/R, refraktær/resistent
I kolonnen for år 2017 er vist eksempler på hvordan incidens raterne er beregnet. Patientantallet er angivet i hele tal.

Tabel 6 viser antallet af patienter, som forventes at modtage behandling med maribavir, hvis maribavir anbefales som første valg til behandling af patienter med R/R CMV i Danmark. Patientantallet er baseret på gennemsnittet af det samlede antal patienter fra Tabel 4 og Tabel 5.

**Tabel 6: Estimeret antal patienter som forventes at modtage maribavir behandling**

| År | 2023 | 2024 | 2025 | 2026 | 2027 |
|---|---|---|---|---|---|
| Antal patienter i Danmark som forventes at være i behandling med lægemidlet de kommende år | 10 | 22 | 22 | 22 | 22 |



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I år 2023 forventes der et langsommere optag end de efterfølgende år, da lægerne først skal introduceres til behandlingen med maribavir. Efter år 2023 forventes det samlet antal patienter, at udgøre den totale population af R/R CMV patienter i Danmark.

***Patient populationens alder***

Gennemsnitsalderen for danske SOT-patienter er opgjort af Scandiatransplant efter anmodning fra Takeda Pharma A/S og er baseret på tidsperioden 2017 til 2021. Scandiatransplant opgørelser viste en median alder for lungetransplanteret på 55 år, hjertetransplanteret på 53,5 år, nyretransplanteret på 52 år, levertransplanteret på 48 år og pancreastransplanteret på 43 år. Den vægtet gennemsnitsalder for SOT-patienter i Danmark beregnes dermed til 50,3 år. Det fremgår af SOLSTICE studiet (randomiseret, open-label, aktiv kontrolleret fase 3 studie af maribavir vs standardbehandling i SOT og HSCT patienter; se afsnit 6 og 7 for detaljeret gennemgang af studiet) at gennemsnitstiden fra transplantation til patienterne i studiet oplever R/R CMV er [redacted] (2,23). Disse tal er baseret på en *individual patient data* (IPD) analyse udført af Takeda Pharma A/S i forbindelse med denne ansøgning, og tallene er dermed ikke publicerede. Gennemsnitsalderen for SOT R/R CMV patienter i Danmark beregnes derfor til [redacted]

Da der ikke findes tilgængelige databaser for stamcelletransplanterede patienter i Danmark er gennemsnitsalderen i stedet baseret på hhv. tidligere Medicinrådsansøgninger og danske registerstudier omhandlende leukæmi, myelomatose, Hodgkins og non-Hodgkins lymfom, da disse udgør de hyppigste årsager til at få udført stamcelletransplantation i Danmark (24). Gennemsnitsalderen for leukæmi er opgjort på baggrund af et dansk registerstudie til 36 år (25). For myelomatose er gennemsnitsalderen estimeret til 71 år på baggrund af en tidligere Medicinrådsansøgning, hvilket også er tilfældet for Hodgkins lymfom, hvor sygdommen indtræder enten omkring 20-30-årsalderen, eller omkring 50-årsalderen (26,27). Det har ikke været muligt at fastlægge gennemsnitsalderen for incidensen af non-Hodgkins lymfom baseret på registerstudier eller tidligere Medicinrådsansøgninger, men iflg. Lægehåndbogen optræder sygdommen oftest i alderen 60-65 år (28). Da årsagerne til udførelse af stamcelletransplantation er mange, og patientgrupperne varierer betragteligt, har det ikke været muligt at fastlægge en samlet gennemsnitsalder for stamcelletransplantation. I SOLSTICE studiet er gennemsnitsalderen for HSCT patienter 52,1 (min 19; max 79) år når de udvikler R/R CMV. SOLSTICE studiet menes på den baggrund, at være repræsentativt i en aldersmæssig sammenhæng ift. den danske befolkning (se afsnit 6 og 7 for detaljeret gennemgang af studiet).

***Subgrupper i R/R CMV patientpopulationen***

Baseret på samtaler med danske læger er der ikke nogen subpopulationer af R/R CMV patienter, som i højere grad kandiderer til maribavir behandling end andre. SOLSTICE studiet har ikke størrelse til med tilstrækkelig statistisk styrke at kunne gennemføre analyser i potentielle subpopulationer. Der vil i bedst muligt udfald kunne undersøges tendenser i potentielle subpopulationer. For en detaljeret gennemgang af tendenserne henvises til afsnit 7.

### 5.1.1 Patientpopulation relevant for denne ansøgning

Patientpopulationen udgøres af patienter med CMV-infektion eller –sygdom, der tidligere har modtaget HSCT eller SOT, og som er refraktær med eller uden resistens overfor en eller flere tidligere behandlinger, herunder ganciclovir, valganciclovir, cidofovir eller foscarnet.



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## 5.2 Current treatment options and choice of comparator(s)

### 5.2.1 Current treatment options

Der eksisterer på nuværende tidspunkt ingen national behandlingsvejledning for patienter, der er R/R overfor behandling af CMV efter SOT eller HSCT. Yderligere findes der ingen lægemidler som er indikerede til behandling af R/R CMV. Behandling med ganciclovir, valganciclovir, cidofovir eller foscarnet til denne patientgruppe betragtes derfor alle som off-label brug.

Behandlingsalgoritmerne herunder er defineret på baggrund af samtaler med danske læger. Generelt beskriver lægerne behandlingstilgangen som individualiseret til den enkelte patients behov, og det kan derfor være vanskeligt at specificere én behandlingsalgoritme, som passer til alle patienter med CMV. Opstillingen af behandlingstilgangen herunder bør derfor betragtes som en generaliseret tilgang, som kan variere afhængigt af den individuelle patient. Yderligere er det i denne ansøgning vurderet nødvendigt, at beskrive de behandlingsgange der ligger forud for den egentlige behandling af R/R CMV patienter, som er den patientpopulation maribavir behandling har indikation til.

Overordnet set inddeles behandlingen af CMV efter transplantation i to stadier, profylaktisk- og præemptiv behandling (Tabel 7), som er hhv. forebyggelse af CMV eller behandling igangsat på baggrund af detekteret CMV niveau hos en patient, der skønnes i risiko for udvikling af CMV sygdom (29,30). Målet med profylaktisk behandling er, at vedligeholde et lavt eller ikke eksisterende CMV niveau hos patienten efter transplantation, når der ikke er tegn på infektion (29). Efterfølgende præemptiv behandling igangsættes først, hvis der findes målbart og behandlingskrævende CMV virus hos patienten (29). Nærværende ansøgning vil fokusere på *præemptiv* behandling, hvilket er formålet med maribavir behandling, men for helhedsforståelsens skyld vil de forudgående behandlingsforløb kort omtales herunder.

**Tabel 7: Definition af behandlingstype**

| Behandlingstype | Definition |
|---|---|
| Profylaktisk | Administreres før detekteret CMV hos patienten, hvilket holder CMV niveauet på lavt eller ikke målbart niveau |
| Præemptiv | Administreres når patienter har målbart CMV niveau; disse patienter kan være symptomatiske eller asymptomatiske. Præemptiv behandling inkluderer første-linje eller anden-linje (eller >). |

Forkortelser: CMV, cytomegalovirus

***Behandling af HSCT-patienter***

Baseret på information fra danske læger bruges letermovir profylaktisk til HSCT patienter fra dag 21 efter transplantation til 100 dage efter transplantation for alle patienter, som er CMV IgG positive før transplantationen. Letermovir er indiceret til profylaktisk behandling og anvendes derfor ikke som præemptiv behandling. Blodprøver tages minimum ugentligt fra dag 21 til dag 150 efter transplantation hos alle transplanterede patienter, og analyseres for CMV-viræmi ved hjælp af kvantitativ PCR. Ved positiv CMV-PCR (> 300-1.000 kopier/mL), afhængig af lokal praksis og analysemetode) igangsættes præemptiv behandling med antivirale lægemidler for at forebygge udvikling af CMV-sygdom.

Kvantificeringen af CMV-kopier i blodet afhænger som nævnt af PCR metoden. Baseret på samtaler med danske læger fremgår det, at analysemetoden varierer afhængigt af hvor i landet analysen er udført. Metoderne anvendt i Danmark udgør *RealTimeCMV* (Abbott), *COBAS ampliPrep/COBAS Taqman* (Roche) og *Artus CMV RGQ MDx* (Qiagen). For at afveje hvorvidt resultaterne fra SOLSTICE studiet er repræsentative for dansk klinisk praksis, er der i forbindelse med denne ansøgning foretaget konverteringer mellem de nævnte analysemetoder. Det er, baseret på konverteringsraterne i Tabel



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8, blevet vurderet, at grænseværdierne i SOLSTICE studiet er repræsentative for dansk klinisk praksis.

**Tabel 8: CMV load konvertering (IU/mL)**

| CMV realtime-PCR | Linear range (IU/mL) | 1 kopi/mL | f.eks. 20.000 kopier/mL |
|---|---|---|---|
| RealTimeCMV (Abbott) | 31,2 til 156 mio. | 1,56 IU/mL | 31.2000 IU/mL |
| COBAS ampliPrep/COBAS Taqman (Roche) | 137 til 9,1 mio. | 0,91 IU/mL | 18.200 IU/mL |
| Artus CMV RGQ MDx (Qiagen) | 159 til 7,94 mio. | 1,64 IU/mL | 32.800 IU/mL |

Tabellen skitserer de mest anvendte analysemetoder til at måle plasma CMV niveauer. Linear range angiver målespektret dvs. nedre og øvre kvantificeringsgrænse, og 1 kopi/mL viser omregningsfaktoren fra kopi/mL til IU/mL.
Ref. (31–33)

Behandling gives i mindst 2 uger og/eller indtil der er opnået minimum én CMV-PCR negativ blodprøve. Den typiske præemptive behandling består af valganciclovir (900 mg, 2 gange dagligt, peroralt). I de tilfælde, hvor patienten ikke kan indtage peroral medicin eller har diarré, behandles der med ganciclovir (5 mg/kg, 2 gange dagligt, intravenøst) i stedet. Såfremt patienten har nedsat knoglemarvsfunktion eller bliver refraktær og/eller resistent, behandles der med foscarnet (60 mg/kg, 2 gange dagligt, intravenøst) (Figur 2). Alle lægemidler skal dosisjusteres ved nedsat nyrefunktion. Ved recidiv af CMV-viræmi efter ophør med behandling genoptages den præemptive behandling udenfor indikation (6). Maribavir forventes at være et alternativ til patienter, der bliver refraktære med eller resistens overfor en eller flere tidligere lægemidler, herunder valganciclovir, ganciclovir eller foscarnet.

***Behandling af SOT-patienter***

Baseret på samtaler med danske læger er behandlingen af SOT-patienterne individualiseret og derfor forholdsvis heterogen. Der bør derfor tages højde for variation i individuelle behandlingsvalg. De fleste SOT-patienter behandles profylaktisk med peroral valganciclovir, hvor dosis kan variere afhængig af patientens infektionsrisiko og nyrefunktion. Infektionsrisikoen baseres på, om donor (D) og/eller recipient (R) tidligere har været inficeret med CMV. Ved høj- og intermediær risiko (D+/R- og D+/R+ og D-/R+) gives profylakse med valganciclovir tabl 450 mg x 1 dagligt i 3 måneder, afpasset efter nyrefunktion. For lavrisikopatienter (D-/R-) gives profylakse i 3 måneder med valganciclovir tabl 450 mg hver 2. dag afpasset efter nyrefunktionen. Ved præemptiv behandling af CMV-infektion behandles med valganciclovir peroralt i højere dosering (900 mg x 2 dagligt), dog stadig tilpasset nyrefunktionen. Hos patienter med CMV-sygdom eller hvor der er tvivl om absorptionen af behandlingen, overvejes behandling med ganciclovir intravenøst. Som led i ganciclovir behandlingen måles CMV-niveauet hos patienten, og hvis der efter 2 målinger ikke har kunne påvises CMV replikation, overgår patienten til sekundær profylaktisk behandling (valganciclovir). Sekundær profylaktiske behandling gives indtil der er gået 4 uger efter første negative CMV-PCR, og dosering er uafhængig af serotype (som for høj- og intermediær risiko patienter) (valganciclovir 450 mg x 1 dagligt). Ved nedsat gastrointestinal absorption eller R/R CMV-infektion kan foscarnet intravenøst anvendes og i yderst sjældne tilfælde anvendes cidofovir intravenøst. Ligesom for HSCT-patienterne forventes maribavir at være et alternativ til patienter, der bliver refraktære med eller uden resistens overfor en eller flere tidligere lægemidler, herunder valganciclovir, ganciclovir, foscarnet eller cidofovir.

I Figur 2 er skitseret den nuværende danske kliniske behandlingspraksis for SOT og allogen HSCT transplanteret patienter for profylaktisk- og præemptiv (1. linje og 2. linje) behandling, samt hvor vi forventer maribavir vil blive indplaceret.



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**Figur 2: Behandlingspraksis for behandling af CMV infektion hos SOT og HSCT patienter i Danmark og forventet indplacering af maribavir**


Forkortelser: HSCT: hematopoietic stem cell transplantation; SOT, solid organ transplantation
(Cidofovir) bruges kun i ganske få tilfælde til behandling af SOT-patienter. Faresymbolerne (!) for 1.linje og 2. linje behandlingerne angiver at disse lægemidler er forbundet med betydelige bivirkninger såsom neutropeni (ganciclovir og valganciclovir) og nefrotoksicitet (foscarnet og cidofovir).

### 5.2.2 Valg af komparator(er)

Som tidligere beskrevet i 5.2 findes der på nuværende tidspunkt ingen lægemidler indiceret til behandling af patienter med R/R CMV. Lægemidlerne, der anvendes i dansk klinisk praksis, er derfor off-label og udgøres af valganciclovir, ganciclovir, foscarnet eller cidofovir. I Tabel 9 ses en oversigt over de fire komparatorer, hvilken transplantattype de anvendes til i Danmark og hvad deres godkendte indikation er.

**Tabel 9: Oversigt over komparatorer**

| Generisk navn | Transplantattype | Indikation |
|---|---|---|
| Ganciclovir | SOT/HSCT | Treatment of CMV disease in immunocompromised patients. Prevention of CMV disease using pre-emptive therapy or universal prophylaxis in patients with drug- induced immunosuppression |
| Valganciclovir | SOT/HSCT | Prevention of CMV disease in CMV-negative adults and children (aged from birth to 18 years) who have received a SOT from a CMV-positive donor. |
| Foscarnet | SOT/HSCT | (Treating CMV retinitis in AIDS patients). Not licensed in transplant patients. |
| Cidofovir | SOT/HSCT | (Treating CMV retinitis in AIDS patients). Not licensed in transplant patients. |



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Forkortelser: CMV, cytomegalovirus; HSCT: hematopoietic stem cell transplantation; R/R, refraktær/resistent; SOT, solid organ transplantation
Ref. (34–37)

### 5.2.3 Beskrivelse af komparator(er)

Yderligere informationer om de fire komparatorer, ganciclovir, valganciclovir, foscarnet og cidofovir, som er vurderede at være relevante for maribavir i denne ansøgning, er beskrevet i Tabel 10, Tabel 11, Tabel 12, og Tabel 13.

**Tabel 10: Ganciclovir som komparator**

| | Ganciclovir |
|---|---|
| **ATC-code** | J05AB06 |
| **Mode of action** | Ganciclovir is a synthetic analogue of deoxyguanosine, which inhibits replication of herpes viruses including CMV. In CMV-infected cells ganciclovir is undergoing phosphorylation to ganciclovir triphosphate by viral protein kinases including, UL97 which results in the virustatic activity of ganciclovir and inhibition of viral DNA synthesis. |
| **Pharmaceutical form** | Powder for solution |
| **Posology** | The recommended dosage is Initially 5 mg/kg every 12 hours for 14–21 days, then maintenance 6 mg/kg once daily, on 5 days of the week, alternatively maintenance 5 mg/kg once daily, maintenance only for patients at risk of relapse; if disease progresses initial induction treatment may be repeated. However dose adjustment is required for patients with renal impairment resulting in individualized doses. |
| **Method of administration** | Intravenous only |
| **Dosing** | In patients with normal renal function, the recommended dosage is 5-6 mg/kg body weight twice daily. |
| **Should the pharmaceutical be administered with other medicines?** | No |
| **Treatment duration/criteria for end of treatment** | The usage is listed as off-label use and there is therefore no public guidance on dosage regime for R/R CMV patients. It is acknowledged that treatment starts once CMV is detected in routinely bloodwork and ends once CMV can no longer be detected. The best public available literature describing treatment duration of ganciclovir is the SOLSTICE study. See section 7 for a detailed description. |
| **Necessary monitoring, both during administration and during the treatment period** | Complete blood counts with differential and platelet counts should be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/µL at the beginning of treatment.<br><br>Monitoring renal function during treatment, especially for elderly patients and those patients receiving concomitant agents that may cause nephrotoxicity.<br><br>Monitoring of CMV DNA levels frequently. |
| **Need for diagnostics or other tests (i.e. companion diagnostics)** | Females of reproductive potential should undergo pregnancy testing before initiation of treatment, complete blood counts with differential and platelet counts should be |



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| | Ganciclovir |
|---|---|
| | performed frequently, all patients should be monitored for renal function before and during treatment |
| **Packaging** | 500 mg in 250 mL (2 mg per mL) solution in a single dose bag for intravenous use |

**Tabel 11: Valganciclovir som komparator**

| | Valganciclovir |
|---|---|
| **ATC-code** | J05AB14 |
| **Mode of action** | Valganciclovir is a L-valyl ester (prodrug) of ganciclovir, which after oral administration is rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of deoxyguanosine, which inhibits replication of herpes viruses including CMV. In CMV-infected cells ganciclovir undergoes phosphorylation to ganciclovir triphosphate by viral protein kinases including UL97 which results in the virustatic activity of ganciclovir and inhibition of viral DNA synthesis |
| **Pharmaceutical form** | Film-coated tablet |
| **Posology** | The recommended dosage is Initially 900 mg (two 450 mg tablets) twice daily for 21 days, then maintenance 900 mg daily, induction regimen may be repeated if retinitis progresses. However dose adjustment is required for patients with renal impairment resulting in individualized doses. |
| **Method of administration** | Oral |
| **Dosing** | In patients with normal renal function, the recommended dosage is 900 mg (two 450 mg tablets) once/twice daily |
| **Should the pharmaceutical be administered with other medicines?** | No |
| **Treatment duration/criteria for end of treatment** | The usage is listed as off-label use and there is therefore no public guidance on dosage regime for R/R CMV patients. It is acknowledged that treatment starts once CMV is detected in routinely bloodwork and ends once CMV can no longer be detected. The best public available literature describing treatment duration of valganciclovir is the SOLSTICE study. See section 7 for a detailed description. |
| **Necessary monitoring, both during administration and during the treatment period** | It is recommended that complete blood counts and platelet counts be monitored frequently in all patients during therapy, Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patients.<br><br>Monitoring of CMV DNA levels frequently. |
| **Need for diagnostics or other tests (i.e. companion diagnostics)** | Renal function in elderly patients is recommended to monitor before treatment |
| **Packaging** | 60 x 450 mg pack |



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### Tabel 12: Foscarnet som komparator

| | Foscarnet |
|---|---|
| **ATC-code** | J05AD01 |
| **Mode of action** | Foscarnet is an organic analogues of inorganic pyrophosphate that inhibits replication of herpesviruses including CMV. It exerts its antiviral activity by a selective inhibition of the pyrophosphate binding site on virus-specific DNA polymerases at concentrations that do not affect cellular DNA polymerases. |
| **Pharmaceutical form** | Solution for infusion |
| **Posology** | It is recommended to initiate 60 mg/kg every 8 hours for 2–3 weeks, alternatively initially 90 mg/kg every 12 hours for 2–3 weeks, then maintenance 60 mg/kg daily, then increased if tolerated to 90–120 mg/kg daily, if disease progresses on maintenance dose, repeat induction regimen. However dose adjustment is required for patients with renal impairment resulting in individualized doses. |
| **Method of administration** | Intravenous only |
| **Dosing** | In patients with normal renal function, the recommended dosage is 60 mg/kg body weight twice daily. |
| **Should the pharmaceutical be administered with other medicines?** | It is recommended to establish diuresis by hydration with 0.5–1.0 litre of normal saline at each infusion. |
| **Treatment duration/criteria for end of treatment** | The usage is listed as off-label use and there is therefore no public guidance on dosage regime for R/R CMV patients. It is acknowledged that treatment starts once CMV is detected in routinely bloodwork and ends once CMV can no longer be detected. The best public available literature describing treatment duration of foscarnet is the SOLSTICE study. See section 7 for a detailed description. |
| **Necessary monitoring, both during administration and during the treatment period** | During initial therapy and during hospitalization, serum creatinine should be monitored daily. It is recommended to monitor serum calcium, magnesium, potassium and phosphorus.<br>Monitoring of CMV DNA levels frequently. |
| **Need for diagnostics or other tests (i.e. companion diagnostics)** | Clinically dehydrated patients should have their condition corrected before initiating therapy. |
| **Packaging** | 24 mg/ml; 10 x 250 ml pack |

### Tabel 13: Cidofovir som komparator

| | Cidofovir |
|---|---|
| **ATC-code** | J05AB12 |
| **Mode of action** | Cidofovir is a monophosphate nucleotide analog of cytosine and needs to be converted to a diphosphate form for activity. Unlike ganciclovir, it is not dependent on viral enzymes for phosphorylation and only uses mammalian cellular kinases, and it acts by competitive |



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| | Cidofovir |
|---|---|
| | inhibition of cytosine incorporation into the viral DNA strand inhibiting elongation of the strand. |
| **Pharmaceutical form** | Powder for solution |
| **Posology** | The recommended dose of cidofovir is initially 5 mg/kg once weekly for 2 weeks, then maintenance 5 mg/kg every 2 weeks, maintenance treatment to be started 2 weeks after completion of induction treatment. However, dose adjustment is required for patients with renal impairment resulting in individualized doses. |
| **Method of administration** | Intravenous only |
| **Dosing** | Initially 5 mg/kg once weekly for 2 weeks, then maintenance 5 mg/kg every 2 weeks, maintenance treatment to be started 2 weeks after completion of induction treatment. |
| **Should the pharmaceutical be administered with other medicines?** | Oral probenecid and adequate intravenous saline prehydration with each cidofovir dose |
| **Treatment duration/criteria for end of treatment** | The usage is listed as off-label use and there is therefore no public guidance on dosage regime for R/R CMV patients. It is acknowledged that treatment starts CMV is detected in routinely bloodwork and ends once CMV can no longer be detected. The best public available literature describing treatment duration of cidofovir is the SOLSTICE study. See section 7 for a detailed description. |
| **Necessary monitoring, both during administration and during the treatment period** | Before each administration of cidofovir, serum creatinine and urine protein levels should be monitored, and the dose must be modified for changes in renal function. During therapy it is recommended to obtain white blood cell differential frequently.<br><br>Monitoring of CMV DNA levels 1-2 times weekly |
| **Need for diagnostics or other tests (i.e. companion diagnostics)** | Treatment with cidofovir must not be initiated in patients with creatinine clearance ≤ 55 ml/min, or ≥ 2+ proteinuria (≥ 100 mg/dl). It is recommended to discontinue potentially nephrotoxic agents at least 7 days before starting cidofovir. |
| **Packaging** | 375 mg in 5 ml (75 mg/ml) concentrate for solution for infusion |

## 5.3 Interventionen

| | Livtencity |
|---|---|
| **Generic name (ATC-code)** | Maribavir (J05AX10) |
| **Mode of action** | Maribavir is a potent and selective, orally bioavailable benzimidazole riboside antiviral drug with a novel mechanism of action against human CMV. Maribavir attaches to the UL97 encoded kinase at the adenosine triphosphate binding site, abolishing phosphotransferase needed in processes such as DNA replication, encapsidation, and nuclear egress making maribavir less susceptible to mutations of the viral DNA polymerase and enabling activity against strains with viral DNA polymerase mutations. |
| **Pharmaceutical form** | Film-coated tablet |



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| | Livtencity |
|---|---|
| **Posology** | The recommended dose of maribavir is 400 mg (two 200 mg tablets) twice daily resulting in a daily dose of 800 mg for 8 weeks. |
| **Method of administration** | Oral twice daily |
| **Dosing** | 400 mg twice daily (200 mg x 2 tablets in the morning and 200 mg x 2 tablets in the evening with or without food |
| **Should the pharmaceutical be administered with other medicines?** | No |
| **Treatment duration/criteria for end of treatment** | Treatment duration is 8 weeks but treatment duration may need to be individualized based on the clinical characteristics of each patient. |
| **Necessary monitoring, both during administration and during the treatment period** | The plasma levels of immunosuppressants must be frequently monitored throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir, and doses should be adjusted, as needed.<br><br>Monitoring of CMV DNA levels frequently. |
| **Need for diagnostics or other tests (i.e. companion diagnostics)** | Not anticipated |
| **Packaging** | 56 x 200 mg pack |

Som tidligere omtalt er ingen af de eksisterende antivirale lægemidler indiceret til behandling af R/R CMV-infektion/-sygdom hos transplanterede patienter, og de anvendes derfor udenfor indikation i Danmark. De almindeligt anvendte behandlingsmuligheder har væsentlige ulemper forbundet med deres anvendelse (f.eks. IV-behandlinger [ganciclovir, foscarnet, cidofovir]), som kræver adskillige indgivelser om dagen og tæt overvågning under behandlingen, hvilket ofte nødvendiggør hospitalsindlæggelse af patienter under den antivirale behandling. Disse anti-CMV lægemidler er forbundet med betydelige bivirkninger såsom neutropeni (ganciclovir og valganciclovir) og nefrotoksicitet (foscarnet og cidofovir), hvilket begrænser deres anvendelse. På grund af toksicitetsrisici er de tilgængelige behandlingsmuligheder oftest forbundet med risiko for suboptimal dosering (f.eks. behandlingsophør, dosisreduktion), hvilket kan reducere effektiviteten i klinisk praksis og øge risikoen for behandlingssvigt, udvikling af resistens og død.

De nuværende tilgængelige anti-CMV-midler virker på ét trin i cellereplikationsvejen, idet de hæmmer DNA-polymerase. Som et resultat heraf kan resistens mod et af de fire anvendte antivirale midler medføre udvikling af resistens også overfor de tre andre, hvilket reducerer effektiviteten og nødvendiggør en reduktion af immunsuppressiv behandling. Der er derfor et behov for en ny behandlingsmulighed for R/R CMV med dokumenteret forbedring af CMV-infektion/-sygdom og samtidig minimering af de bivirkninger, der ses med de eksisterende anti-CMV lægemidler.

Maribavir repræsenterer en ny anti-CMV-klasse (benzimidazol-ribosid), der har anti-CMV-aktivitet på tværs af CMV-livscyklus, hvilket resulterer i, at maribavir påvirkes i mindre grad af mutationer på den virale DNA-polymerase og muliggør effekt mod stammer med virale DNA-polymerasemutationer. Maribavir imødekommer det behandlingsbehov der er for patienter med CMV-infektion og/eller -sygdom opstået efter transplantation, som er behandlingsrefraktære eller resistente overfor 1 eller flere af de nuværende anti-CMV behandlinger. Maribavir vil være tilgængelig som en oral formulering; patienter vil ikke kræve hospitalsindlæggelse for at modtage behandlingen, hvilket reducerer byrden med behandlingsadministration og -overvågning. Maribavir har en favorabel sikkerhedsprofil og kræver ikke dosisjustering



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på baggrund af nyrefunktion og kan indgives med eller uden mad, hvilket resulterer i en bekvem administration til patienter.

På baggrund af information fra de danske læger på advisory boardet og øvrige læger, som vi har talt med forventes maribavir indplaceret som 1. linje R/R behandling af CMV hos SOT- og allogen HSCT-patienter i den nuværende danske behandlingspraksis. Maribavir vil således give danske læger en ny behandlingsmulighed for denne vanskelige behandlingstunge patientpopulation, hvor eksisterende antiviral CMV behandling ikke er effektiv eller tolerabel. Endeligt kan tilgængeligheden af maribavir være med til at sikre, at de investeringer, som er foretaget for at sikre vellykkede transplantationer, ikke er forgæves som følge af CMV-infektion/-sygdom.

# 6. Literature search and identification of efficacy and safety studies

## 6.1 Identification and selection of relevant studies

A clinical systematic literature review (SLR) was conducted to identify relevant publications to assess the efficacy and safety of anti-CMV agents (namely maribavir, ganciclovir, valganciclovir, foscarnet, and cidofovir) for the treatment of refractory or resistant (R/R) CMV infection/disease in SOT or HSCT recipients. Electronic database searches of MEDLINE® (via PubMed) and CENTRAL (via Cochrane Library) were performed on 5 July 2022. The search on the clinical trials registers was performed on 15 August 2022. The search databases and strategies are provided in Appendix A.

A detailed overview of the SLR methodology and search results are provided in Appendix A.2. Potentially relevant clinical studies were reviewed and assessed by two reviewers, working independently, for relevance based on titles and abstracts and final set of studies eligible for review were identified using predefined inclusion and exclusion criteria specified in Appendix A.2.3. Citations considered to describe potentially eligible articles were reviewed in full-text form for formal inclusion in the final review. Disagreements between reviewers were resolved during a consensus meeting.

The literature search identified 221 potentially relevant publications through MEDLINE® (via PubMed) and CENTRAL (via Cochrane library) according to the search strings specified in Appendix A.2.1 and Appendix A.2.2. With duplicates removed (n = 3), 218 records were eligible for systematic review. These records were screened on title and abstract based on the PICO (Population, Interventions, Comparators, Outcomes) framework defined (Table 95 in Appendix A.2.3), which resulted in the exclusion of 207 records. The remaining 11 records underwent a more rigorous screening which further resulted in the exclusion of 9 publications. As a result, 2 publications were found relevant (section 6.2), however, one key study was the pivotal trial which forms the evidence base for the efficacy and safety of the intervention compared to comparator in the population relevant to the scope of this application, and is presented in detail in Section 7:

- The phase 3 trial, SOLSTICE (TAK-620-303, also referred to as Study 303 in this application), investigated the efficacy, safety, and tolerability of maribavir 400 mg (twice daily (BID)) compared with investigator-assigned anti-CMV treatment (IAT; ganciclovir [IV], valganciclovir [oral], foscarnet [IV], or cidofovir [IV]) in SOT or HSCT recipients with CMV infections that are R/R to ganciclovir, valganciclovir, foscarnet or cidofovir (2).

The SLR identified 1 additional study, TAK-620-202 (Study 202), a phase 2 multicenter, randomized, dose-ranging, parallel-group study assessing the efficacy, safety, and tolerability of dose-blinded (patients, investigators, and study personnel were blinded to dose) maribavir administered BID at 3 doses (400, 800, and 1200 mg) in SOT and HSCT recipients experiencing R/R CMV infections (38). This study provides non-comparative data for the intervention in the population relevant to the scope of this submission, however, as this study is superseded by the SOLSTICE phase 3 trial

data from Study 202 are not included in this application. The data from Study 202 and SOLSTICE was not possible to combine.

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) flow diagram showing the number of references identified and the number of included and excluded records is available in Appendix A.2.4, and a list of references excluded after full-text screening is provided in Table 100 in Appendix A.2.4, including the reasons for exclusion of each reference.

### 6.2 List of relevant studies

Information on the relevant study that was used in the assessment can be found in Table 14. Detailed study characteristics of the study are provided in Appendix B.

**Table 14: Relevant key studies included in the assessment**

| Reference (title, author, journal, year) | Trial name | NCT number | Phase | Dates of study | Used in comparison of |
|---|---|---|---|---|---|
| Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial. Avery RK, Alain S, Alexander BD, Blumberg EA, Chemaly RF, Cordonnier C, Duarte RF, Florescu DF, Kamar N, Kumar D, Maertens J, Marty FM, Papanicolaou GA, Silveira FP, Witzke O, Wu J, Sundberg AK, Fournier M; SOLSTICE Trial Investigators. *Clin Infect Dis.* 2022;75:690-701<br><br>doi: 10.1093/cid/ciab988 | SOLSTICE (TAK-620-303) | NCT02931539 | 3 | December 2016 to August 2020 | Maribavir vs. IAT (ganciclovir, valganciclovir, foscarnet, or cidofovir) |

Abbreviations: IAT, investigator-assigned treatment; NCT, national clinical trial

An assessment of the quality of the relevant clinical effectiveness evidence is presented in Table 101 in Appendix A. SOLSTICE was a well-performed RCT with a low risk of bias.

A search was performed on 15 August 2022 for completed and ongoing trials at ClinicalTrials.gov and ClinicalTrialsRegister.eu involving R/R CMV and drug terms maribavir, ganciclovir, valganciclovir, foscarnet, or cidofovir. No studies were found during the search.



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# 7. Efficacy and safety

## 7.1 Efficacy and safety of maribavir compared to investigator-assigned anti-CMV treatment for R/R CMV infection/disease in SOT or HSCT recipients.

### 7.1.1 Relevant studies

As stated in the previous section, SOLSTICE (TAK-620-303), the phase 3 trial comparing maribavir with IAT (ganciclovir, valganciclovir, foscarnet, or cidofovir) is the pivotal phase 3 randomized controlled trial providing the main source of efficacy and safety data relevant to this application. For detailed study characteristics refer to Appendix B. For baseline characteristics of patients included in the study, please see Appendix C.

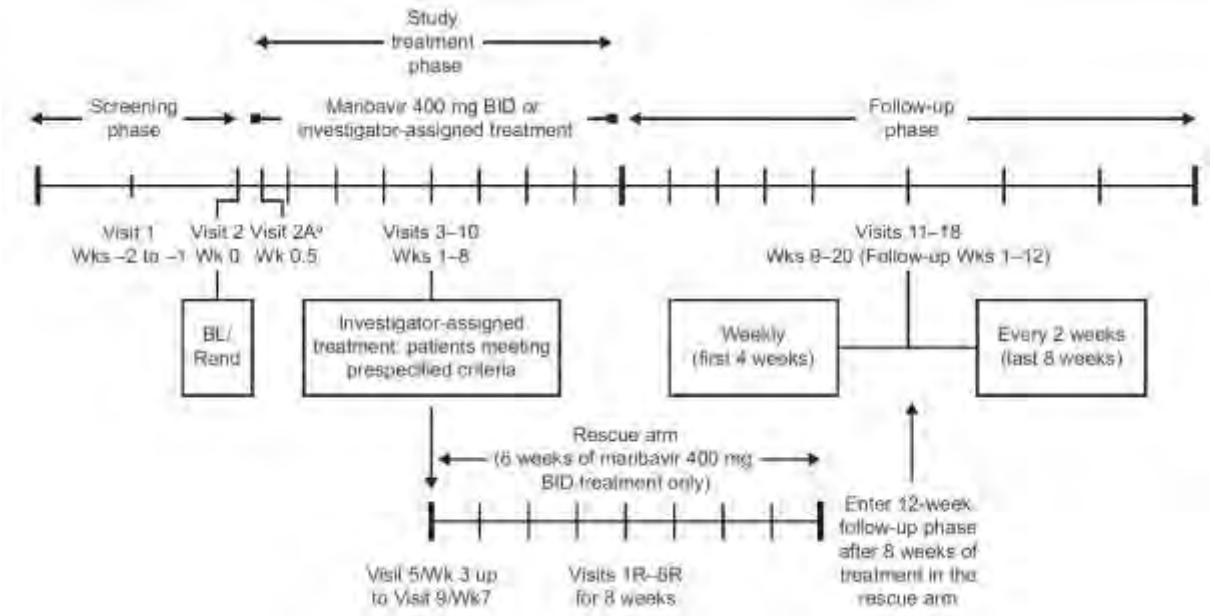
**SOLSTICE – study design**

SOLSTICE was a global multicenter, randomized, open-label, active-controlled phase 3 trial designed to assess the efficacy and safety of maribavir compared to IAT in HSCT and SOT transplant recipients with CMV infections that were R/R to treatment with ganciclovir, valganciclovir, foscarnet or cidofovir.

An overview of the study design of the SOLSTICE trial is presented in Figure 3. The trial consisted of 3 phases: a 2-week screening period, followed by randomization 2:1 to 400 mg BID maribavir or IAT for an 8-week treatment period, and a 12-week follow-up phase (in which patients were off study-assigned therapy).

The study was conducted between December 2016 and August 2020 at 101 study locations in 12 countries across North America, Europe and Asia Pacific, including one center in Denmark. A total of 136 patients (38.6%) were enrolled from Europe (2,23).

**Figure 3: Overview of the study design of the SOLSTICE study**




[a]Visit 2A/2A(R) was only required for patients receiving tacrolimus, cyclosporine, everolimus, or sirolimus at visit 2/2R.
Abbreviations: BID, twice daily; BL, baseline; R, rescue; Rand, randomization; Wk, week.
Ref. (2)

Eligible patients were HSCT and SOT recipients (aged ≥12 years) with documented CMV infection refractory to ganciclovir, valganciclovir, foscarnet, and/or cidofovir. Refractory CMV infection was defined as failure to achieve >1 $\log_{10}$ decrease in CMV DNA level after ≥14 days of treatment. Patients with resistant CMV infection were also included

if they met refractory criteria. Resistance was defined as ≥1 CMV genetic mutation associated with resistance to valganciclovir/ganciclovir, foscarnet, and/or cidofovir (2).

A total of 415 patients were screened and 352 were randomized (maribavir, n = 235; IAT, n = 117) (2). Although the study was open to patients aged ≥12 years, no patients aged ≤18 years were enrolled. Randomization was done through a centralized interactive response technology system and stratified by transplant type (SOT/HSCT) and CMV DNA level. Patients were evaluated weekly until week 12 then every two weeks through to week 20. At every visit blood sample for CMV DNA test were taken and patients were assessed for symptomatic CMV infection. The choice of specific IAT was at investigators' discretion and could include mono- or combination therapy (≤2 drugs) with any of the four approved IATs except combination of cidofovir and foscarnet. For patients in the IAT group, changes to dose or dosing schedule of anti-CMV therapies were permitted, as well as discontinuation of one therapy, if two were originally selected (39). Addition of another anti-CMV therapy was not permitted and only switches between ganciclovir and valganciclovir were allowed (2). No change to dose or dosing schedule was allowed for patients in the maribavir group. Anti-CMV therapy was continued even if patients achieved viraemia clearance before week 8. Reduction or modifying of immunosuppressant drug use was permitted. A maribavir rescue arm was an option for patients originally assigned IAT after ≥3 weeks of treatment (39). After 3 weeks, patients in the IAT arm could stop treatment (at the discretion of the investigator) for lack of confirmed viraemia clearance and/or intolerance to the assigned treatment, and enter into the rescue arm. Rescue treatment consisted of maribavir 400 mg BID for 8 weeks for patients in the IAT arm (2).

Concomitant medications taken during the on-treatment observation period were similar to medications used prior to the trial and was consistent between treatment arms: i.e., immunosuppressants (maribavir: 92.3%; IAT: 94% and corticosteroids for systemic use (maribavir: 75.6%; IAT: 72.4%) (39).

Overall, treatment groups were well balanced with respect to the demographics and baseline characteristics. The majority of patients had received SOT prior to enrolment (60.4% vs. 59.0%, in the maribavir and IAT arms, respectively). The most common SOT types were kidney (52.1% vs. 46.4%), lung (28.2% vs. 31.9%), and heart (9.9% vs. 13.0%) in the maribavir and IAT arms, respectively. The demographics and baseline characteristics are summarized in Table 102 and Table 103 in Appendix C. Despite the wide heterogeneity in local and international CMV management practices, Danish clinical experts have verified that the SOLSTICE patient population is generalizable to Denmark.

In the intention-to-treat (ITT) population, the majority of patients who received IAT were treated with foscarnet (40.5%), ganciclovir (24.1%) or valganciclovir (24.1%) (Figure 4). Overall, the majority of the patients receiving maribavir completed the study; whilst for patients receiving IAT, the majority discontinued treatment early. The most common reason for discontinuation in the maribavir group was lack of efficacy, while for the IAT group, it was AEs (Figure 4).

In the SOT population, patients who received IAT were treated with ganciclovir or valganciclovir ([redacted]), foscarnet [redacted]), foscarnet in combination with ganciclovir or valganciclovir [redacted]), or cidofovir ([redacted]) (23). In the HSCT population, the majority of patients who received treatment with IAT were treated with valganciclovir or ganciclovir [redacted]), foscarnet [redacted]), cidofovir [redacted]), or foscarnet in combination with ganciclovir or valganciclovir [redacted]). SOT patients were more commonly treated with ganciclovir/valganciclovir, whilst HSCT patients were more commonly treated with dual therapy or cidofovir (23).



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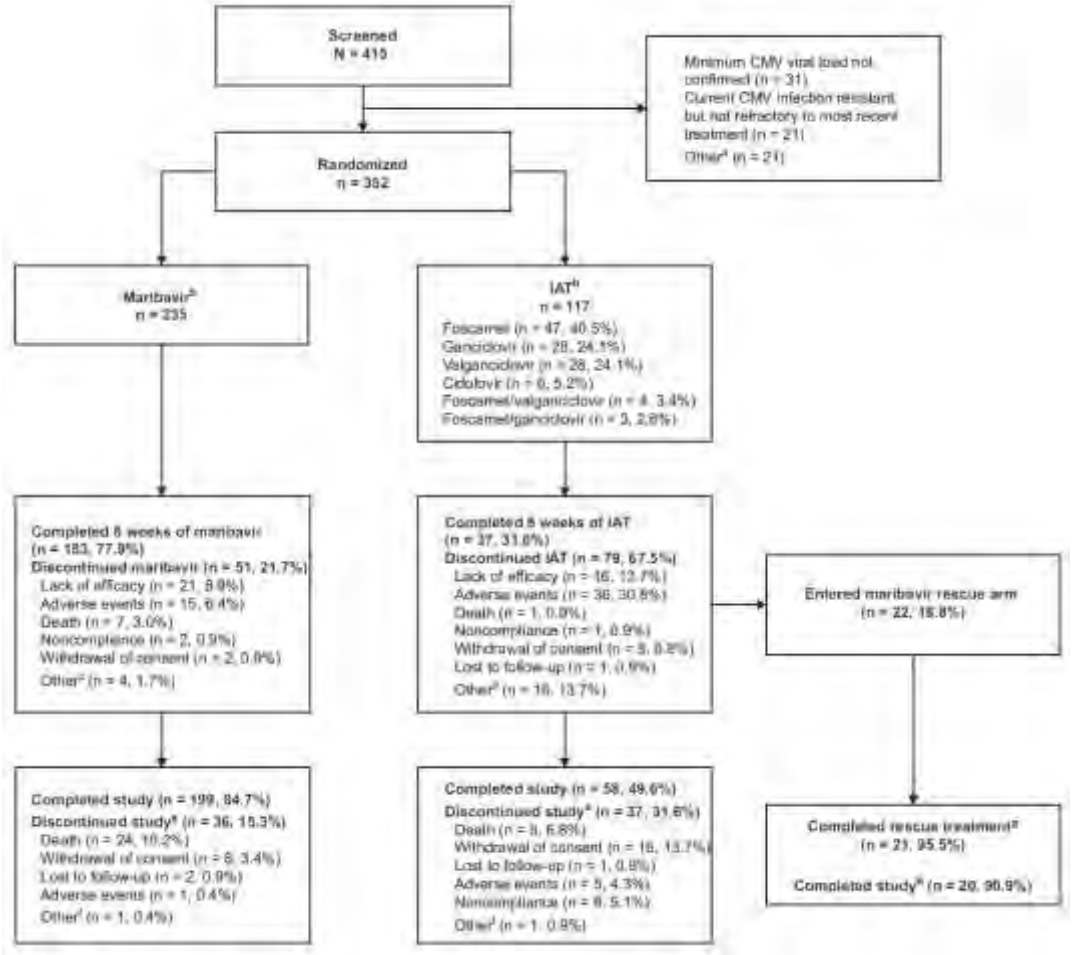
**Figure 4: Patient disposition at enrollment, randomization, and follow-up**




Abbreviations: CMW, cytomegalovirus; IAT, investigator-assigned treatment.
Percentages were calculated based on the number of patients randomized to each treatment group. Percentages may not total to 100% due to rounding. [a]Patients could have multiple reasons for not being randomized. Other reasons were: patient did not receive an HCT or SOT (n = 1); CMV infection not confirmed refractory to most recent treatment (n = 2); investigator not willing to treat the patient with ganciclovir, valganciclovir, foscarnet, or cidofovir (n = 2); platelet count <25 000/mm3 (n = 5); hemoglobin <8 g/dL (n = 1); eGFR ≤30 mL/min/1.73 m2 (n = 1); pregnancy (n = 1); patient was not willing/not able to comply fully with study procedures/restrictions (n = 3); current refractory or resistant CMV infection due to inadequate adherence to prior treatment (n = 2); serum aspartate aminotransferase >5 × ULN at screening, or serum alanine aminotransferase >5 × ULN at screening, or total bilirubin ≥3.0 × ULN at screening (n = 1); received any investigational agent with known anti-CMV activity within 30 days before initiation of study treatment or investigational CMV vaccine at any time (n = 1); and active malignancy (n = 1). [b]One patient per group was randomized but did not receive trial medication. Percentage for each IAT type was calculated based on n = 116. [c]Other reasons for treatment discontinuation in the maribavir group included investigator decision to switch to letermovir, CMV detected in patient's cerebrospinal fluid, nothing-by-mouth status with mental status change with risk for aspiration, and disease progression (in 1 patient each). [d]Other reasons for treatment discontinuation in the IAT group were: low viral load/CMV clearance (with concern of toxicity with continued administration of IAT (n = 9), patient safety (n = 3), patient/investigator request (n = 2), no efficacy and patient ineligible for rescue therapy (n = 1), and peripherally inserted central catheter issues (n = 1). [e]These results are based on investigator determination for the primary reason for study discontinuation. [f]Other reasons for study discontinuation in maribavir or IAT group included investigator discretion to discontinue 1 patient before dosing with maribavir, and no efficacy with IAT for a patient who was not eligible for rescue therapy. [g]Per protocol, maribavir rescue arm treatment was discontinued in 1 patient due to CMV encephalitis. [h]One patient was unable to complete follow-up visits in the study due to hospitalization in a different city and therefore did not complete the maribavir rescue study period. Note: Overall, 350/352 patients received treatment as two randomised subjects (one in each treatment group) were not dosed. Death shown in the figure is patients discontinuation treatment/study due to death.
Ref. (2)

### 7.1.2 Efficacy and safety – results per study

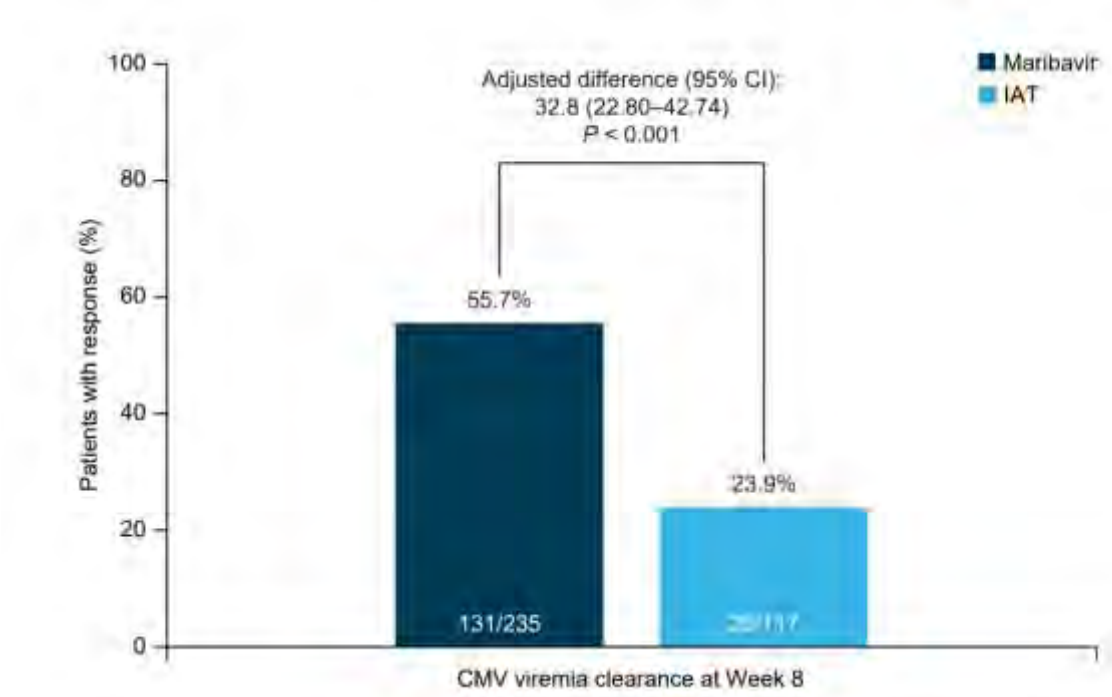
Based on the objectives of literature search as described in Appendix A, SOLSTICE was the only relevant study for the present application and a summary of the key efficacy and safety findings for the SOLSTICE trial is provided below. For detailed efficacy and safety results, please refer to Appendix D and Appendix E. The included clinical endpoints in this application were validated and confirmed by the Danish clinical experts at the advisory board as clinical relevant.

**SOLSTICE: Primary endpoint**

***Confirmed CMV viraemia clearance at the end of study week 8***

SOLSTICE demonstrated that maribavir is a highly effective treatment for the clearance of CMV compared with IAT at week 8. In the ITT population, a total of 131 of the 235 patients who received maribavir (55.7%) and 28 of the 117 who received IAT (23.9%) achieved confirmed CMV viraemia clearance at the end of study week 8 (Figure 5). After adjusting for the stratification factors (transplant type of SOT vs. HSCT and baseline plasma CMV DNA viral load group of low vs. pooled intermediate/high), the difference was statistically significant (32.8%) (95% CI: 22.8–42.7; p<0.001) (Figure 5). The number of patients needed to treat with maribavir vs. IAT to achieve an instance of additional CMV clearance at week 8 was 3 (95% CI: 2–4). Patients who received maribavir rescue or alternative anti-CMV treatment before the end of week 8, or who failed to achieve confirmed CMV viremia clearance at week 8 (including missing virologic data), were considered non-responders and were included in the analysis as failures of the primary endpoint. Moreover, Kaplan–Meier median (95% CI) time to first confirmed CMV viraemia clearance (within study week 8) occurred earlier in the maribavir vs. IAT groups (22.0 [21.0–23.0] vs 27.0 [22.0–30.0] days; p = 0.04, log-rank test) (2).

**Figure 5: Confirmed CMV viraemia clearance at week 8 by treatment group (ITT population)**




Abbreviations: CI, confidence interval; CMV, cytomegalovirus; IAT, investigator-assigned treatment; ITT, intention-to-treat
Note: Patients with confirmed CMV viraemia clearance at the end of week 8 were considered as responders regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. Plasma CMV DNA assessments after starting alternative anti-CMV treatment or rescue treatment were not evaluable for the assessment of study-assigned treatment effect.
Ref. (2)

***Sensitivity analyses***

Various methods were used to investigate the impact of early discontinuation on the primary endpoint of CMV viraemia clearance at the end of study week 8. The sensitivity analyses were prespecified to assess the robustness of the primary efficacy endpoint using alternate definitions of CMV viraemia clearance response, as described in Table 15. Overall, the results of the sensitivity analyses were consistent with the primary analysis (Figure 5) (39). Only a small proportion of patients (31.6%) received the full 8 weeks treatment with IAT, most discontinued due to AEs or a lack of efficacy (Figure

4). Additional reported sensitivity analyses on CMV viraemia clearance analysis were also consistent with the primary analysis (Table 107 in Appendix D).

**Table 15: Sensitivity analyses of the primary endpoint (ITT population)**

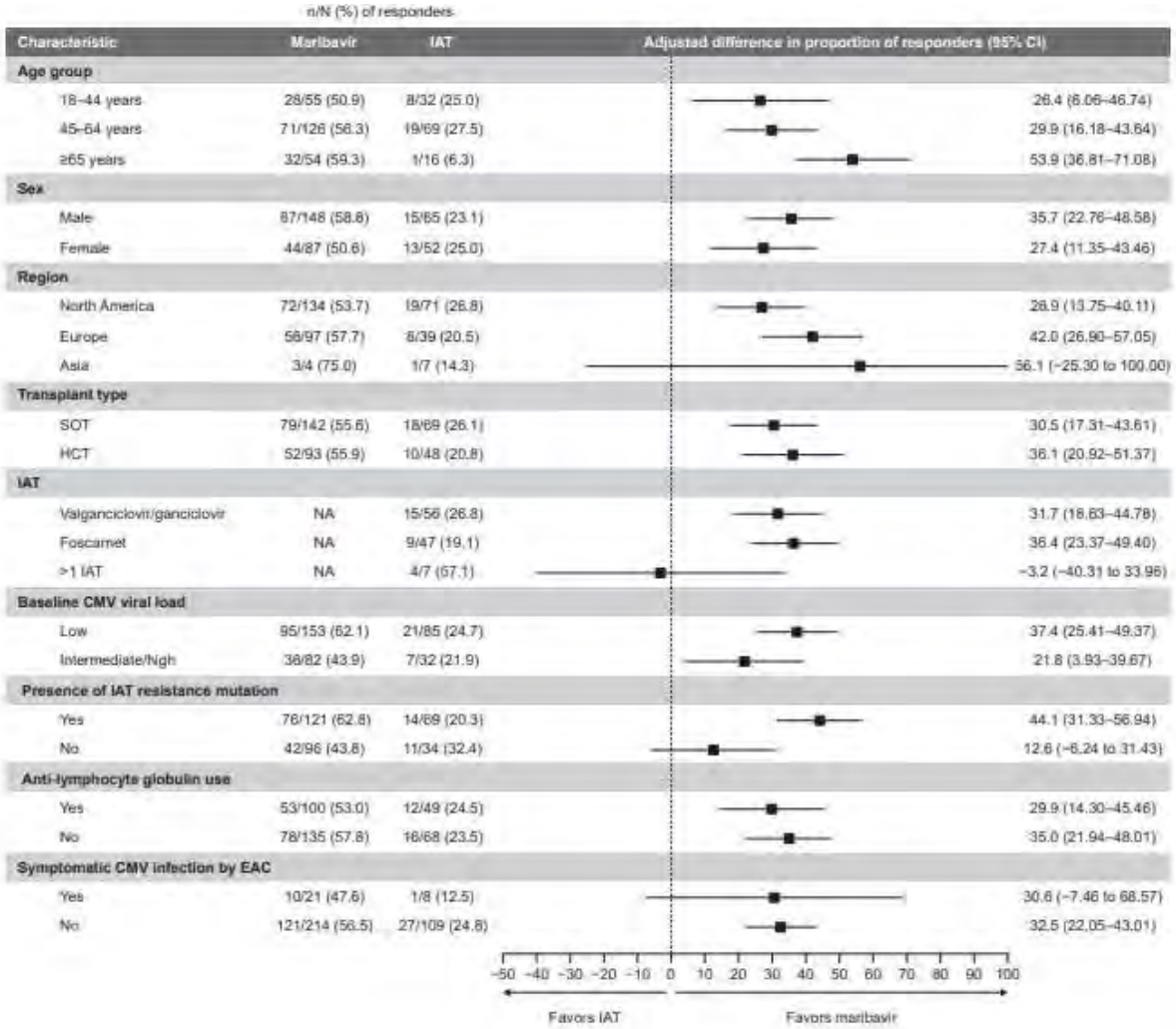
| CMV viraemia clearance at end of week 8 (Response) | Maribavir (n = 235) | IAT (n = 117) | Adjusted difference in proportion of responders (95% CI) |
|---|---|---|---|
| Based on alternate definitions of response | | | |
| Patients who met criteria of confirmed CMV viraemia clearance at the time of premature study discontinuation were included as a responder, n (%) | 137 (58.3) | 39 (33.3) | 26.1 (15.6–36.7) |
| Patients with confirmed CMV viraemia clearance at any time during the treatment phase were included as a responder, n (%) | 174 (74.0) | 61 (52.1) | 23.6 (13.2–33.9) |
| Patients with confirmed CMV viremia clearance at week 8 regardless of initiating alternative anti-CMV treatment before week 8 in the IAT group, but not in the maribavir group, were included as a responder, n (%) | 131 (55.7) | 41 (35.0) | 21.7 (11.0–32.5) |

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; IAT, investigator-assigned treatment; ITT, intention-to-treat
Ref. (39)

***Subgroup analyses***

The results of subgroup analysis of the primary endpoint remained generally consistent across pre-specified subgroups as summarized in the forest plot in Figure 6. A greater proportion of patients with baseline genotypic resistance to IAT achieved viraemia clearance at the end of week 8 in the maribavir vs. IAT group (62.8% vs. 20.3%; adjusted difference: 44.1%; 95% CI: 31.33–56.94). A numeric treatment difference between maribavir and IAT was also observed among patients with refractory (non-resistant) CMV infection (43.8% vs. 32.4%; adjusted difference: 12.6%; 95% CI: −6.24 to 31.43) (2). Looking at the transplant type subgroups (Figure 6), a higher proportion of patients with R/R CMV infection treated with maribavir vs. conventional therapies in the IAT group achieved CMV clearance at week 8. More specifically, a higher proportion of SOT recipients treated with maribavir achieved CMV clearance (55.6%) compared with patients in the IAT arm (26.1%; adjusted difference: 30.5%; 95% CI: 17.31–43.61). Similarly, a greater proportion of HSCT recipients with R/R CMV infection achieved CMV clearance with maribavir than with IAT at week 8 (55.9% vs. 20.8%; adjusted difference, 36.1%; 95% CI: 20.92–51.37). Irrespective of the baseline CMV viral load, a higher proportion of patients treated with maribavir vs. IAT achieved CMV clearance at week 8 (62.1% vs. 24.7%; adjusted difference: 37.4%; 95% CI: 25.41–49.37) and (43.9% vs. 21.9%; adjusted difference: 21.8%; 95% CI: 3.93–39.67) in low and intermediate/high baseline CMV viral loads, respectively (Figure 6).

**Figure 6: Confirmed CMV viraemia clearance at week 8 in subgroups**




Abbreviations: CI, confidence interval; CMV, cytomegalovirus; EAC, endpoint adjudication committee; HCT, hematopoietic cell transplant; IAT, investigator-assigned treatment; NA, not applicable as adjusted between-group differences used the full maribavir group; SOT, solid organ transplant. Between-group differences adjusted for applicable stratification factor (transplant type of SOT vs. HSCT and baseline plasma CMV DNA level (low vs. intermediate/high)). Six patients received cidofovir as IAT (data not shown).
Ref. (2)

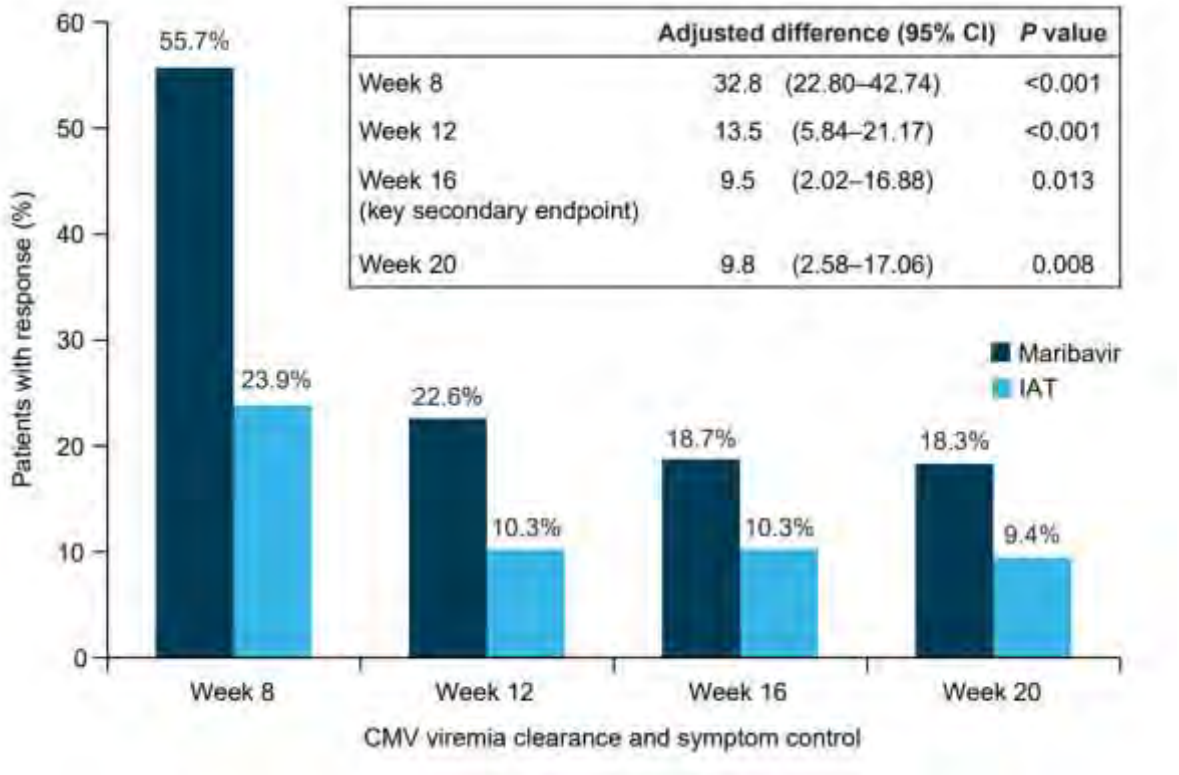
**SOLSTICE: Secondary endpoints included in the assessment**

***Confirmed CMV viraemia clearance and CMV infection symptom control (key secondary endpoint)***

The key secondary endpoint evaluated a composite of CMV viraemia clearance and CMV infection symptom control at week 8 (on-treatment period) and the maintenance of the benefit through week 16. In the ITT population, a greater proportion of patients in the maribavir group (18.7%) achieved CMV viraemia clearance and symptom control at the end of week 8 and maintained through week 16 compared with IAT (10.3%) (Figure 7). Thus, more patients benefited from maribavir treatment and hence more benefited from sustained composite outcomes of clearance and symptom control inclusive of the off-treatment period. The adjusted difference of 9.5% (95% CI: 2.02–16.88; p=0.013) was statistically significant (Figure 7). This effect was consistent at weeks 12 (22.6% vs. 10.3%; p<0.001) and 20 (18.3% vs. 9.4%; p=0.008) (2).

Symptom control was defined as patients who were symptomatic at baseline and achieved improvement or resolution of symptoms, or asymptomatic at baseline and no new symptoms of tissue invasive disease or CMV, at week 8 through week 16. Any negative outcome within the continuum resulted in the patient being counted as a non-responder for the key secondary outcome. Moreover, if a patient achieved confirmed CMV viraemia clearance and symptom control at the end of week 8, but these effects were not maintained through week 16 (including missing virologic data), discontinued, received alternative anti-CMV therapy, or administered maribavir as rescue treatment during this time, they were considered non-responders for the key secondary endpoint (39).

**Figure 7: Confirmed viraemia clearance and symptom control at week 8 and maintained through week 12, week 16 (key secondary endpoint), and week 20 (end of study) (ITT population)**




Abbreviations: CI, confidence interval; CMV, cytomegalovirus; IAT, investigator-assigned treatment.
Patient with response (both CMV viraemia clearance and CMV infection symptom control) at week 8 regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy, and maintenance of this treatment effect through week 16 was considered as a responder.
Ref. (2)

***Recurrence of CMV viraemia***

Another endpoint measured was recurrence of CMV viraemia. Clinically relevant recurrence (i.e., recurrence among responders, after week 8, who received alternative anti-CMV treatment) occurred less frequently in patients randomized to maribavir (26.0%) than IAT (35.7%). Among the 22 patients who initially received IAT and subsequently received maribavir rescue treatment (rescue population) due to lack of response, 11 (50.0%) achieved confirmed CMV viraemia clearance at week 8 of the maribavir rescue treatment phase (2). The analysis of recurrence of CMV viraemia during the first 8 weeks, the follow-up period, and any time on study by treatment is presented in Table 16. Additional data on recurrence can be found in appendix Q.

**Table 16: Analyses of recurrence of CMV viraemia (ITT population)**

| CMV viraemia recurrence | Maribavir (n = 235) | IAT (n = 117) |
|---|---|---|
| **Number of patients with clinically relevant recurrence (recurrence among responders, after week 8 who received alternative anti-CMV treatment), n/N (%)[a]** | [redacted] (26.0) | [redacted] (35.7) |
| **CMV viraemia clearance after study-assigned treatment at any time on study, n (%)[b]** | 184 (78.3) | 65 (55.6) |
| **Patients with CMV viraemia recurrence** | | |
| During the first 8 weeks, n (%) | 33 (17.9) | 8 (12.3) |
| During the follow-up weeks, n (%) | [redacted] | [redacted] |
| Any time on study, n (%) | [redacted] | [redacted] |

Abbreviations: CMV, cytomegalovirus; IAT, investigator-assigned treatment; ITT, intention-to-treat
[a]This exploratory analysis examined recurrence requiring treatment in patients who either completed therapy at week 8 or discontinued treatment prior to week 8 (but did not receive any alternative anti-CMV therapy before the assessment of the primary endpoint at week 8) AND who achieved viraemia clearance per the primary endpoint. [b]This pre-specified analysis examined recurrence of CMV viraemia was defined as plasma CMV DNA concentrations ≥LLOQ, when assessed by central specialty laboratory, in 2 consecutive plasma samples separated by at least 5 days after achieving confirmed viraemia clearance.
Ref. (2,23)

***All-cause mortality***

All-cause mortality on study was assessed for the entire study period regardless of the use of rescue treatment or alternative anti-CMV treatment. Overall, 40 deaths were reported where 8 deaths were due to CMV disease (maribavir: 4 (1.7%); IAT: 4 (3.4%)) (2). Maribavir was associated with a similar rate of all-cause mortality when compared with IAT over the course of the study. At week 20, the observed incidence of all-cause mortality was 11.5% for the maribavir group, compared with 11.1% for the IAT group (2). The distribution of time to all-cause mortality at this time-point was similar between the maribavir and IAT groups. The HR for the comparison of maribavir and IAT was [redacted] (95% CI: [redacted], indicating no significant difference between the treatment groups (23). Subjects who were alive at last contact were censored in the analysis. The time to all-cause mortality by treatment group is shown in Table 17.

The similarity in the rate of all-cause mortality between maribavir and IAT may be due to the trial design. The limited follow-up duration did not allow for the quantification of a mortality benefit.

**Table 17: Time to all-cause mortality by treatment group (ITT population)**

| Time to all-cause mortality by treatment group | Maribavir (n = 235) | IAT (n = 117) |
|---|---|---|
| **Number of patients who died, n (%)** | 27 (11.5) | 13 (11.1) |
| Number of patients censored, n (%) | 208 (88.5) | 104 (88.9) |
| Observed event time for those who died, days, median (min, max) | [redacted] | [redacted] |
| **Kaplan-Meier estimates of time to death** | | |



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| Time to all-cause mortality by treatment group | Maribavir (n = 235) | IAT (n = 117) |
|---|---|---|
| 25th, days (95% CI) | [redacted] | |
| 50th, days (95% CI) | | |
| 75th, days (95% CI) | | |
| p-value | | |
| **HR (95% CI)** | | |
| Treatment Group: Maribavir vs. IAT | | |

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; HR, Hazard ratio; IAT, investigator-assigned treatment; ITT, intention-to-treat; Max, maximum; Min, minimum; NR, not reached
Ref. (2,23)

**SOLSTICE: Exploratory outcomes included in the assessment**

***Graft outcomes (rejection or graft loss)***

The outcome of graft failure was a clinical determination that the graft irreversibly and irrevocably ceased functioning (e.g., in the case of a renal transplant, the patient returned to permanent dialysis, if dialysis-dependent prior to transplant, or returned to insulin dependency in the case of pancreas transplant) as determined by the investigator (23). In both treatment groups, few patients experienced adverse graft outcomes during the study up to 20 weeks (23). Table 18 provides an overview of graft status at baseline for SOT and HSCT groups.

No SOT recipients experienced new onset of chronic allograft dysfunction (chronic rejection) or graft loss. Among the 141 patients with HSCT (maribavir: 93 patients; IAT: 48 patients), new graft-versus-host disease (GvHD) was reported during the study for [redacted] HSCT recipients in the maribavir group and [redacted] HSCT recipients in the IAT group (Table 19) (23).

**Table 18: Graft status at baseline (ITT population)**

| | Maribavir (n = 235) | IAT (n = 117) | Total (n = 352) |
|---|---|---|---|
| **SOT** | | | |
| Functioning with complications, n (%) | [redacted] | | |
| Functioning, n (%) | | | |
| Other, n (%) | | | |
| **HSCT** | | | |
| Partially engrafted, n (%) | | | |
| Functioning with complications, n (%) | | | |



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| | Maribavir (n = 235) | IAT (n = 117) | Total (n = 352) |
|---|---|---|---|
| Functioning, n (%) | [redacted] | | |

Abbreviations: HSCT, hematopoietic stem cells transplant; IAT, investigator-assigned treatment; ITT, intention-to-treat; SOT, solid organ transplant
Ref. (23)

**Table 19: Transplant graft status (ITT population)**

| | SOT | | HSCT | |
|---|---|---|---|---|
| | Maribavir (n = 142) | IAT (n = 69) | Maribavir (n = 93) | IAT (n = 48) |
| **Acute rejection[a]** | [redacted] | | | |
| Yes | | | | |
| No | | | | |
| Missing | | | | |
| **Chronic rejection[a]** | | | | |
| Yes | | | | |
| No | | | | |
| Missing | | | | |
| **Graft loss[a]** | | | | |
| Yes | | | | |
| No | | | | |
| Missing | | | | |
| **New GvHD[a]** | | | | |
| Yes | | | | |
| No | | | | |
| Missing | | | | |
| **Time to acute rejection for those with the event (days)** | | | | |
| n | | | | |
| Mean (SD) | | | | |



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| | SOT | | HSCT | |
|---|---|---|---|---|
| | Maribavir (n = 142) | IAT (n = 69) | Maribavir (n = 93) | IAT (n = 48) |
| Median | [redacted] | | | |
| Q1, Q3 | | | | |
| Min, Max | | | | |
| **Time to chronic rejection for those with the event (days)** | | | | |
| n | | | | |
| **Time to graft loss for those with the event (days)** | | | | |
| n | | | | |
| Mean (SD) | | | | |
| Median | | | | |
| Q1. Q3 | | | | |
| Min, Max | | | | |
| **Time to new GvHD among HSCT patients (days)** | | | | |
| n | | | | |
| Mean (SD) | | | | |
| Median | | | | |
| Q1, Q3 | | | | |
| Min, Max | | | | |

Abbreviations: GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; IAT, investigator-assigned; ITT, intention-to-treat; Max, maximum; Min, minimum; NR, not reached; Q, quartile; SD, standard deviation; SOT, solid organ transplant
[a]Percentages are based on the number of patients in the subset.
Ref. (23)

**SOLSTICE: Health-related quality of life**

Two patient-reported outcome (PRO) questionnaires were included in the clinical study to measure health-related quality of life (HRQoL), specifically EuroQoL Group 5-Dimension 5-Level (EQ-5D-5L) and Short Form-36 version 2 (SF-36v2) instruments. Patients were provided with an electronic diary (eDiary) in which they recorded intake of oral study treatment during the treatment period and completed HRQoL assessments (SF-36v2/EQ-5D-5L) during the treatment and follow-up periods. Overall, there was a slight reduction in health states over the treatment and follow-up phases for all patients. The changes in EQ-5D-5L (Table 20) were [redacted]

[redacted] (23). Table 21 provides an overview of the completion rate of EQ-5D-5L by study week and treatment group. During the study, completion rates for the EQ-5D-5L ranged from 75% to 85% in the maribavir group and from 73% to 81% in the IAT group. Failure to complete the EQ-5D-5L at baseline was mainly attributed to technical issues with the device(s) used to collect the data [redacted] Other reasons for missing baseline data are patients- and site-related issues.

| | Maribavir (n = 235) | | IAT (n = 117) | |
|---|---|---|---|---|
| | Baseline value | Change from baseline at week 8 | Baseline value (SD) | Change from baseline at week 8 |
| n | [redacted] | | | |
| Mean (SD) | | | | |
| Median | | | | |
| Q1, Q3 | | | | |
| Min, Max | | | | |

Abbreviations: IAT, investigator-assigned treatment; ITT, intention-to-treat; SD, standard deviation.
These data represent Version 2.1 of the EQ-5D-5L questionnaire.
Single index utilities are scored on a 0 to 1 scale where 0 is defined as death and 1 is full health. Scores below 0 are possible and indicate health states worse than death.
Ref. (23)

**Table 21: EQ-5D-5L questionnaire completion rate by study week and treatment group (ITT population)**

| | Maribavir (n = 235) | | | IAT (n = 117) | | |
|---|---|---|---|---|---|---|
| Week | Patients with a study visit n (%) | # of patients with PRO completed n (%) | Completion rate (%) | Patients with a study visit n (%) | # of patients with PRO completed n (%) | Completion rate (%) |
| [redacted] | | | | | | |

Abbreviations: IAT, investigator-assigned; PRO, patient reported outcomes.
Completion rate is computed as (# of patients with PRO completed/patients with a study visit * 100%).
Ref. (23)

Based on the SF-36v2, there was [redacted] from baseline to the end of both treatments. Patients treated with maribavir demonstrated [redacted] in physical and mental sub-domains of the SF-36 (Table 22) (23).

**Table 22: Summary of SF-36v2 domain score (ITT population)**

| | Maribavir (n = 235) | | IAT (n = 117) | |
|---|---|---|---|---|
| **Domains** | **Baseline mean (SD)** | **Change from baseline at week 8 mean (SD)** | **Baseline mean (SD)** | **Change from baseline at week 8 mean (SD)** |
| **Patients** | [redacted] | | | |
| **Physical component score** | | | | |
| **Mental component score** | | | | |

Abbreviations: IAT, investigator-assigned treatment; ITT, intention-to-treat; SD, standard deviation; SF-36v2, short form 36 Version 2
Ref. (23)

**SOLSTICE: Hospitalization**

For patients on treatment, those receiving maribavir were [redacted] less likely to be hospitalized compared with patients receiving IAT [redacted] Over the full study period, patients receiving maribavir were [redacted] less likely to be hospitalized [redacted] (Table 23).

**Table 23: Incidence of hospitalization for patients receiving maribavir or IAT (randomized population)**

| | Maribavir (n = 235) | IAT (n = 117) | Adjusted difference in rates of hospital admissions, IRR (95% CI) |
|---|---|---|---|
| **On-treatment phase[a]** | [redacted] | | |
| Patients with ≥1 admission, n (%) | | | |
| Adjusted incidence rate, admissions/person/year (95% CI) | | | |
| **Follow-up phase[b]** | | | |
| Patients with ≥1 admission, n (%) | | | |
| Adjusted incidence rate, admissions/person/year (95% CI) | | | |
| **Full study period[c]** | | | |
| Adjusted incidence rate, admissions/person/year (95% CI) | | | |



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Abbreviations: CI, confidence interval; IAT, investigator-assigned treatment; IRR, incidence rate ratio

[a] On-treatment adjusted rates are adjusted for duration of time on treatment (52 days for maribavir, 35.7 days for IAT)
[b] Follow-up phase rates are adjusted for duration of follow-up (80.8 for maribavir and 58.1 for IAT)
[c] Adjusted rates for the full study period are adjusted for duration of time in study (132.1 days for maribavir, 92.9 days for IAT)
Ref. (40)

While on treatment, patients receiving maribavir had a statistically significant reduction of [redacted]n LOS, compared with IAT [redacted] (Table 24). In the IAT group, patients experienced an increased pre-rescue LOS, but this was not statistically significant compared to maribavir.

**Table 24: LOS for patients receiving maribavir or IAT (randomized population)**

| | Maribavir (n = 235) | IAT (n = 117) | Adjusted difference in LOS, IRR (95% CI) |
|---|---|---|---|
| **On-treatment phase[a]** | [redacted] | | |
| Total LOS per patient (days), mean (SD) | | | |
| Adjusted duration of LOS, days/person/year (95% CI) | | | |
| **Follow-up phase[b]** | | | |
| Total LOS per patient (days), mean (SD) | | | |
| Adjusted duration of LOS, days/person/year (95% CI) | | | |
| **Full study period[c]** | | | |
| Adjusted duration of LOS, days/person/year (95% CI) | | | |

Abbreviations: CI, confidence interval; IAT, investigator-assigned treatment; IRR, incidence rate ratio; LOS, length of stay
[a] On-treatment LOS are adjusted for duration of time on treatment (52 days for maribavir, 35.7 days for IAT)
[b] Follow-up phase rates are adjusted for duration of follow-up (80.8 for maribavir and 58.1 for IAT)
[c] LOS for the full study period are adjusted for duration of time in study (132.1 days for maribavir, 92.9 days for IAT)
Ref. (40)

**SOLSTICE: Safety results**

The safety population (N=350) was used for safety analyses in the SOLSTICE trial and consisted of all randomized patients who received at least one dose of study medication. For this analysis, patients were included in the treatment group corresponding to the study medication they actually received, however, safety data for intravenous ganciclovir and oral valganciclovir were combined as switch between these two treatments was allowed. The on-treatment observation period starts at the date of study treatment initiation through 7 days after the last dose of study treatment, or through 21 days after the last dose of cidofovir (if cidofovir is the IAT). As the plasma elimination half-life for maribavir is approximately 5-7 hours it is not expected for maribavir to be implicated in AEs past the on-treatment observation period. For additional safety data please see Appendix E.

***Treatment exposure***

Within the safety population, the median duration of treatment was longer with maribavir than with conventional therapies in the IAT arm (57.0 [2–64] and 34.0 [4–64] days, respectively) as well as the mean exposure to maribavir ([redacted] vs. IAT [redacted]) due to early discontinuation of treatment in the IAT group (Table 25) (2,23).

**Table 25: Treatment exposure of the safety population**

| | Maribavir (n = 234) | IAT (n = 116) |
|---|---|---|
| **Exposure duration[a]** | | |
| n[b] | [redacted] | |
| Mean (SD), days | | |
| Median (range), days | 57.0 | 34.0 |
| Min, max, days | 2, 64 | 4, 64 |
| **Actual exposure to study-assigned treatment[c]** | | |
| n[b] | [redacted] | |
| Mean (SD), days | | |
| Median, days | | |
| Min, max, days | | |

Abbreviations: IAT, investigator-assigned treatment; Min, minimum; Max, maximum; SD, standard deviation
[a]Exposure duration: Number of days between the date of the first exposure and the date of last exposure of the drug administered
[b]Two patients in the IAT group (valganciclovir) and 4 patients in the maribavir group did not have any eDiary data collected for administration of oral study-assigned treatment. These patients are not included in this table
[c]Actual exposure days to study-assigned treatment: Number of days in which at least one dose of study-assigned treatment was taken/administered
Ref. (2,23)

***Treatment-emergent adverse events***

The majority of patients in both treatment groups had at least one treatment-emergent adverse event (TEAE) in the on-treatment observation period (maribavir: 97.4%; IAT: 91.4%), reflecting the medical complexity of this patient population (Table 26 and Table 108 in Appendix E) (23). Dysgeusia (altered sense of taste) was the most frequently reported TEAE in the maribavir group (maribavir: 37.2%; IAT: 3.4%) (Table 26); this was reported as mostly mild[redacted], usually resolved either on treatment or shortly after the last dose of maribavir (Kaplan-Meier median time to resolution off treatment: 7 days), and rarely led to treatment discontinuation (0.9% of patients in maribavir group) (2,23). Neutropenia was the most frequently reported TEAE in the IAT group (maribavir: 9.4%; IAT: 22.4%), with the highest frequency observed in patients treated with valganciclovir/ganciclovir (33.9%). Rates of nausea (maribavir: 21.4%; IAT: 21.6%), vomiting (maribavir: 14.1%; IAT: 16.4%), and diarrhea (maribavir: 18.8%; IAT: 20.7%) were similar between treatment groups, but acute kidney injury (maribavir: 8.5%; IAT 9.5%; foscarnet: 21.3%), hypokalaemia (maribavir: 3.4%; IAT: 9.5%; foscarnet: 19.1%), and leukopenia (maribavir: 3.0%; IAT: 6.9%; valganciclovir/ganciclovir: 12.5%) occurred less frequently in the maribavir group, compared with IAT (Table 26) (2,39). It is notable to mention that the favorable safety profile of maribavir was despite the fact that the duration of exposure to maribavir was in mean[redacted] than to IAT (Table 25).

Drug levels of immunosuppressants were monitored during SOLSTICE as maribavir (400 mg BID) has previously been shown to increase the whole blood trough concentration of tacrolimus by 57% in a clinical drug interaction study (41). As expected, in the SOLSTICE trial increased blood immunosuppressant drug levels were reported as TEAEs in 21 (9.0%)

patients in the maribavir group (tacrolimus: n = 19; sirolimus: n = 2) and in 1 (0.9%) patient in the IAT (valganciclovir/ganciclovir) group (2).

An overall summary of TEAEs during the on-treatment observation period by treatment group can be found in Table 109 in Appendix E. Frequently occurring TEAEs occurring in ≥5% of patients during the on-treatment observation period by treatment group can be found in Table 110 in Appendix E.

**Table 26: Frequently occurring TEAEs in ≥10% of patients in the maribavir or IAT group (safety population)**

| System organ class preferred term, n (%) | Maribavir (n = 234) | IAT (n = 116) | IAT type[a] | | |
|---|---|---|---|---|---|
| | | | Ganciclovir/ valganciclovir (n = 56) | Foscarnet (n = 47) | Cidofovir (n = 6) |
| **Any TEAE** | 228 (97.4) | 106 (91.4) | 51 (91.1) | 43 (91.5) | 5 (83.3) |
| **Blood and lymphatic system disorders** | | | | | |
| Anemia | 29 (12.4) | 14 (12.1) | 4 (7.1) | 9 (19.1) | 0 |
| Leukopenia | 7 (3.0) | 8 (6.9) | 7 (12.5) | 1 (2.1) | 0 |
| Neutropenia | 22 (9.4) | 26 (22.4) | 19 (33.9) | 7 (14.9) | 0 |
| **Gastrointestinal disorders** | | | | | |
| Diarrhoea | 44 (18.8) | 24 (20.7) | 13 (23.2) | 9 (19.1) | 1 (16.7) |
| Nausea | 50 (21.4) | 25 (21.6) | 8 (14.3) | 14 (29.8) | 1 (16.7) |
| Vomiting | 33 (14.1) | 19 (16.4) | 7 (12.5) | 8 (17.0) | 2 (33.3) |
| **General disorders and administration site conditions** | | | | | |
| Fatigue | 28 (12.0) | 10 (8.6) | 7 (12.5) | 3 (6.4) | 0 |
| Oedema peripheral | 17 (7.3) | 9 (7.8) | 3 (5.4) | 5 (10.6) | 0 |
| Pyrexia | 24 (10.3) | 17 (14.7) | 6 (10.7) | 9 (19.1) | 2 (33.3) |
| **Infections and infestations** | | | | | |
| CMV viraemia[b] | 24 (10.3) | 6 (5.2) | 4 (7.1) | 1 (2.1) | 0 |
| **Metabolism and nutrition disorders** | | | | | |
| Hypokalaemia | 8 (3.4) | 11 (9.5) | 1 (1.8) | 9 (19.1) | 1 (16.7) |
| Hypomagnesemia | 9 (3.8) | 10 (8.6) | 2 (3.6) | 7 (14.9) | 1 (16.7) |
| Hypophosphatemia | 4 (1.7) | 5 (4.3) | 0 | 5 (10.6) | 0 |



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| System organ class preferred term, n (%) | Maribavir (n = 234) | IAT (n = 116) | IAT type[a] | | |
|---|---|---|---|---|---|
| | | | Ganciclovir/ valganciclovir (n = 56) | Foscarnet (n = 47) | Cidofovir (n = 6) |
| **Nervous system disorders** | | | | | |
| Dysgeusia | 87 (37.2) | 4 (3.4) | 2 (3.6) | 0 | 1 (16.7) |
| Headache | 19 (8.1) | 15 (12.9) | 6 (10.7) | 8 (17.0) | 0 |
| Paresthesia | 4 (1.7) | 5 (4.3) | 0 | 5 (10.6) | 0 |
| **Renal and urinary disorders** | | | | | |
| Acute kidney injury | 20 (8.5) | 11 (9.5) | 1 (1.8) | 10 (21.3) | 0 |
| **Vascular disorders** | | | | | |
| Hypertension | 9 (3.8) | 8 (6.9) | 1 (1.8) | 6 (12.8) | 0 |

Abbreviations: IAT, investigator-assigned treatment; TEAE, treatment-emergent adverse event
Data are presented as n (%). The cidofovir group was not considered in the application of the 10% cutoff due to low patient numbers (n = 6).
[a]Overall, 7 patients received a combination of valganciclovir/ganciclovir and foscarnet (not included in the table). [b]Events such as worsening of CMV viremia were coded to the preferred term of CMV viremia. TEAEs were coded using MedDRA, Version 23.0.
Ref. (2)

***TEAEs leading to discontinuation***

During the on-treatment observation period, any TEAEs leading to discontinuation of study-assigned treatment were reported for a greater proportion of patients in the IAT group than in the maribavir group (31.9% vs. 13.2%, respectively) (Table 27 and Table 108 in Appendix E) and treatment-related TEAEs leading to discontinuation of study-assigned treatment were 23.3% vs. 4.7% in IAT and maribavir groups, respectively (Table 108 in Appendix E). Treatment discontinuation due to TEAEs by IAT type was [redacted] (23). While [redacted] patients in the maribavir group discontinued treatment for TEAEs in the system organ class (SOC) of blood and lymphatic system disorders including neutropenia, hematologic toxicities led to treatment discontinuation for [redacted] patients in the IAT group [redacted] of ganciclovir/valganciclovir-treated patients) (Table 27) (23). Neutropenia led to treatment discontinuation for 11 (19.6%) ganciclovir/valganciclovir-treated patients (2). In the maribavir group [redacted] cases of TEAEs in the SOC of renal and urinary disorders resulted in discontinuation and in the IAT group treatment discontinuation was reported for [redacted] patients and 6 (12.8%) discontinued foscarnet due to treatment-related acute kidney injury (2,23). In the maribavir group, [redacted] were the most common type of TEAE that led to treatment discontinuation, and the incidence of TEAEs in this SOC was comparable between the maribavir and IAT groups [redacted] respectively) (Table 27) (23).

Moreover, dysgeusia, which was by far the most frequently reported on-treatment TEAE for maribavir and the most common TEAE considered related to maribavir (Table 26), led to treatment discontinuation for only 2 (0.9%) maribavir-treated patients (Table 27) (2).

**Table 27: TEAEs leading to discontinuation by treatment (safety population)**

| System organ class preferred term, n (%) | Maribavir (n = 234) | IAT (n = 116) | IAT type[a] | |
|---|---|---|---|---|
| | | | Ganciclovir/ valganciclovir (n = 56) | Foscarnet (n = 47) |
| Any TEAE leading to discontinuation | [redacted] | | | |
| Blood and lymphatic system disorders | | | | |
| Anaemia | | | | |
| Leukopenia | | | | |
| Neutropenia | | | | |
| Thrombocytopenia | | | | |
| Gastrointestinal disorders | | | | |
| Diarrhoea | | | | |
| Nausea | | | | |
| Infections and infestations | | | | |
| CMV infection | | | | |
| CMV infection reactivation | | | | |
| CMV viraemia | | | | |
| Encephalitis CMV | | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | | |
| Acute lymphocytic leukaemia recurrent | | | | |
| Nervous system disorders | | | | |
| Dysgeusia | | | | |
| Renal and urinary disorders | | | | |
| Acute kidney injury | | | | |
| Renal failure | | | | |
| Renal impairment | | | | |

Abbreviations: CMV, cytomegalovirus; IAT, investigator-assigned treatment; TEAE, treatment-emergent adverse event
Data are presented as n (%). The cidofovir group was not considered in the application of the 10% cutoff due to low patient numbers (n = 6). TEAEs were coded using MedDRA, Version 23.0.
Ref. (2,23)

***Adverse events of special interest – tissue invasive disease***

Most patients did not have CMV tissue invasive disease or CMV syndrome at baseline [redacted] During the on-treatment observation period, TEAEs in the adverse events of special interest (AESI) class of tissue invasive CMV disease/syndrome were reported for [redacted] of patients in each treatment group (Table 28) (23).

**Table 28: Tissue invasive disease during on-treatment observation period (safety population)**

| AESI class preferred term, n (%) | Maribavir (n = 234) | IAT (n = 116) |
|---|---|---|
| **Tissue invasive CMV disease/syndrome** | [redacted] | |
| CMV chorioretinitis | | |
| CMV colitis | | |
| CMV enteritis | | |
| CMV gastrointestinal infection | | |
| CMV mucocutaneous ulcer | | |
| CMV syndrome | | |

Abbreviation: AESI, adverse event of special interest; CMV, cytomegalovirus; IAT, Investigator-assigned treatment
Note: A continuing non-adverse event of special interest (non-AESI) that changed in severity was collected as one AE at the highest level of severity.
Ref. (23)

***Adverse events of special interest – deaths due to TEAEs***

A total of 40 deaths were reported in SOLSTICE and no difference in all-cause mortality between the two treatment groups were observed (maribavir: n = 27; 11.5% and IAT: n = 13; 11.1%) (2). This included [redacted] in the maribavir group who died within the first week of initiating treatment (before receiving a sufficient course of therapy) as well as [redacted] in each treatment group) who died more than 20 weeks after the first dose of study-assigned treatment (i.e., after the 20-week study observation period) (23). Fatal serious TEAEs were considered related to study-assigned treatment (per the investigator) for 1 (0.4%) maribavir-treated patient and 1 (0.9%) IAT-treated patient (Table 108 in Appendix E).

The most common TEAEs leading to death were due to respiratory failure or relapse or progression of underlying disease. Details are presented in Table 111 in Appendix E.

**Summary of study design, efficacy, and safety data from the SOLSTICE trial**

| Trial design |
|---|



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- SOLSTICE was a phase 3, multicenter, randomized, open-label, active-controlled study
- The aim was to establish the efficacy, safety profile, and tolerability of maribavir 400 mg twice daily compared with investigator-assigned anti-CMV treatment (IAT; ganciclovir [IV], valganciclovir [oral], foscarnet [IV], or cidofovir [IV]) in transplant recipients with CMV infections that are refractory or resistant to treatment
- Patients were randomized 2:1 (maribavir: IAT) and treatment duration was 8 weeks followed by a 12 week follow-up period
- The primary outcome was proportion of confirmed confirmed CMV viraemia clearance at the end of study week 8
- Secondary and exploratory outcomes included confirmed CMV viraemia clearance and CMV infection symptom control at week 16, recurrence of CMV viraemia, and all-cause mortality.
- In SOLSTICE, 350/352 (99.4%) patients received treatment and 73.4% completed the study

**Efficacy**

- In the randomized population, maribavir met the primary endpoint with a greater proportion of patients (55.7%) achieving confirmed CMV viraemia clearance at the end of study week 8 compared with IAT (23.9%), an adjusted difference of 32.8% (95% CI: 22.8%, 42.7%; p<0.001)
- Key results for secondary outcomes were (maribavir vs. IAT, respectively):
  - Confirmed CMV viraemia clearance and CMV infection symptom control followed by maintenance through week 16: 18.7% vs. 10.3% (adjusted difference 9.5% [95% CI: 2.0, 16.9; p=0.013])
  - All-cause mortality at week 20: 11.5% vs. 11.1%; HR: [redacted] the limited follow-up duration did not allow for the quantification of a mortality benefit
  - Clinically relevant recurrence of CMV viraemia at any time: 26.0% vs. 35.7%

**Safety**

- The safety set (N=350) was used for safety analyses in SOLSTICE and consisted of all randomized patients who received at least one dose of study medication
- Within the safety population, the mean exposure to maribavir ([redacted] SD: [redacted]) was longer than IAT due to early discontinuation of treatment in the IAT group ([redacted] SD: [redacted]
- Maribavir had a favourable safety profile and was generally well-tolerated compared to IAT in patients with refractory or resistant CMV in SOLSTICE
- The majority of participants had AE that were mild or moderate in severity
  - Dysgeusia was the most frequently reported treatment-emergent adverse event (TEAE) in the maribavir group (maribavir: 37.2%; IAT: 3.4%)
  - Neutropenia was the most frequently reported TEAE in the IAT group (maribavir: 9.4%; IAT: 22.4%), with highest frequency in patients treated with valganciclovir/ganciclovir (33.9%)
  - TEAEs leading to discontinuation of study-assigned treatment were reported for a greater proportion of patients in the IAT group than in the maribavir group (maribavir: 13.2%; IAT: 31.9%).
- A total of 40 deaths were reported for this study: two patients in the maribavir group who died within the first week of initiating treatment as well as four patients (2 in each treatment group) who died more than 20 weeks after the first dose of study-assigned treatment

### 7.1.3 Comparative analyses of efficacy and safety

As SOLSTICE (TAK-620-303) is the only relevant trial included in this application, a comparative analysis is not applicable.

# 8. Health economic analysis

The following sections describe the inputs used in the Danish cost-utility model of maribavir in the treatment of post-transplant R/R CMV. It should be noted that a hierarchy of evidence framework was adopted when determining the most appropriate inputs for the economic model. In this framework, data from the SOLSTICE (Study 303) clinical study



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report (CSR) are prioritised, followed by data from the Study 303 individual patient data (IPD) analysis (2,23,42). Thereafter, real-world evidence data and published literature are considered as potential sources for model input parameters.

### 8.1 Model

Based on expert health economist advice and a review of previous economic evaluations, a Markov approach was determined to be the most appropriate modelling method for this decision problem (Appendix M Validation of model). The model has been separated into two stages: 1) 0 – 78 weeks and 2) 78 weeks to lifetime horizon. Stage 1 begins with the onset of R/R CMV and includes a three state Markov model with the states being clinically significant CMV infection (csCMV), non-clinically significant CMV infection (n-csCMV) and a dead state. Stage 2 includes a two state Markov model with the states being alive or dead. It should also be noted that the approach (transitioning to an alive dead model after a period of time) is in line with accepted NICE precedence (43). However, unlike the prophylactic anti-CMV model (TA591) which began at the time of transplant, the maribavir R/R model begins with the onset of R/R CMV. Incorporation of time since transplant (TST) is discussed in further detail in a later section.

The choice to adopt a 2-state Markov model was decided through discussions with clinicians, a UK advisory board for maribavir (Takeda UK Ltd 2021) and supporting evidence from the multinational, observational OTUS SOT and HSCT studies commissioned by Takeda (OTUS, (Takeda Pharmaceuticals Company Limited 2021) (detailed description about study design and results of the OTUS study can be found in supplementary documentation). The OTUS studies evaluate real-world data in the United States and Europe to better understand the burden of CMV infection and outcomes for patients with CMV. Clinicians advised that the treatment of patients with CMV was not for an indefinite period and that a patients' immunity recovers over time, which results in natural clearance of CMV without the need for an intervention. In addition, clinicians explained that there was a likelihood for heterogeneity in the treatment pathway in later time horizons as there are no clinical guidelines to inform long-term treatment of CMV in an R/R population in these later stages. In these rarer longer-term cases, physicians would determine treatment for patients on a case-by-case basis and therefore predicting outcomes for these patients would require more complex modelling methods (i.e., a discrete-event simulation) which is not feasible in the absence of robust clinical data.

Real-world data from OTUS was used to determine the appropriate duration of the Stage 1 Markov (i.e., the time when the model should stop tracking CMV status and transition to an alive-dead model). Specifically, data from OTUS provide evidence that SOT and HSCT patients with R/R CMV may experience multiple recurrences with current standard of care (Table 29 and Table 30). If a treatment cycle is assumed to be 35.98 days (average time on treatment in the IAT arm of Study 303), and the time between each recurrent episode reflects the duration of clearance, it can be inferred from the OTUS data that CMV events can recur after 155.4 weeks from the start of the CMV index episode for SOT patients and after 77.1 weeks from the start of the CMV index episode for HSCT patients (Table 29 and Table 30). While data from OTUS provides evidence for a Stage 1 Markov to exceed 78 weeks (i.e., 155.4 weeks for the SOT cohort) clinicians indicated that in later time horizon treatment patterns for patients can be highly heterogenous and would be determined on a case-by-case basis. Therefore, in light of this advice from clinicians and the data from OTUS, transitioning to Stage 2 Markov at 78 weeks is deemed a pragmatic assumption.

**Table 29: Time between recurrent CMV episodes – SOT (OTUS)**

| CMV episode | Recurrence | Time since end of previous CMV episode to start of new episode (days) | Duration of treatment (days)[a] | Cumulative duration since CMV index episode (days) | Cumulative duration since CMV index episode (weeks) |
|---|---|---|---|---|---|
| [redacted] | | | | | |

[redacted]

*Source: OTUS - (Takeda Pharmaceuticals Company Limited 2021)*
*[a]: Duration of treatment is the mean IAT time on treatment from Study 303*

**Table 30: Time between recurrent CMV episodes – HSCT (OTUS)**

| CMV episode | Recurrence | Time since end of previous CMV episode to start of new episode (days) | Duration of treatment (days)[a] | Cumulative duration since CMV index episode (days) | Cumulative duration since CMV index episode (weeks) |
|---|---|---|---|---|---|
| [redacted] | | | | | |

*Source: OTUS - (Takeda Pharmaceuticals Company Limited 2021)*
*[a]: Duration of treatment is the mean IAT time on treatment from Study 303*

**CMV Markov model (stage 1; 0-78 weeks)**

During the first 78 weeks (Stage 1), the model adopts a 3-state Markov model. The Markov model structure is illustrated in Figure 8, where the arrows represent the transitions allowed in the model. The three health states in the model are; csCMV, n-csCMV and dead. csCMV is defined as those patients who have CMV (i.e., plasma CMV DNA concentration > LLOQ), and require treatment, and n-csCMV is defined as patients who have plasma CMV DNA <LLOQ or CMV DNA >LLOQ not requiring treatment. These health state definitions were selected because it was deemed appropriate to not only split patients in the model according to their CMV status, but to further identify patients according to those who required treatment when they had CMV and those who did not. Danish clinicians who attended the maribavir advisory board indicated that there are some patients who have CMV and are not treated because their CMV DNA concentration reading is above the LLOQ due to a minor fluctuation in viremia. There is an expectation that in some cases, a patient's natural immunity will clear the virus, and therefore monitoring and waiting is preferred over immediately initiating treatment. The three health states in the Stage 1 Markov were selected because it adequately allows the model to capture the primary endpoint from Study 303 (CMV viraemia clearance) and important secondary endpoints (recurrence of CMV viraemia) as described in section 7. Further information on the three health states in the model are below:

- **Clinically significant CMV (csCMV)**: All patients enter the model with clinically significant R/R CMV requiring treatment. This state is occupied by patients who do not achieve CMV viremia clearance (i.e., clearance defined as plasma CMV DNA concentration <LLOQ) or patients who in a previous cycle occupied the n-csCMV health state but then experience a clinically significant recurrence (i.e., plasma CMV DNA concentration >LLOQ which requires treatment).
- **No clinically significant CMV (n-csCMV)**: subjects who achieve CMV clearance or subjects who have achieved clearance and do not experience a clinically significant recurrence occupy the n-csCMV health state (i.e., plasma CMV DNA <LLOQ or CMV DNA >LLOQ not requiring treatment).
- **Dead**: All patients in the model have a risk of transitioning to the dead state; this is a final health state.



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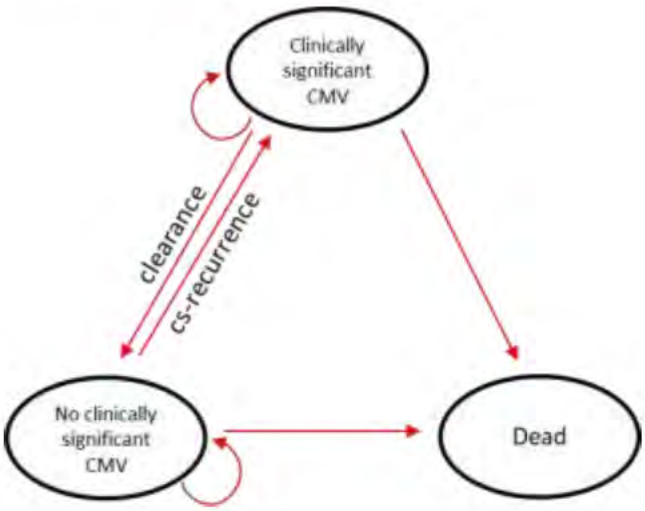
**Figure 8: Stage 1; 0-78 weeks**




Each feasible transition in the 3-state Markov model is described below:

- **csCMV → n-csCMV (clearance)**: patients may have response to treatment and achieve **CMV clearance** (i.e., plasma CMV DNA concentration <LLOQ in two consecutive readings). When this occurs, patients will transition from the csCMV to the n-csCMV state
- **csCMV → csCMV (no clearance)**: patients may have no response to treatment and remain in the csCMV health state
- **n-csCMV → csCMV (cs-recurrence):** patients may have a **clinically significant recurrence (cs-recurrence)** of CMV which occurs when a patient who has achieved CMV clearance has a CMV viral load >LLOQ which requires treatment with an anti-CMV agent
- **n-csCMV → n-csCMV (no cs-recurrence)**: patients who maintain CMV clearance and do not have a cs-recurrence remain in the n-csCMV health state
- **csCMV → dead** or **n-csCMV → dead:** patients who are alive in the csCMV or n-csCMV health states are at risk of **mortality**
- **Dead**: This is an absorbing final state

Another important component of the model structure is that the transitions between the cs-CMV state and n-csCMV state are time dependent with tunnel states used to track time since clearance (Table 31 and Table 32). This relationship was incorporated into the model following findings from a logistic regression analysis to assess the impact of specific covariates on clearance and recurrence in the Study 303 trial (Table 31 and Table 32). These findings demonstrated that time since clearance had a statistically significant impact on the odds of recurrence requiring treatment, with each additional day post-clearance lowering the odds by a factor of 0.95 (Table 31). However, despite TST being an important prognostic factor for key outcomes in SOT and HSCT patients, the logistic regression indicated that there was not a statistically significant relationship between TST and clearance or recurrence.

**Table 31: Logistic regression of confirmed CMV viraemia clearance response at week 8 from Study 303**

| Covariate | Adjusted OR (95% CI) | P value |
|---|---|---|
| [redacted] | | |



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[redacted]

*Abbreviations: CI, confidence interval; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; IAT, investigator assigned treatment; SOT, solid organ transplantation*
*Source: Completed by Takeda biostats to support submission*

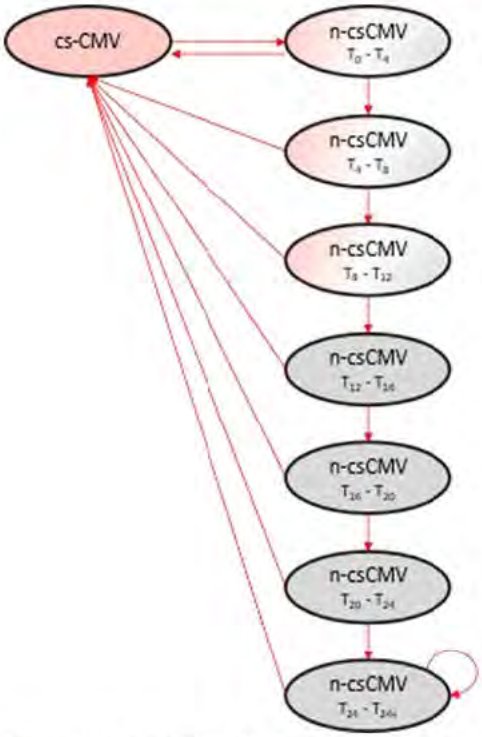
**Table 32: Logistic regression of confirmed CMV viraemia recurrence requiring treatment after clearance at week 8 from Study 303**

| Covariate | Adjusted OR (95% CI) | P value |
|---|---|---|
| [redacted] | | |

*Abbreviations: CI, confidence interval; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; IAT, investigator assigned treatment; SOT, solid organ transplantation*
*Source: Completed by Takeda biostats to support submission*

Utilisation of tunnel states allows for the dependence between the time spent in the n-csCMV state and the probability of a recurrence to be appropriately captured. Patients are tracked in 4-weekly cycles for up to 24 weeks after clearance (i.e., entry into the n-csCMV health state). As the duration of health state occupancy in the n-csCMV increases (i.e., patients maintain their clearance), the risk of recurrence reduces up to week 24 where the risk becomes constant (see section 8.2.3).
Figure 9 shows the transitions between the csCMV and n-csCMV health states.

**Figure 9: Transitions between the csCMV and n-csCMV health states**

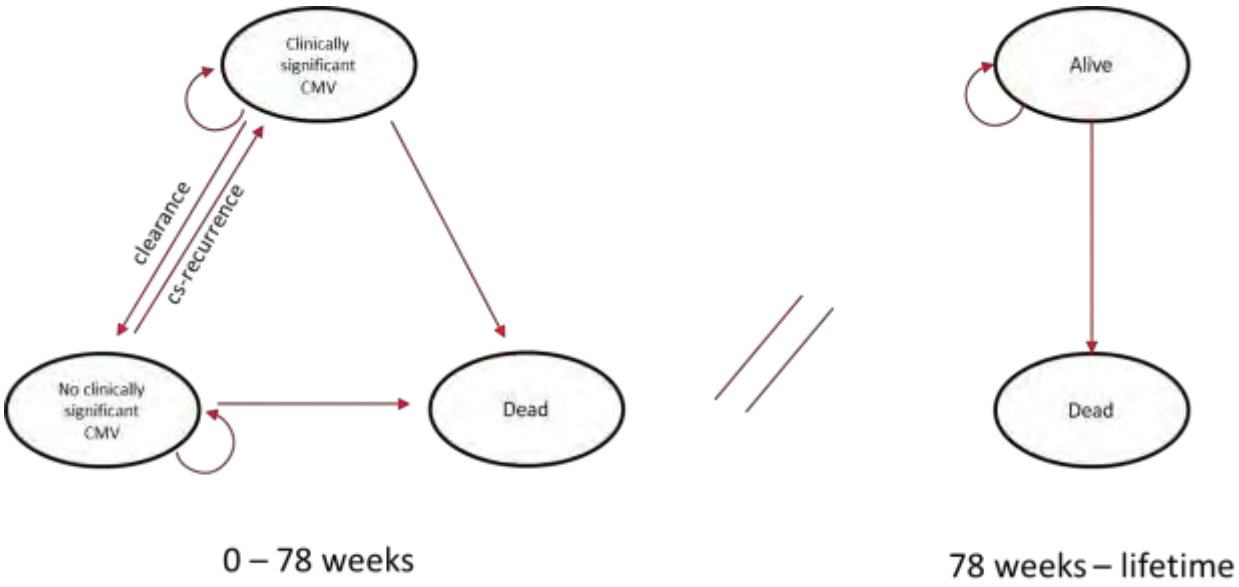



*(1) Clearance from the cs-CMV (red) state to n-csCMV (T0-T4) is informed by data from Study 303 (2) Recurrence from a hybrid n-csCMV state (red and grey) to the red cs-CMV state is informed by transitions from Study 303 or OTUS depending on whether patients are on the 1st clearance episode or 2nd clearance episode (3) Recurrence transitions from a grey n-csCMV state to a red cs-CMV state is informed by data from OTUS (4) The time points Tn - Tn+4 reflect the time in weeks patients have spent in the n-csCMV health state (5) Upon entry to the final n-csCMV tunnel state T24 - T24+ the model no longer tracks n-csCMV occupancy in 4-week increments (i.e., all patients in the n-csCMV T24 - T24+ health state have maintained clearance for a minimum of 24 weeks with no maximum time point known).*

**Alive/Dead Markov model (stage 2; 78 weeks-lifetime)**

The Markov model structure in Stage 2, from 78 weeks to the lifetime horizon (i.e., beyond 78 weeks), is illustrated in Figure 10 (alongside the Stage 1 Markov) where the arrows represent the transitions allowed in the model. From 78 weeks onwards, the model no longer tracks CMV status (i.e., whether patients are in the csCMV or n-csCMV health state) and adopts a 2-state Markov model with Alive and Dead health states. All patients who occupy either the csCMV or n-csCMV health state at 12 months (in Stage 1) enter the 'Alive' state.

**Figure 10: Markov model structure (0 to lifetime)**




Each feasible transition in the 2-state Markov model is described below:

- **Alive → Alive**: patients who do not die (i.e., 1 - p[transplant specific mortality]) remain in the alive state
- **Alive → Dead**: all patients in the alive state are at risk of background transplant specific mortality and general population mortality
- **Dead**: This is an absorbing final state

**Time horizon**

For the base case analysis, the model uses a lifetime horizon to ensure that all costs and benefits of treatment are captured. This method is in alignment with modelling guidelines from the Danish Medicines Council (44). A lifetime horizon, in a Markov model with discrete health states and fixed cycle lengths requires running the model until patients who have entered the dead state approaches 100%. A time horizon of 47 years in a starting cohort aged 53 is assumed to represent a lifetime horizon with all patients assumed dead at age 100. The Age of the population align with the baseline patient profile in Study 303 and is assumed representative for the Danish population and is evaluated to show similar results to data extraction from Scandiatransplants database. See section 5.

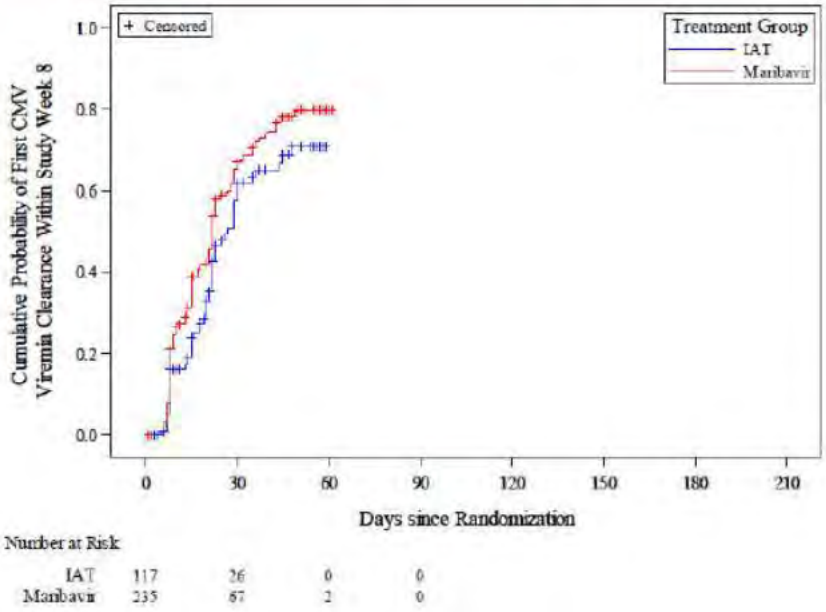
**Cycle length**

The model uses a 4-week cycle length for the first 3 years, and thereafter, switches to annual cycles. A 4-week cycle length was adopted to allow flexibility to explore earlier and faster clearance in the maribavir arm as observed in the Study 303 trial (Figure 11). However, to allow closer alignment with the primary endpoint of the trial, the first health state transition events occur at week 8 in the base case. The model includes a half-cycle correction from week 12 (cycle 3) onwards. It is not included before week 12 of the model to preserve the observations of the trial data in the first 8

weeks and to ensure alignment of the model with this endpoint. The model adjusts to annual cycles after year 3 to allow users to explore the tracking of CMV status up to year 3 in a sensitivity analysis. In addition, adjusting to annual cycles limits the number of active cells in the excel workbook to allow for faster model calculations.

A limitation of adjusting to annual cycles is that the switch from 4-week cycles to 1-year cycles does not occur precisely at year 3, rather it occurs after 2.99 years. The impact of this is that for Year 4, the annual mortality applied covers a period which is slightly greater than 1 year and therefore mortality is slightly underestimated during this period. The reason for this is because the 4-week cycles are calculated by multiplying each 4-week intervals by 7 and dividing by 365.25 to account for each fourth year when there are 366 days. Under this method, the closest time point to 3 years is 2.99 years and this was decided as the most appropriate time point to then switch to yearly cycles. Given the underestimation is occurring in both the intervention and comparator arm in the model, this limitation has no important impact on the final model conclusion.

**Figure 11: CMV Viremia clearance by treatment group - 8 weeks**




### Model perspective

The base case perspective for the cost-effectiveness analysis is the Danish payer perspective. The perspective on costs is based on the Danish Medicines Council guidelines. The perspective on health outcomes are patient quality-adjusted life-years (QALYs).

### Discount rate

Costs and health outcomes are discounted using the current annual socio-economic discount rates available at www.fm.dk. The applied discount rates are presented in Table 33.

**Table 33: Applied annual discount rates**

| Period | Annual discount rate |
|---|---|
| **0-35 years** | 3.5% |
| **36-70 years** | 2.5% |
| **>70 years** | 1.5% |

*Source:* (45)



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### Features of the economic model

Table 34 shows the factors, the included values and the justification for choosing set values in the economic model.

**Table 34: Features of the economic model**

| Current economic analysis | | |
|---|---|---|
| **Factor** | **Chosen values** | **Justification for the current approach** |
| Model structure | 2 sequential Markov models: 3-state CMV Markov (stage 1; 0-78 weeks) followed by alive/dead Markov after 78 weeks (stage 2; 78 weeks – lifetime) | The Markov approach for stage 1 allows the model to capture important distinctions in CMV status and thus the ability to link these states to other important model outcomes (quality of life, mortality, and incidence of important clinical events). The choice to adopt a 2-state model from 78 weeks onwards was based data from OTUS and dialog with Danish physicians. The physicians explained that almost all patients with CMV would be off treatment at 78 weeks because their immunity recovers enough such that their natural defences are able to keep CMV viremia at a sufficiently low level without the need for CMV treatment. |
| Cycle length | 4-weeks (week 0 to year 3)<br>1 year (year 3 to lifetime) | Study 303 CSR indicates that patients on treatment with maribavir achieve faster clearance compared with IAT. As a result, the model retains functionality to incorporate this earlier treatment effect, however, in the base case the first transition events occur at week 8. After 3-years, the model switches to an annual cycle length as the alive/dead model does not require 4-week cycles due to CMV no longer being tracked. The annual cycle length also increases the speed of the model. |
| Time horizon | Lifetime | This time horizon is sufficient to ensure that all cost and benefit differences between maribavir and IAT are captured, as suggested by the Danish Medicines Council guidelines. |
| Perspective | Danish payer perspective, with functionality for societal perspective | In line with the methods described by the Danish Medicines Council |
| Discounting | 0-35 years 3.5%, 36-70 years 2,5%, and >70 years 1,5% | In line with the methods described by the Danish Medicines Council |
| Source of utilities | Utilities were obtained from Study 303 and the vignette study. Utilities were collected using EQ-5D-5L, with imputation used to account for missing data. The utilities derived from the EQ-5D were applied in the model. Health effects are expressed in QALYs | The vignette study (see supplementary documentation) data was combined with the Study 303 trial data (with imputation) to define health state values. In addition, the vignette disutility values were used alone to define disutility values for graft loss, as no graft loss events were observed in the Study 303 trial. |
| Source of costs | Sourced from the Danish DRG-system, Rigshospitalets Labportal, and medicinpriser.dk. | In line with the methods described by the Danish Medicines Council. However, prices from Rigshospitalets Labportal are included to show a more representative costing of monitoring the decease, even though it's not listed as a source in the methods described by the Danish Medicines Council. |

*Abbreviations: CMV, cytomegalovirus; CSR, clinical study report; DRG, diagnose relaterede grupper; IAT, investigator assigned treatment; QALY, quality-adjusted life-years*

### Patient population of Economic model

The patient cohort is initialised with a set of user amendable baseline characteristics derived from Study 303 combined with data from Danish clinical practise (distribution of SOT and HSCT) (Table 36). Patient age and sex are used to estimate all-cause mortality of the cohort in the Alive/Dead Markov (Stage 2) using general population lifetables from dst.dk (HISB8) alongside transplant specific (SOT or HSCT) background mortality taken from literature (NHS Organ Donation Annual Activity Report for SOT and Hematological Malignancy Research Network for HSCT) (46,47). The maximum value, at each model time point, between either the general population lifetables or literature mortality is used to estimate all-cause mortality in the Stage 2 Markov.



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The TST parameter describes the duration of time in days that has passed since patients had their transplant. The model includes a separate TST parameter for SOT and HSCT to ensure that the Stage 2 Markov applies the appropriate time-dependent mortality risk by transplant type. Take for example, SOT patients with a median TST of 258 days; upon entry into the Phase 2 Markov after 78 weeks, the model will apply 291 days of mortality risk from year 2 to year 3 TST and then apply a full 52 weeks of year 3 to year 4 TST mortality risk (and so on) to patients from 292 days onwards. Since the Study 303 outcomes were not adjusted for TST, additional exploratory analyses were undertaken to evaluate whether any meaningful difference existed in TST by treatment arm to rule out the possibility that differences in CMV clearance and recurrence were due to TST rather than treatment effect. The results show that TST was balanced between the two arms (i.e., there was no meaningful statistical difference) and therefore the differences in CMV clearance and recurrence should not be attributed to TST (Table 35).

**Table 35: Mean and median time since transplant by treatment arm**

| Category | IAT (N=116) | Maribavir (N=234) |
|---|---|---|
| **Time since solid organ transplant (days)** | | |
| N (%) | | |
| Mean (SD) | | |
| Median | | |
| 95% CI | | |
| p-value | | |
| Mean | | |
| SEM | | |
| 95% CI | | |
| p-value | | |
| Min, Max | | |
| **Time since hematopoietic stem cell transplant (days)** | | |
| N (%) | | |
| Mean (SD) | | |
| Median | | |
| 95% CI | | |
| p-value | | |
| Mean | | |
| SEM | | |
| 95% CI | | |
| p-value | | |
| Min, Max | | |
| **Overall time since transplant (days)** | | |
| N (%) | | |
| Mean (SD) | | |
| Median | | |
| 95% CI | | |
| p-value | | |
| Mean | | |
| SEM | | |
| 95% CI | | |
| p-value | | |
| Min, Max | | |

*Source: Completed by Takeda biostats to support HTA submissions*



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**Table 36: Baseline patient characteristics**

| Patient characteristic | Value (SE) |
|---|---|
| Mean age | 53 (0.70) [a] |
| Sex (% of male patients) | 61% (0.03) [b] |
| Median time since transplant (days) – SOT | [redacted] |
| Median time since transplant (days) – HSCT | |
| Mean patient weight (kg) | 74.80 (0.97) [a] |
| Type of transplant (% SOT patients) | 73% * |

*Abbreviations: SE, standard error; SOT, solid organ transplant; HSCT, hematopoietic stem cell transplantation*
*Source: Study 303 CSR (Takeda Pharmaceuticals Company Limited 2021) and local input*
*[a] standard error is calculated as* $\frac{Standard\ deviation}{\sqrt{n}}$*, where n is the total number of patients in the trial (352) and the standard deviation is from the Study 303 CSR*
*[b] standard error is calculated as* $\sqrt{\frac{p*(1-p)}{n}}$*, where p is the probability and n is the total number of individuals in the trial*
*[c] Completed by Takeda biostats to support HTA submissions*

Finally, the model separately tracks SOT and HSCT patients (i.e., there are separate Markov traces for these patients). The baseline type-of-transplant parameter is used to derive a weighted average cost-effectiveness result for the overall ITT population.

**Treatment pathway**

All patients entering the model are randomized to treatment with maribavir or IAT for the treatment of R/R CMV. A cohort of patients in the CMV Markov will require retreatment: 1) Patients who do not achieve clearance and remain in the csCMV health state at week 8, and 2) Patients who achieve clearance and then have a csCMV recurrence between weeks 8 and 78 (i.e., patients who occupied the n-csCMV health state in the prior cycle and occupy the csCMV health state in the current cycle). From weeks 0 to 8, all patients are assumed to remain on their respective study assigned treatment (maribavir or IAT), with costs adjusted by a time on treatment parameter to account for treatment discontinuation (see section 8.5). From week 8 onwards, all patients who occupy the csCMV health state (minus those who discontinue from treatment see section 8.5) are assumed to receive treatment with IAT.

In the intervention arm, patients receive maribavir as their first treatment and IAT as a retreatment intervention (patients who have clinically significant recurrence). For the comparator arm, patients receive IAT as their first treatment and IAT as a retreatment. The model allows users to define IAT drug distribution based on transplant type and whether patients are receiving an initial IAT treatment or retreatment. In the base case, it is assumed the IAT distribution is the same as the proportions observed in Study 303 and does not vary between SOT and HSCT. This assumption was used to ensure alignment with Study 303. The model retains functionality to allow for different IAT treatment distributions for the initial treatment and retreatment. The four IAT distribution options included in the model are:

- IAT distribution for SOT patients – initial treatment
- IAT distribution for SOT patients – retreatment
- IAT distribution for HSCT patients – initial treatment
- IAT distribution for HSCT patients – retreatment

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

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

Table 37 shows the input data used in the model and where they were obtained. Section 8.2.2 shows how they were obtained.

**Table 37: Input data used in the model**

| Name of estimates | Results source | Input value used in the model | How is the input value obtained/estimated |
|---|---|---|---|
| **Transition probabilities** ***Clearance, discontinuation, recurrence, and mortality*** | SOLSTICE 303 (2)<br>SOLSTICE 303 CSR (23)<br>Study 303 IPD analysis (42)<br>OTUS (see supplementary documentation) | Table 73<br>Table 41<br>Table 29 and Table 30<br>Section 8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice | See the tables listed in the left column |
| **Disease complications** ***Graft loss*** | Hakimi, Aballea et al. (2017) (13)<br>GENOME Canada study (see supplementary documentation) | Table 60<br>Table 59<br>Table 81<br>Table 70<br>Table 61 | See the tables listed in the left column |
| **GvHD and relapse in underlying condition** | Hahn, McCarthy et al. (2008) (48)<br>Cantoni, Hirsch et al. (2010) (49)<br>HMRN data (50) | See section 8. Health economic analysis<br>See section 8.4 | See the tables listed in the left column |
| **Adverse reactions (occurrence)** | SOLSTICE 303 (2) | Table 82<br>Table 71<br>Table 63 | See the tables listed in the left column |
| **Utility values** | SOLSTICE 303 (2)<br>Study 303 IPD analysis (42)<br>Vignette study (see supplementary documentation)<br>NICE 2019 (43) | Table 69<br>See section 8.4.2 Health state utility values used in the health economic model | See the tables listed in the left column |



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| Name of estimates | Results source | Input value used in the model | How is the input value obtained/estimated |
|---|---|---|---|
| **Utility values (adverse events)** | Sullivan, Slejko et al. 2011 (51)<br>Ossa, Briggs et al. 2007 (52)<br>Nafees, Lloyd et al. 2017 (53)<br>Bullement, Nathan et al. 2019 (54)<br>Nafees, Stafford et al. 2008 (53)<br>Beusterien, Davies et al. 2010 (55)<br>Tolley, Goad et al. 2013 (56) | Table 71 | See the tables listed in the left column |
| **Treatment/administration/monitoring/AE costs** | Medicinpriser.dk (57)<br>DRG 2022 (58)<br>Labportal.rh.dk (59) | Se section 8.5 Resource use and costs<br>Table 78<br>Table 77<br>Table 79<br>Table 80 | See the tables listed in the left column |
| **Time on treatment** | SOLSTICE 303 CSR (23) | Table 73 | See the tables listed in the left column |
| **Population characteristics** | SOLSTICE 303 (2) | Table 36 | See the tables listed in the left column |
| **IAT distribution** | SOLSTICE 303 (2) | Table 72 | See the tables listed in the left column |

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

**Patient population**

The Danish patient population: see section 5

Patient population in the clinical documentation submitted: see section 7

Patient population in the health economic analysis submitted: see section 7

The population in the model consists of patients with CMV who are R/R to CMV treatment after HSCT or SOT. The model population is aligned with the inclusion criteria used in Study 303:

- Participants ≥12 years of age with a life expectancy ≥8 weeks, however no patients under the age of 18 were enrolled and therefore the minimum user defined starting age in the model is 18
- Recipient of HSCT or SOT



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- Documented CMV in whole blood or plasma, with a screening value of greater than or equal to ≥2730 IU/mL in whole blood or ≥910 IU/mL in plasma in 2 consecutive assessments, separated by ≥1 day
- Current CMV infection that is refractory to the most recently administered of the four anti-CMV treatment agents (valganciclovir, ganciclovir, foscarnet, and cidofovir)

Takeda Denmark A/S held an advisory board in 2022 to uncover potential differences between the study population and the Danish population of R/R CMV patients. All the physicians present at the advisory board stated that they believed the 303 Study to be representative for the Danish patient population with regard to types of transplants and current antiviral CMV treatments. Table 38 shows the baseline characteristics for the study, model population, and Danish clinical practice. However, it should be noted that direct comparison with the Danish population is difficult due to lack of registries or publications that concern the Danish population.

**Table 38: Patient population**

| Patient population | Clinical documentation | | Used in the model | | Danish clinical practice |
|---|---|---|---|---|---|
| **Age (year)** | 53 | | 53 | | 51,01 years (data supplied by Scandiatransplant by request of Takeda Denmark A/S) |
| **SOT & HSCT, %** | SOT<br>HSCT | 60%<br>40% | SOT<br>HSCT | 60%<br>40% | N/A (Danish physicians could not give exact estimates of how many patients that becomes R/R CMV after transplantation, and there is no Danish registries that contain this data). An estimate has been based on a published literature review and is assumed to be 73% SOT and 23% HSCT. See section 5. |
| **Distribution of the anti-CMV treatments, %** | Ganciclovir/ Valganciclovir<br>Foscarnet<br>>1 anti-CMV | 51%<br>43%<br>6% | Ganciclovir/ Valganciclovir<br>Foscarnet<br>>1 anti-CMV | 51%<br>43%<br>6% | N/A (Danish physicians could not give exact estimates of how many patients receive treatment with the listed anti-CMV treatments, but stated that they are the ones used in Danish clinical practice and they expect the distribution to be representative. See section 5. |
| **Presence of anti-CMV treatment resistance mutation** | Yes<br>No | 59%<br>41% | Yes<br>No | 59%<br>41% | N/A (Danish physicians don't test for resistance on a regular basis and the percentage of Danish patients who are categorized as resistant is therefore not possible to determine) |



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| Patient population | Clinical documentation | Used in the model | Danish clinical practice |
|---|---|---|---|
| **Sex (male %)** | 61% | 61% | N/A (Danish physicians could not give exact estimates of the distribution of sex, but they expect the distribution to be representative. See section 5. |
| **Weight (Kg)** | 74.8 | 74.8 | N/A (Danish physicians could not give exact estimates of the mean weight, but they expect the weights to be representative. See section 5. |

*Abbreviations: CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; Kg,, kilogram; R/R, refractory with or without resistance; SOT, solid organ transplantation*

**Intervention**

Intervention as expected in Danish clinical practice: see section 5.3

Intervention in the clinical documentation submitted: see section 7

Intervention as in the health economic analysis submitted: see section 7

The intervention of interest in the model is maribavir (Table 39).

**Table 39: Intervention**

| Intervention | Clinical documentation (including source) | Used in the model (number/value including source) | Expected Danish clinical practice (including source if known) |
|---|---|---|---|
| **Posology** | Maribavir 400 milligrams (mg) (2x200 mg tablets) administered twice daily for 8 weeks | Maribavir 400 milligrams (mg) (2x200 mg tablets) administered twice daily for 8 weeks | The recommended dose of maribavir is 400 mg (two 200 mg tablets) twice daily resulting in a daily dose of 800 mg for 8 weeks. |
| **Length of treatment (time on treatment) (mean/median)** | Mean time on treatment in the 303 study is 7.50 weeks (SE 0.75) | Mean time on treatment in the 303 study is 7.50 weeks (SE 0.75) | The mean time on treatment from the 303 study is expected to be representative for Danish clinical practice. |
| **Criteria for discontinuation** | Development of any exclusion criteria that interfered with analysis of the study results (i.e., withdrawal from the study). See Figure 4. | The rate of discontinuation in the model is based in data from the 303 study. See section 7. | Expected to be equal to the ones observed in the 303 study (2). |



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| Intervention | Clinical documentation (including source) | Used in the model (number/value including source) | Expected Danish clinical practice (including source if known) |
|---|---|---|---|
| **The pharmaceutical's position in Danish clinical practice** | Treatment of R/R CMV patients who have received SOT- or HSCT. See section 5. | Treatment of R/R CMV patients who have received SOT- or HSCT. See section 5. | Treatment of R/R CMV patients who have received SOT- or HSCT. See section 5. |

*Abbreviations: CMV, cytomegalovirus; HSCT, haemopoietic stem cell transplantation; mg, milligrams; R/R, refractory with or without resistance; SOT, solid organ transplantation*

**Comparators**

The current Danish clinical practice: see section 5.2.1 and 5.2.2
Comparator(s) in the clinical documentation submitted: see section 7
Comparator(s) in the health economic analysis submitted: see section 7

The comparator in the model is IAT which is aligned with the comparator arm in Study 303 and is a blend of the four most commonly used anti-CMV agents:

- IV ganciclovir
- Oral valganciclovir
- IV foscarnet
- IV cidofovir

Study 303 was conducted as an open-label design, principally because of the need for the physician to individualize drug selection for treatment-refractory patients in the IAT arm. Further, it would in practice not be possible to blind the physicians due to administration differences between the drugs. The open-label design enabled physicians to choose the appropriate therapy based on clinical data and judgement, institutional guidelines, and other relevant published literature. The IAT arm used in Study 303 was deemed consistent with how anti-CMV agents are provided to R/R patients in Danish clinical settings. See references in Table 40.

**Table 40: Comparator(s)**

| Comparator | Clinical documentation (including source) | Used in the model (number/value including source) | Expected Danish clinical practice (including source) |
|---|---|---|---|
| **Posology** | See section 5.2.3 | See section 5.2.3 | See section 5.2.3 |
| **Length of treatment** | See section 5.2.3 | See section 5.2.3 | See section 5.2.3 |
| **The comparator's position in the Danish clinical practice** | See section 5.2.3 | See section 5.2.3 | See section 5.2.3 |

**Relative efficacy outcomes**

The relative efficacy outcomes in the submitted clinical documentation: see section 7.
Relevance of the documentation for Danish clinical practice: see Appendix D Efficacy and safety results per study).
The relative efficacy outcomes in the submitted health economic analysis: see section 7.



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### Transition probabilities

Transition probabilities in the model are defined by three key clinical parameters: clearance, recurrence, and mortality. Clearance (defined as plasma CMV DNA concentration <LLOQ in two consecutive readings, separated by at least 5 days) is the primary treatment effect associated with an anti-CMV agent and defines the transition from csCMV to n-csCMV. Clinically significant recurrence (defined as those who after achieving clearance, have a plasma CMV DNA >LLOQ which requires treatment with an anti-CMV agent) defines the transition from n-csCMV to csCMV. Finally, as illustrated in the Markov structural diagrams (Figure 10), all patients are at risk of mortality. The input values which inform the transition probabilities are described in the sections below, with an overview of all transition probabilities in Appendix N Transition matrices.

### Clearance

Clearance probabilities for maribavir were taken directly from Study 303. For the IAT arm, no published evidence was identified which reported clearance data for any of the individual IAT drugs in an R/R population. Therefore, the clearance probabilities for IAT were also taken from Study 303. The first health state transition events in the model occur at week 8 and are informed by the primary endpoint value from Study 303 (confirmed CMV viremia clearance at the end of week 8). For maribavir, the response (i.e., CMV viraemia clearance) observed in Study 303 was 55.7% and for IAT was 23.9% (Figure 5). These values were used directly to inform the transition between the csCMV and n-csCMV health state between weeks 0 to 8 (Table 41).

From week 8 to 78, patients who occupy the csCMV health state in either the maribavir or IAT arm are assumed to receive IAT retreatment. Therefore, the clearance probabilities utilised from week 8 through week 78 are derived from the IAT arm of Study 303. Specifically, the response observed at week 8 in the IAT arm of Study 303 (23.9%) has been converted into a 4-week transition probability and used for the remaining cycles of the CMV Markov. Retreatment with maribavir instead of IAT in the maribavir arm in the intervention arm is also included as a scenario analysis (section 8.7.1 Deterministic sensitivity analyses). From week 78 onwards (i.e., the start of the Alive/Dead Markov), the model no longer tracks CMV status, and therefore, clearance probabilities are no longer of relevance.

**Table 41: Clearance transition probabilities from csCMV to n-csCMV**

| Time point | Maribavir: Mean (SE) | IAT: Mean (SE) |
|---|---|---|
| Week 0 to 8 | [redacted] | |
| Week 8 to 78 | | |
| Week 78 onwards | | |

*Source: Study 303 CSR* (23)

*^The 23.9% mean value has been converted into a 4-week probability to align with the 4-week cycle lengths in the model*

*NA: Not applicable; SE: standard error - calculated using the formula:* $\sqrt{\frac{p*(1-p)}{n}}$*, where p is the incidence percentage and n is the number of individuals in the trial arm.*

### Clinically significant recurrence

Clinically significant recurrences (i.e., CMV recurrences that require treatment) are included in the model with decreasing rates of recurrences based on time since clearance (i.e., duration of time patients occupy the n-csCMV health state). The model structure is such that the transitions between the cs-CMV state and n-csCMV state have tunnel states to track time since clearance which allows for the inclusions of the decreasing rates of recurrence. This approach is validated by findings from the logistic regression analysis on the outcomes of clearance and clinically significant recurrence in the Study 303 trial and by data from the OTUS studies (Table 31 and Table 32).

Logistic regression models were run on Study 303 to assess the impact of different covariates on the odds of clearance and clinically significant recurrence. The results of the logistic regression analysis are given in Table 31. The odds of recurrence requiring treatment were also shown to be impacted by treatment group (with maribavir decreasing the odds of recurrence by a factor of 0.32), and despite not being statistically significant at the 5% threshold, the p-value was very small at 0.06. This shows a strong relationship between the treatment received and the likelihood of recurrence, and thus, provides support for the use of treatment-specific risks for recurrence requiring treatment. Additionally, time since clearance showed a statistically significant impact on the odds of clinically significant recurrence, showing that each additional day post-clearance lowers the odds by a factor of 0.95.

The data from OTUS also validates the use of decreasing rates of recurrences with longer time in clearance, with the results providing further evidence of different rates of recurrences for patients who have their 1st clearance versus 2nd clearance. The OTUS study (Table 42, Table 43, Table 44 and Table 45) demonstrates that when time since clearance is low (week 0 to 8 and week 8 to 20) patients have the highest risk of recurrence, and when time since clearance is high (week 20 to week 52 and week 52 to week 104) the risk of recurrences is lower.

**Table 42: KM estimates to first CMV recurrence from OTUS (SOT)**

| Time | Percentage having event | Additional events between time points | Total (N) | Events (n) | Censored |
|---|---|---|---|---|---|
| Day 56 (week 8) | [redacted] | | | | |
| Day 140 (week 20) | | | | | |
| Day 365 (week 52) | | | | | |
| Day 730 (week 104) | | | | | |

*Source: OTUS - (Takeda Pharmaceuticals Company Limited 2021)*

**Table 43: KM estimates to first CMV recurrence from OTUS (HSCT)**

| Time | Percentage having event | Additional events between time points | Total (N) | Events (n) | Censored |
|---|---|---|---|---|---|
| Day 56 (week 8) | [redacted] | | | | |
| Day 140 (week 20) | | | | | |
| Day 365 (week 52) | | | | | |
| Day 730 (week 104) | | | | | |

*Source: OTUS - (Takeda Pharmaceuticals Company Limited 2021)*

**Table 44: KM estimates to second CMV recurrence from OTUS (SOT)**

| Time | Percentage having event | Additional events between time points | Total (N) | Events (n) | Censored |
|---|---|---|---|---|---|
| Day 56 (week 8) | [redacted] | | | | |
| Day 140 (week 20) | | | | | |
| Day 365 (week 52) | | | | | |
| Day 730 (week 104) | | | | | |

*Source: OTUS - (Takeda Pharmaceuticals Company Limited 2021)*

**Table 45: KM estimates to second CMV recurrence from OTUS (HSCT)**

| Time | Percentage having event | Additional events between time points | Total (N) | Events (n) | Censored |
|---|---|---|---|---|---|



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| | |
|---|---|
| Day 56 (week 8) | [redacted] |
| Day 140 (week 20) | |
| Day 365 (week 52) | |
| Day 730 (week 104) | |

*Source: OTUS - (Takeda Pharmaceuticals Company Limited 2021)*

Clinically significant recurrence probabilities for maribavir and IAT were taken from Study 303 and OTUS. For patients who achieve clearance at week 8, the rates for the first clinically significant recurrence are informed by the treatment on which the patient achieved clearance. These treatment-specific rates of recurrence are only applied in the first 12 weeks following the first clearance event (from study week 8 through study week 20) and are taken directly from the recurrence rates observed in Study 303. It should be noted as the model has separate transition probabilities for mortality, the clinically significant recurrence rates from Study 303 were adjusted for mortality to avoid underestimating risk of recurrence (Table 46). Unadjusted results from the CSR for patients who cleared at week 8 and had a clinically significant recurrence between week 8 and 20 are 25.95% for maribavir and 35.71% for IAT (Table 46). Mortality-adjusted results from the CSR for patients who cleared at week 8 and had a clinically significant recurrence between week 8 and 20 are 26.98% for maribavir and 37.03% for IAT (Table 46). These adjusted values have been converted into 4-week probabilities and then incorporated into the model (see Table 47).

**Table 46: Probability of recurrence between week 8 and week 20 – Study 303 figures and calculations**

| | IAT | Maribavir | Pooled |
|---|---|---|---|
| Cleared at week 8 (# of patients)* | [redacted] | | |
| Clinically significant recurrence by week 20 (# of patients) | | | |
| No recurrence (# of patients) | | | |
| Died (# of patients) | | | |
| Probability of recurrence (unadjusted for mortality) | | | |
| Probability of recurrence (adjusted for mortality) | | | |

*Source: Study 303 CSR (Takeda Pharmaceuticals Company Limited 2021), number of patients who died provided by Takeda biostats to support HTA submissions*

**Number of patients who cleared at week 8 who died before or at week 20*

Treatment-specific rates of clinically significant recurrence are used between weeks 8 and 20 for the first recurrence event following clearance with maribavir or IAT at week 8 and are taken from Study 303. All other recurrences (i.e. first recurrences that occur between weeks 21 and 78 and all recurrences after a second clearance event) are independent of treatment and informed exclusively by data from OTUS. The recurrence rates from OTUS were calculated by first converting the probability of recurrence (equal to the percentage of additional events found in Table 42, Table 43, Table 44 and Table 45) for each respective timepoint into 4-week probabilities for SOT and HSCT, respectively. Then each of these probabilities were weighted by the baseline distribution of patients in the SOT (73%) and HSCT (27%) populations (Table 36) and summed together to give an overall probability of recurrence. Rates for first recurrences occurring 16 weeks, 20 weeks, or 24+ weeks from first clearance (study week 8) are shown in Table 47. Rates for subsequent recurrences are presented in Table 48.

**Table 47: 4-week probability of first recurrence after CMV clearance (study week 8) by time since clearance**

| Weeks since 1st clearance | IAT | Maribavir | Source |
|---|---|---|---|
| 4 | [redacted] | | |
| 8 | | | |
| 12 | | | |
| 16 | | | |
| 20 | | | |
| 24 onwards | | | |



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*Source: Study 303 CSR (Takeda Pharmaceuticals Company Limited 2021)*
*†26.0% mortality-adjusted recurrence rate from Study 303 converted into a 4-week probability*
**35.0% mortality-adjusted recurrence rate from Study 303 converted into a 4-week probability*
*Ω Data from OTUS converted into a 4-week probability*

**Table 48: 4-week probability of subsequent recurrences after second CMV clearance by time since clearance**

| Weeks since 2nd clearance | IAT | Maribavir | Source* |
|---|---|---|---|
| 4 | [redacted] | | |
| 8 | | | |
| 12 | | | |
| 16 | | | |
| 20 | | | |
| 24 onwards | | | |

*Source: OTUS - (Takeda Pharmaceuticals Company Limited 2021)*
** Data from OTUS converted into a 4-week probability*

**Mortality 0 to 8**

In the Study 303 IPD analysis, it was observed that neither treatment, transplant type nor health state had a statistically significant impact on mortality in the first 8 weeks of the study. However, following discussions with clinicians, it was advised that because the underlying disease states for SOT and HSCT patients are different, it would be most appropriate to use transplant-specific mortality rates.

To allow the model to match the primary study endpoint in the Study 303 trial, there are no clearance, recurrence or mortality events between week 0 to 8 in the economic model. Therefore, the first mortality counts are observed in week 8 in the economic model and are aligned with the mortality that was observed in the Study 303 IPD analysis and are transplant specific. Mortality was assumed to be the same for the csCMV and n-csCMV health states for weeks 0-8 (Table 49).

**Table 49: Mortality rates for weeks 0 to 8**

| Time point | SOT Mean (SE) | HSCT Mean (SE) |
|---|---|---|
| Week 8 | [redacted] | |

*Source: Study 303 IPD Analysis (Takeda Pharmaceuticals Company Limited 2021)*
*SE: standard error, this was calculated as* $\sqrt{\frac{p*(1-p)}{n}}$*, where p is the incidence percentage and n is the number of individuals in the trial arm.*

**Week 8 to end of Stage 1**

In the KM plot (Figure 12), in the first 8 weeks (day 0 to day 56), there is overlap in the curve and thereafter (from days 56 to 140) there is a clear separation between the maribavir and IAT curves with higher mortality observed in the IAT arm at day 140. These observations provide supporting evidence that superiority of maribavir in achieving CMV clearance over IAT is resulting in later mortality benefits.

Further supporting the relationship between CMV status and mortality outcomes are publications by Camargo, Kimble et al. 2018 (60) and Hakimi, Aballea et al. 2017 (13). Camargo et al., 2018 explored the impact of persistent viraemia (patients who failed to clear CMV by treatment day 35) versus cleared viraemia (patients who cleared within 35 days of treatment) on all-cause mortality in HSCT, and Hakimi et al., 2017 (13) explored the differences in all-cause mortality depending on an early CMV infection in SOT (CMV within 3-months post-SOT (E-CMV)) or late CMV infection (CMV beyond 3-months post-SOT (L-CMV-3M) or CMV beyond 6-months but less than 2-years post-SOT (L-CMV-6M)). Both studies showed a relationship between CMV status and mortality for both HSCT (60) and SOT (13), with higher mortality observed in patients with CMV (see Table 50 and Table 51). It should be noted that the mortality risks from Hakimi et al., (2017) (13) represent a heterogenous population that does not necessarily represent the same population as the Study 303 trial. Regardless, it still provides further evidence that CMV has an impact on mortality and therefore supports the appropriateness of the health-state specific mortality estimates used in our base case model. This relationship between mortality and CMV was further confirmed by clinicians participating in the Danish advisory board.

| | 100 days post HSCT | | 200 days post HSCT | | 365 days post HSCT | |
|---|---|---|---|---|---|---|
| | Unresolved CMV viremia at day 35 | Resolved CMV viremia within 35 days | Unresolved CMV viremia at day 35 | Resolved CMV viremia within 35 days | Unresolved CMV viremia at day 35 | Resolved CMV viremia within 35 days |
| All-cause mortality | 22% | 7% | 30% | 12% | 49% | 22% |
| 4-week probability | 6.72% | 2.01% | 2.22% | 1.39% | 3.17% | 1.68% |

*Source: Camargo et al., 2018* (60)

**Table 51: All-cause mortality – SOT**

| | E-CMV | | L-CMV-3M | | L-CMV-6M | |
|---|---|---|---|---|---|---|
| | With CMV, n (%) | Without CMV, n (%) | With CMV, n (%) | Without CMV, n (%) | With CMV, n (%) | Without CMV, n (%) |
| All-cause mortality (overall) | 77/1082 (7.12) | 61/2146 (2.84) | 51/962 (5.30) | 27/2028 (1.33) | 24/586 (4.10) | 12/1245 (0.96) |
| 4-week probability | 0.57% | 0.22% | 0.42% | 0.10% | 0.32% | 0.07% |

*Source: Hakimi et al., 2017* (13)



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*E-CMV: Early CMV infection: infection within 3 months of transplant;, L-CMV-3M: infection occurring 3 or more months post-transplant; L-CMV-6M: infection occurring 6 or more months post-transplant. The reported all-cause mortality from Hakimi et al. is a 1-year mortality. These have been converted into 4-week probabilities by converting the 1-year mortality probability into a 1-year rate, which was then converted into a 4-week probability. The formulas used are:* $Rate = \frac{-ln(1-prob)}{time}$, $Probability = 1 - e^{-(rate*time)}$

The mortality transition probabilities used in the model were taken from the Study 303 IPD analysis. In the IPD analysis, patients were classified into two categories, response (patients achieving CMV viraemia clearance) and no response (all patients not achieving CMV viraemia clearance) at week 8 as per the primary end-point of Study 303 (see Section 7). Then, the number of mortality events in each category at any point from week 8 up to the end of the trial (week 20) were calculated. This produced a 12-week probability of mortality for these two categories, where response is defined as n-csCMV and no response as csCMV. The 12-week probabilities were converted into 4-week probabilities and used to estimate the transition probabilities for mortality from week 8 to 78 (Table 52).

Background sex- and age-specific general population mortality were not added to the transplant-specific mortality rates because the mortality probabilities taken from Study 303 were considered to implicitly account for a patient's background risk through the mortality risk figures that were calculated. Therefore, inclusion of background sex- and age-specific population on top of the Study 303 IPD mortality figures would represent competing risks.

**Table 52: Mortality rates for weeks 8 to 78**

| Time point | csCMV (SE) | n-csCMV (SE) |
|---|---|---|
| Weeks 8 to 78 | [redacted] | |

*Source: Study 303 IPD Analysis (Takeda Pharmaceuticals Company Limited 2021)*
*^Rates have been presented as 4-week probabilities*
*SE: standard error, calculated as* $\sqrt{\frac{p*(1-p)}{n}}$, *where p is the incidence percentage and n is the number of individuals in the trial arm.*

Patients in the IPD analysis were not further categorized for mortality by health state and transplant type due to sample size, where patient numbers become too few in each respective category to provide robust and plausible estimates. Specifically, in the SOT cohort, 0% mortality and 1.8% mortality were observed over 12 weeks in the response group and no-response group, respectively (Table 53). Once these are converted into 4-week probabilities, this would result in 4-week probabilities of 0% and 0.6% for the n-csCMV and csCMV health states, respectively. Using these values as input parameters in the model may result in mortality being underestimated for the SOT cohort. Therefore, to ensure the model take a conservative approach and retains clinical validity, health state only mortality has been used in the base case rather than health state and transplant.

**Table 53: Time to all-cause mortality by response vs no response from week 8 to 20 by transplant type**

| Time point | Response at week 8 | | No response at week 8 | |
|---|---|---|---|---|
| | HSCT | SOT | HSCT | SOT |
| Number of subjects who died [n (%)] | [redacted] | | | |

*Source: Study 303 IPD Analysis (Takeda Pharmaceuticals Company Limited 2021)*
*HSCT=Hematopoietic stem cell transplant; SOT=Solid organ transplant*

The model includes the option to use data on the risk of CMV-related mortality from week 8 onwards for SOT and HSCT from published literature in a scenario analysis. For HSCT, the data comes from Camargo et al., (2018) (60) and for SOT, the literature data comes from Hakimi, Aballea et al. (2017) (13) (Table 50 and Table 51). In the model, when selecting the use of published literature, for Hakimi et al., (2017) (13), the beyond 6-months mortality (0.32% for csCMV and 0.07% for n-csCMV, see Table 51) is used as this most closely corresponds to the TST used in the model (258 days for SOT patients, see section 8.1 Model).



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**Week 78 and onwards**

**SOT**

Transition probabilities in the Stage 2 Markov are governed by long-term mortality estimates. In the absence of availability trial data or real-world evidence study results, pragmatic desk research was completed to identify published long-term, transplant-specific mortality rates.

For patients who received SOT, mortality was estimated based on data taken from the NHS Organ Donation and Transplantation Annual Activity Report (46). The NHS Organ Donation Annual Activity Report was chosen as it was the best European data available. One-, two-, five-, and ten-year post-transplant patient survival estimates for first non-paediatric heart, lung, liver, and kidney transplants of all donor types (shown in Table 54) were converted into their corresponding annual conditional survival probabilities by calculating the survival rates between each published time point. For lung, donor after circulatory death (DCD) donor types, and the survival probabilities were available only for one-, two- and three-year post-transplant and so this organ and donor type was only included for the first three years post-transplant in the mortality calculations.

**Table 54: SOT survival probabilities**

| Organ | Donor Type | 1-year Survival % | 2-year Survival % | 5-year Survival % | 10-year Survival % |
|---|---|---|---|---|---|
| **Kidney** | DBD | 97 | 95 | 89 | 77 |
| **Kidney** | DCD | 97 | 95 | 86 | 76 |
| **Kidney** | Living | 99 | 98 | 95 | 87 |
| **Heart** | DBD | 84 | 78 | 70 | 64 |
| **Lung** | DBD | 83 | 75 | 58 | 38 |
| **Lung** | DCD | 76 | 68 | 61* | N/A |
| **Liver** | DBD | 94 | 92 | 84 | 68 |

*Source: NHS Organ Donation Annual Activity Report* (46)
*DBD: donor after brain death; DCD: donor after circulatory death; N/A: not available*
**3-year survival estimate, as the 5-year survival estimate was not available*

The annual conditional survival probabilities for each organ and year category were then converted into annual conditional mortality probabilities as shown in Table 55. To account for years where there is no published data available (e.g. year 6), a constant rate of mortality is assumed between the most recent available year and the next available year. This method requires the difference to be taken between available years to then derive a constant annual probability to be applied in each year. For example, the difference between the 5- and 10-year survival probabilities are used to derive an annual mortality probability for year 6, 7, 8 and 9. SOLSTICE reported the baseline transplant distribution, the donor type for each transplant has not been reported. Therefore, a simple average mortality was taken between donor types for each available organ. This average organ mortality was then weighted using the baseline transplant distribution from OTUS to calculate the average SOT mortality. The calculations used to derive the average mortality have been provided as an additional excel sheet in the model listed as question 46.

| Organ | Donor type | Annual probability at year 1 | Annual probability at year 2 | Annual probability at year 5 | Annual probability at year 10 |
|---|---|---|---|---|---|
| Kidney | DBD | 0.03 | 0.02 | 0.02 | 0.03 |
| Kidney | DCD | 0.03 | 0.02 | 0.03 | 0.02 |
| Kidney | Living | 0.01 | 0.01 | 0.01 | 0.02 |
| Heart | DBD | 0.16 | 0.07 | 0.04 | 0.02 |
| Lung | DBD | 0.17 | 0.10 | 0.08 | 0.08 |
| Lung | DCD | 0.24 | 0.11 | - | - |



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| | | | | | |
|---|---|---|---|---|---|
| Liver | DBD | 0.06 | 0.02 | 0.03 | 0.04 |
| Liver | DCD | 0.06 | 0.01 | 0.04 | - |
| Average | - | **0.10** | **0.05** | **0.04** | **0.04** |

*Source: NHS Organ Donation Annual Activity Report* (46)
*DBD: donor after brain death; DCD: donor after circulatory death*

The weighted average annual probabilities (using the baseline distribution for each baseline SOT as the weighting) were then compared to the general population age- and sex-adjusted mortality values (47) and the largest mortality rate of the two was selected for each age in the model (starting at age 53). In selecting the appropriate annual probability to compare to the general population mortality, an adjustment was made for TST (a baseline model input parameter from Study 303 of 258 days for the SOT population). To do this, the time point used to select either the 1-, 2-, 5-, or 10-year probability was equal to the time elapsed in the model plus TST of 258 days. For example, the SOT TST is set to 258 days and upon entry into the Stage 2 Markov, from the 78-week Stage 1 Markov, the model will apply 291 days of mortality risk from year 2 to year 3 TST and then apply a full 365 days from year 3 to year 4 TST mortality risk (and so on) to patients from 292 days onwards.

**HSCT**

The methods used to predict long-term mortality for patients with HSCT, during the first five years of the maribavir model, are data from the Haematological Malignancy Research Network (HMRN). In alignment with the previous approach conducted for the application of letermovir and approved by NICE, data beyond 5 years were not applied, as the HMRN data showed high attrition. The mortality rate for each year was converted to an annual probability, shown in Table 56.

**Table 56: HSCT mortality rate and annual probability**

| Years post-transplant | Mortality rate | Annual probability |
|---|---|---|
| 2- years post-transplant | 0.19 | 0.173 |
| 3- years post-transplant | 0.11 | 0.104 |
| 4 -years post-transplant | 0.05 | 0.049 |
| 5 -years post-transplant | 0.06 | 0.058 |

*Source: NICE committee papers* (43)
*HMRN: The Haematological Malignancy Research Network; HSCT=Hematopoietic stem cell transplant*

To address the issue relating to modelling HSCT mortality in the period beyond the 5 years of data available from the HMRN, the model uses data from Martin et al. (2010) (61). Martin et al. 2010 provides KM plots for survival starting from 5 years post HSCT, split by three different age groups: less than 18 years; 18 to 45 years; and, greater than 45 years. The latter subgroup represents the closest age match to the Study 303 population, and therefore, these data are the most relevant to use to inform the model. Survival curves were fit to the data to extrapolate and inform mortality rates beyond 5 years post-HSCT, with general population mortality rates being used at the point that the extrapolated rates from Martin et al. 2010 become lower than the general population. A recreation of the plot for the greater than 45-year age group is provided in Figure 13.



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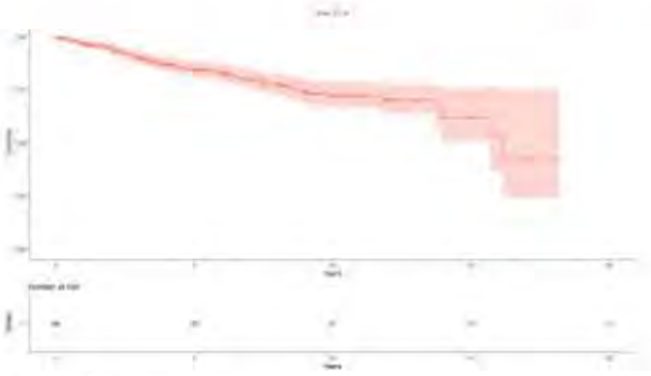
**Figure 13: Kaplan-Meier recreated from Martin et al. 2010 for the greater than 45 years age group**



*Source Martin et al.* (61)

Parametric survival models were fitted to the data based on the methods recommended by the methodology of the Danish Medicines Council. The standard parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma) were all fitted to the data and Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics were produced to help determine the best fitting model. The extrapolated survival models superimposed onto the KM plot are shown in Figure 14, and the goodness-of-fit statistics are given in Table 57.

**Figure 14: Fitted survival curves for Martin et al. 2010 for the greater than 45 years age group**



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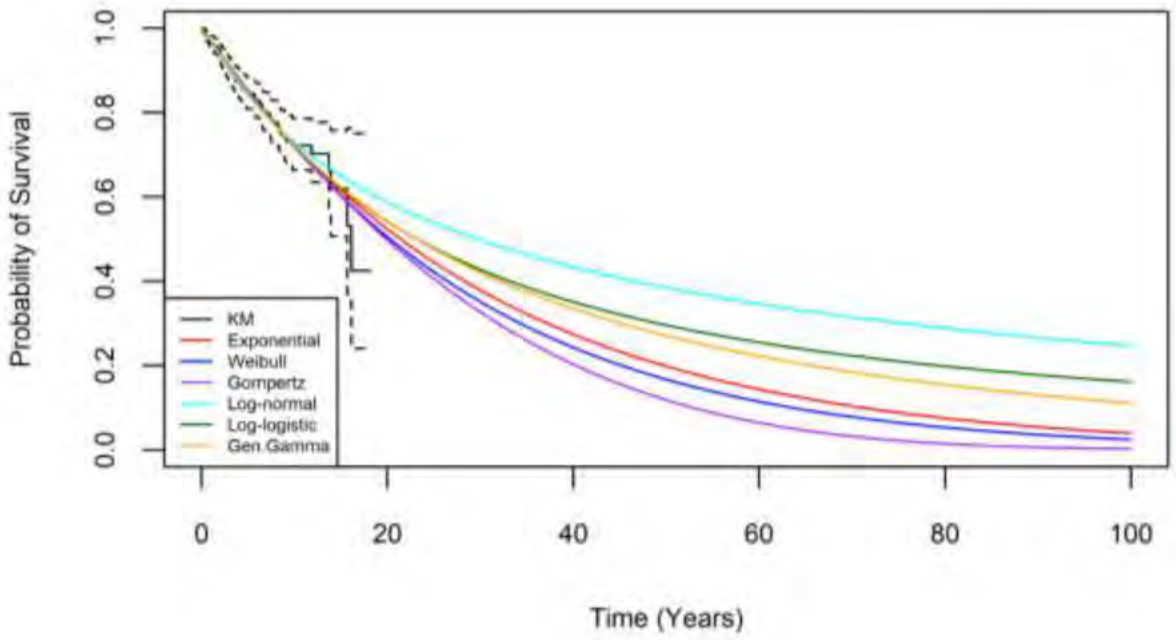


*Source* *Martin et al.* (61)

**Table 57: Goodness-of-fit statistics for survival models fitted to Martin et al. 2010**

| Survival model | AIC | BIC |
|---|---|---|
| Exponential | 728.71 | 732.90 |
| Weibull | 730.42 | 738.79 |
| Gompertz | 730.57 | 738.94 |
| Log-logistic | 730.49 | 738.87 |
| Log-normal | 731.18 | 739.56 |
| Generalised gamma | 732.03 | 744.58 |

*Source: Completed by Takeda biostats to support submission*

The exponential model appears to have the best fit based on AIC and BIC, although there is not a great difference in AIC across all fitted models. The exponential model appears to show a good visual fit also, so this has been applied in the base case analysis. A scenario using the Gompertz extrapolation is also provided to demonstrate the impact of this similarly fitting but most extreme (highest overall mortality) model.

**SOT graft loss**

Though Study 303 did not observe any graft loss events, discussion with clinicians during an advisory board (Danish advisory board held by Takeda Pharma A/S in 2022) indicated that graft preservation is an important factor for CMV treatment in SOT patients. Clinicians explained that graft loss events would be more likely to be observed over a longer time horizon than the 20-week study period of Study 303, with greater frequency in a cohort with CMV. This assertion is supported by the results from a retrospective cohort study of 20,473 patients in France by Hakimi, Aballea et al. (2017) (13). Hakimi et al., show that patients may still experience graft loss events up to 3-years post-transplant. For example, if an CMV patient had their first CMV episode 2 years post-transplant, they may still experience a graft loss event at the end of the study period (1-year) and would therefore be 3-years from their transplant. Furthermore, data from OTUS provides evidence that patients may still experience graft loss events up to 2-years post-transplant. In the overall cohort, 4.7% of patients had a graft loss event by 365 days, while 5.7% of patients had a graft loss event by 730 days.

Additional evidence for longer-term risk of graft loss can also be sourced from the retrospective GENOME Canada study, which was designed to define the impact of viremia on graft and patient outcomes in Canadian renal transplant patients with uniform management for prognostic implications of CMV viremia, immune suppression, and antiviral therapy. Data from GENOME Canada provide further evidence that patients with CMV may still experience graft loss beyond 12 months from transplant. In fact, patients who had a first CMV episode lasting greater than 22 days had graft loss events at approximately 9-years post-transplant (see Figure 15 below).

Given the published evidence, graft loss events were included in the model for SOT patients. To inform the probability of graft loss in the model, Hakimi, Aballea et al. (2017) (13) was deemed the best available source on graft loss outcomes for CMV patients. In the model, the risk of graft loss for patients in the n-csCMV health state is taken directly from Hakimi, Aballea et al. (2017). The study presents risk of graft over 1 year based on the timepoint of infection from three categories: E-CMV (infection within 3 months of transplant), L-CMV-3M (infection occurring 3 or more months post-transplant) and L-CMV-6M (infection occurring 6 or more months post-transplant) (Table 58). Based on this, the L-CMV-6M category was deemed most appropriate as it can theoretically include risk for patients who have had an event up to 3-years post-transplant (first CMV event at 2 years and followed for 12 months thereafter). The baseline TST for SOT patients was 258 days and the duration of the Stage 1 Markov is 78 weeks totalling a total time of 2.19 years. L-CMV-6M is the only category from the Hakimi et al., (2017) (13) study that extends to this longer time horizon.

**Table 58: Overall graft failure (Table 3, Hakimi et al., 2017)**

| | E-CMV | | L-CMV-3M | | L-CMV-6M | |
|---|---|---|---|---|---|---|
| | With CMV, n (%) | Without CMV, n (%) | With CMV, n (%) | Without CMV, n (%) | With CMV, n (%) | Without CMV, n (%) |
| Graft failure (overall) | 117/1082 (10.81) | 202/2146 (9.41) | 61/962 (6.34) | 75/2028 (3.70) | 30/586 (5.12) | 21/1245 (1.69) |
| 4-week probability | 0.88% | 0.76% | 0.50% | 0.29% | 0.40% | 0.13% |

*Source: Hakimi, Aballea et al. (2017)* (13)

The value used for the n-csCMV health state is the L-CMV-6M probabilities of graft loss for study participants without CMV (1.69%), converted into 4-week probabilities (0.01%). A relative risk (RR) of graft loss for patients with CMV versus those without CMV is then applied to the n-csCMV value to derive the csCMV utility. This RR is derived from the reported rates of CMV and no CMV for the L-CMV-6M cohort in Hakimi, Aballea et al. (2017) (13) **and** is equal to 3.04. This RR is

then applied to the 4-week n-csCMV probability of graft loss which then gives the probability of graft loss for patients in the csCMV health state (0.4%) (Table 59).

**Table 59: Risk of graft loss for patients with csCMV and n-csCMV**

| Health state | Risk of graft loss: Mean (SE) |
|---|---|
| csCMV | 0.0040 (0.0008) |
| n-csCMV | 0.0013 (0.0010) |
| Relative Risk | 3.04 |

*Source: Hakimi, Aballea et al. (2017)* (13)

*SE: standard error, calculated as* $\sqrt{\frac{p*(1-p)}{n}}$*, where p is the incidence percentage and n is the number of individuals in the trial arm; csCMV: clinically significant CMV; n-csCMV: non-clinically significant CMV*

When a graft loss event occurs in the model, the distribution of organ transplant at baseline in Study 303 (Table 60) is used to estimate the specific organ impacted during the graft loss (i.e., 11% of graft loss events per cycle are assumed to impact the heart). It should be noted that patients are only at risk of a single graft loss event (i.e., a single retransplant) in the model. Studies in the literature have indicated that patients who have a retransplant have an elevated risk of mortality (Table 60). Therefore, in the base case, individuals who suffer from graft loss experience an increased risk of mortality. This increased mortality is applied by multiplying the organ-specific mortality hazard ratio by the background mortality.

**Table 60: Baseline distribution of transplant type and mortality risk for retransplant patients**

| Baseline transplant type | Proportion of transplant type at baseline: Mean (SE) ‡ | HR of mortality for retransplant patients: Mean (SE) |
|---|---|---|
| Heart | [redacted] | |
| Kidney | | |
| Lung | | |
| Liver | | |
| Other | | |

*Sources: Proportion of transplant type at baseline: Study 303 CSR (Takeda Pharmaceuticals Company Limited 2021); HR of mortality: Heart transplant* (62)*; Kidney transplant:* (63)*; Lung transplant:* (64)*; Liver transplant:* (65)

*SE: standard error; HR: hazard ratio; CI: confidence interval*

*^: 1- sum of all other baseline transplant types *: weighted average of all other transplant types, weight is the proportion of transplant type at the baseline; ‡ Values do not sum to 1 due to rounding; [a]: standard error is assumed to be 20% of the value; [b]: standard error is calculated as* $\frac{upper\ 95\%\ CI - lower\ 95\%\ CI}{3.92}$

*For the proportion of transplant type at baseline, the SE was assumed to be 20% of the mean value as neither a standard deviation nor standard error was reported in the clinical study report. A SE of 20% of the mean value was used for the "Other" transplant HR SE as this value is the weighted average of all the other reported transplant HR values, and therefore a SE was not presented and could not be directly calculated. Of note is the fact that the SE for the proportion of transplants at baseline are calculated using 20% and for the HR, most SE's are calculated using reported confidence intervals, except for the Other transplant type which uses 20%.*

Additionally, discussions with clinicians indicated that patients who have had a kidney transplant would not be expected to receive a retransplant immediately. Instead, these patients are likely to receive dialysis before receiving their transplant. Therefore, in the base case, all renal transplant patients who experience graft loss are assumed to have a retransplant and the additional cost and disutility of dialysis while they wait for a transplant. The cost of dialysis is applied as an upfront 2-year cost when a patient experiences dialysis, whilst disutility is applied each cycle. The time patients wait for a transplant (653 days or 1.79 years) is based on data from Scandiatransplant requested by Takeda Denmark A/S as part of this application. Scenario analysis will be conducted where all kidney recipients who experience graft loss are on dialysis for their lifetime with no retransplant. There will also be additional functionality in the model



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to set a proportion of patients that will receive lifetime dialysis, while the remaining proportion of patients will receive a retransplant (patients who receive a retransplant will still incur the costs of dialysis for the duration of time they are on the waiting list to receive the transplant).

Also considered in the model and included as a scenario was the impact of dialysis on mortality. Patients who are on dialysis may also have an increased risk of mortality compared to patients who have had a retransplant. To estimate this increased risk, a paper by Rayner et al. (2004) (66) was used, this looked at mortality and hospitalisation rates for haemodialysis patients treated across five European countries, (France, Germany, Italy, Spain, and UK). This paper reported that the RR of mortality for a dialysis patient in the UK was 1.39 (Table 61). The excess mortality associated with dialysis is applied in the scenario analysis where it is assumed that all renal transplant patients receive lifetime dialysis.

**Table 61: Dialysis inputs for kidney recipients experiencing graft loss**

| Parameter | Base case | Source |
|---|---|---|
| Proportion of patients on lifetime dialysis | 0 | User to define this value. Excluded from the base case |
| Years of dialysis (mean) | 1.79 | Delivered by Scandiatransplant on request by Takeda Pharma A/S |
| Dialysis mortality - Hazard ratio - | 1.39 | Rayner et al. (2004) |

*Sources: Scandiatransplant.org, Rayner et al. (2004)* (66)

[a]*: The disutility of dialysis is the differece between the utilty of hemodialysis and renal transplantation*

**HSCT – GvHD and relapse in underlying conditions**

In Study 303, whilst GvHD events were captured, there was insufficient data to indicate whether there was an enhanced risk of GvHD in patients with active CMV relative to cleared CMV. This was further supported by the literature which indicated evidence of a bi-directional relationship (i.e., GvHD causes CMV), with only a single study identified to support CMV causing GvHD (Cantoni et al., 2010) (49). Discussions with clinicians during the advisory board (Danish advisory board held by Takeda Pharma A/S in 2022) also confirmed the uncertainty of the CMV and GvHD relationship. Due to limited clinical evidence of a causal relationship, the incidence of GvHD was not included in the base case, however, there is the option to explore this event as part of a scenario analysis with GvHD incorporated as a cyclical risk in the model.

For the scenario, data from published literature is used to estimate the baseline risk of GvHD in patients. The literature used was published by Hahn, McCarthy et al. (2008) (48) and reports the 100-day probability of GvHD in a HSCT population as 35%, which represents the baseline risk of GvHD in patients with no CMV. This was then converted into 4-week probabilities (11%) and incorporated in the model to estimate the cyclical risk of GvHD in patients with no CMV and used as a proxy for the n-csCMV health state. The hazard rate (2.18) for GvHD risk in patients with active CMV (vs no CMV) was identified from a study by Cantoni, Hirsch et al. (2010) (49) and multiplied by the baseline risk from Hahn, McCarthy et al. (2008) (48) to estimate the risk of GvHD in patients with csCMV.

Based on request by the Danish Medicine Counsel a second scenario has been included. While health state specific GvHD is not available from the SOLSTICE trial, a pooled risk of GvHD has been added as an option to the model. The overall 20-week rate of new GvHD events has been converted into a 4-week probability. See table below.

**Table 62: Calculation of SOLSTICE GvHD incidence rate**



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| | Value | Calculation |
|---|---|---|
| Total number of HSCT patients | [redacted] | |
| Number of patients experiencing GvHD | | |
| 20-week rate | | |
| 4-week probability | | |

*Source: SOLSTICE CSR*

*The 20-week rate has been converted into a 4-week probability using the formula* $1 - e^{(-rt)}$ *where r is the rate and t is the time period*

**Adverse reaction outcomes**

20-week incidence rate of AEs is calculated from the Study 303 IPD analysis by dividing the number of each AE by the total number of patients in the treatment arm. The model includes AEs considered clinically important by clinical experts and any TEAE with an incidence of more than 10% in either the maribavir or IAT arm. The following AEs were considered clinically important by clinicians: acute kidney injury, febrile neutropenia, leukopenia, renal impairment, and thrombocytopenia. While dysgeusia is mentioned as an AE of special interest, it has no associated cost as it was noted in the CSR that the majority of cases were mild. The model assumes the risk of AEs for ganciclovir, valganciclovir, foscarnet or cidofovir is the same as the risk observed in the IAT arm. These incident events were converted into 4-week probabilities and then implemented as a treatment-specific cyclical risk in the model (Table 63).

**Table 63: Incidence of clinically important and treatment emergent adverse events – 4-week probabilities**

| AE type | Maribavir (SE) | IAT (SE) |
|---|---|---|
| Acute kidney injury | [redacted] | |
| Anaemia | | |
| Diarrhoea | | |
| Dysgeusia | | |
| Fatigue | | |
| Febrile neutropenia | | |
| Headache | | |
| Leukopenia | | |
| Nausea | | |
| Neutropenia | | |
| Pyrexia | | |
| Renal impairment | | |
| Thrombocytopenia | | |
| Vomiting | | |

*Source: Study 303 IPD Analysis (Takeda Pharmaceuticals Company Limited 2021)*
*AE: Adverse Event; IAT: Investigator-assigned anti-CMV treatment*

*SE: standard error- it was calculated using the formula:* $\sqrt{\frac{p*(1-p)}{n}}$*, where p is the incidence percentage and n is the number of individuals in the trial arm.*

AE frequencies have been calculated by dividing the number of events (m) of each AE by the total number of patients in the maribavir (N=234) and IAT (N=116) treatment arms to generate a 20-week incidence rate. This 20-week incidence rate has then been converted into a 4-week probability using the formula:



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*Probability=1-e^-(rate*time)*

An Excel sheet has been included in the health economic model where the AE incidence calculations has been provided. The sheet is name question 19.

**For summary of input data**

A summary of the clinical efficacy outcome, the clinical documentation, and how it is used in the model can be seen in Table 64 (the sections described above).

**Table 64: Summary of input data**

| Clinical efficacy outcome | Clinical documentation | Used in the model (value) |
|---|---|---|
| **Confirmed CMV viraemia clearance at the end of study week 8** | See section 7 and appendix D | Used for transition probabilities. See Table 41 |
| **CMV viraemia clearance and symptomatic CMV infection improvement or resolution at the end of Study Week 8, and maintenance of this treatment effect through Study Week 16** | See section 7 and appendix D | Used for transition probabilities. See Table 41 |
| **Recurrence of CMV viraemia** | See section 7 and appendix D | Used for transition probabilities. See Table 42, Table 43, Table 44, Table 45, Table 46, Table 47, and Table 48 |
| **Clinically relevant recurrence of CMV viraemia** | See section 7 and appendix D | Used for transition probabilities. See Table 42, Table 43, Table 44, Table 45, Table 46, Table 47, and Table 48 |
| **AEs** | See section 7 and appendix D | Used for transition probabilities. See Table 63 |

**Table 65: Relevance of clinical efficacy outcomes and measurement methods for Danish clinical practice**

| Clinical efficacy outcome | Clinical documentation (measurement method) | Relevance of outcome for Danish clinical practice | Relevance of measurement method for Danish clinical practice |
|---|---|---|---|
| **For included efficacy outcomes see appendix D** | Appendix D | Appendix D | Appendix D |

## 8.3 Extrapolation of relative efficacy

### 8.3.1 Time to event data – summarized:

All time to event data has been described in section 8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice).



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

HRQoL was evaluated in Study 303 using the EQ-5D-5L and the SF-36v2. Further, a HRQoL SLR was conducted to identify studies reporting health-related utility values associated with CMV in SOT or HSCT recipients. The search did not exclude publications related to prophylaxis, as these studies might provide relevant utility values (e.g. GvHD, acute graft rejection). No studies were directly relevant for the decision problem, since they did not provide health-related utility values for patients with R/R CMV who have cleared CMV or are receiving pre-emptive therapy. However, the HRQoL SLR did help inform about graft loss and adverse event disutility. See appendix H for further detail about the HRQoL SLR.

#### 8.4.1 Overview of health state utility values (HSUV)

Table 66 below shows the HSUV measured during the 303 SOLSTICE trial. However, the following sections describes more in detail how the different utility values have been derived and how they are used as part of the economic modelling.

**Table 66: Overview of the HSUV measured during clinical trials forming the basis for the relative efficacy (see section 7)**

| | Results [SE] | Instrument | Tariff (value set) used | Comments |
|---|---|---|---|---|
| **EQ-5D-5L utility scores by study week 8 (study 303)** | | | | |
| **n-csCMV (SOT)** | [redacted] | EQ-5D-5L | DK | See Appendix N Transition matrices for more detail. |
| **csCMV -aCMV (SOT)** | | EQ-5D-5L | DK | See Appendix N Transition matrices for more detail. |
| **csCMV - sCMV (SOT)** | | EQ-5D-5L | DK | See Appendix N Transition matrices for more detail. |
| **n-csCMV (HSCT)** | | EQ-5D-5L | DK | See Appendix N Transition matrices for more detail. |
| **csCMV -aCMV (HSCT)** | | EQ-5D-5L | DK | See Appendix N Transition matrices for more detail. |
| **csCMV - sCMV (HSCT)** | | EQ-5D-5L | DK | See Appendix N Transition matrices for more detail. |

*Abbreviations: CMV, cytomegalovirus; aCMV, asymptomatic CMV; sCMV, symptomatic CMV; n-csCMV, non-clinically significant CMV; csCMV, clinically significant CMV*

#### 8.4.2 Health state utility values used in the health economic model

**Health state quality of life**

Week 0 to 78

Outputs from the mixed modelling conducted as part of the Study 303 IPD analysis indicated that transplant type and response status (i.e., csCMV or n-csCMV) had a statistically significant effect on utilities and that the treatment arm did not have a significant impact. In addition to the HRQoL data for patients with R/R CMV in Study 303, Takeda carried out a UK vignette study (Supplementary documentation) in 2021 to generate appropriate health-related utilities data, provide support to the utility estimates from Study 303 and reduce overall uncertainty. Health state descriptions were

developed in conjunction with UK clinicians before valuation by a sample of the UK public. The vignette study explored utilities by health state (csCMV and n-csCMV) as well as by symptomatic status for csCMV. Overall, the results identified the substantial impact of CMV on utility in both SOT and allogeneic HCST patients with CMV infection. Given the findings of both the Study 303 IPD analysis and vignette, health-state and transplant-specific utility values were used for utilities in Stage 1 CMV Markov. The utilities for the n-csCMV state were taken from the Study 303 IPD analysis while the utilities for the csCMV were derived by combining results from the Study 303 IPD analysis utilities and the vignette study.

Multiple imputation (MI) and pattern mixture modelling methods were used to account for potential bias due to missing data in the Study 303 IPD analysis of n-csCMV and cs-CMV utility scores at week 8. An initial assessment of the data showed that there was differential patient dropout between maribavir and IAT which could be attributed largely to discontinuations and rescue treatment in the IAT arm. A Missing not at random (MNAR) mechanism is appropriate when the missing scores are reliant on unobserved factors. As the exact nature of the missing EQ-5D data could not be defined, a range of alternative models were performed to assess the impact of the results on the mixed modelling repeated measures (MMRM) model, which assumes data are missing at random (MAR). The results of this analysis showed there is no evidence that the nature of the missing data impacts on the comparisons between treatments from the MMRM model. As a conservative approach in the economic model, estimates were based on imputation assuming MAR to account for the missing data.

Whilst missing utility values were imputed using MI techniques, including all randomized subjects, rescue subjects were omitted if the imputed visit fell after the start of rescue therapy. The imputation was performed several times and with a fixed seed value using a Markov-chain Monte Carlo method. Utility scores were recalculated using the imputed values. The mixed models were performed by each imputation and the estimates were combined to produce adjusted results. The mixed model included utility score as the dependent variable, and baseline plasma CMV DNA concentration as the stratification factor. Treatment group, health state at week 8 (responder vs non-responder), visit week, the treatment group*visit week interaction, treatment group*health state interaction, missing data pattern (MDP), and the MDP*treatment group interaction were treated as fixed effects. Transplant type was included as an additional covariate in the model. Visit week was treated as a repeated measure. Due to model over-parameterization, MDP and the interaction between MDP*visit week was omitted. Models were run using an unstructured covariance matrix.

From the mixed modelling results it was observed that the effect of health state and transplant type remained significant on the utilities. Despite differential dropout across the groups, with higher dropout in IAT group (compared to the maribavir group), and differing trends prior to dropout during the treatment period, the MI model confirmed the conclusions from the original mixed modelling results of utilities without imputation assuming MAR, with models showing significant difference between health state at week 8 and transplant type and no differences between the treatment groups with respect to EQ-5D-5L index scores over the 20 week study period. The results from the multiple imputation are presented in Table 67.

The values used in the model for the n-csCMV value were the response (at week 8) utilities (0.84 for SOT and 0.70 for HSCT). The week 8 values are preferred over week 0 to 20 values because of the fluctuations in health states that occur between week 0 to 20 which may compromise the true impact of health state on quality of life. Additionally, the week 8 utility values align with the timing of the primary endpoint of the study, which was used for the clearance transition probabilities.

**Table 67: Utility imputation analysis**

| | SOT | | HSCT | | Overall / pooled | |
|---|---|---|---|---|---|---|
| | Without imputation^ | Imputation (only protocol | Without imputation^ | Imputation (only protocol | Without imputation^ | Imputation (only protocol |

| | visits and no rescue)* | visits and no rescue)* | visits and no rescue)* |
|---|---|---|---|
| Response (at week 8), utilities at week 8 | [redacted] | | |
| No response (at week 8), utilities at week 8 | | | |

*Source:^ Study 303 IPD Analysis* (42), **Completed by Takeda biostats to support HTA submission*

To reinforce the findings of the 303 SOLSTICE trial, a vignette was used to further established the impact of CMV health state on QoL. The vignette established 12 health state scenarios (the vignettes) through literature reviews, qualitative interviews with UK based health care professional and CMV patients. The vignette used two composite time trade-off (TTO) surveys to derive QoL scores for each vignette. TTO surveys were developed based on these vignettes and 510 respondents from the UK general public were surveyed to then develop two sets of utility data using the TTO methodology. The utilities taken from the final vignette results are included in Table 68 (the vignette study is found under supplementary documentation in this application).

**Table 68: Vignette study utilities**

| Health state | Mean (SE) |
|---|---|
| Clinically significant - Symptomatic | [redacted] |
| Clinically significant - Asymptomatic | |
| csCMV SOT^ | |
| csCMV HSCT^ | |
| Non-clinically significant | |
| Disutility adjustment csCMV (SOT) | |
| Disutility adjustment csCMV (HSCT) | |

*Source: Vignette study (Takeda Pharmaceuticals Company Limited, 2021b)*
*^to calculate the SOT and HSCT values, for each transplant type the asymptomatic and symptomatic csCMV utility values from the vignette study were multiplied by the respective proportion of patients with asymptomatic and symptomatic csCMV in SOLSTICE and then the result added together to give the mean csCVM value. 10% of patients with SOT were asymptomatic at baseline and 90% were symptomatic. 6% of patients were asymptomatic at baseline and 94% of patients were symptomatic.*

The utility scores from the vignette study were combined with Study 303 to derive the utility score for the csCMV health state. The first step involved taking a weighted average of the symptomatic (0.10 SOT, 0.06 HSCT) and asymptomatic (0.90 SOT, 0.94 HSCT) csCMV utility values reported in the vignette study. The weighting depended on the proportion of patients with asymptomatic and symptomatic CMV at baseline in Study 303. The SOT- and HSCT-specific weighted csCMV utility value from the vignette was subtracted from the vignette n-csCMV utility score to derive a disutility score for each transplant type. This disutility was then subtracted from the respective SOT and HSCT n-csCMV transplant and health state specific utility values at week 8 in Study 303 to calculate the csCMV utility for SOT and HSCT respectively. The derived utility values for csCMV, along with the n-csCMV values from the Study 303 IPD analysis are shown in Table 69.

**Table 69: Week 0 to 78 health state utility**

| Health state | Mean (SE) | Source |
|---|---|---|
| n-csCMV (SOT) | [redacted] | Study 303 IPD analysis |
| csCMV - aCMV (SOT) | | Study 303 IPD analysis and vignette study |
| csCMV - sCMV (SOT) | | |
| n-csCMV (HSCT) | | Study 303 IPD analysis |

| Health state | Mean (SE) | Source |
|---|---|---|
| csCMV - aCMV (HSCT) | [redacted] | Study 303 IPD analysis and vignette study |
| csCMV - sCMV (HSCT) | | |

*Source: Study 303 Analysis (Takeda Pharmaceuticals Company Limited 2021), Vignette study (Takeda Pharmaceuticals Company Limited, 2021b*
*Abbreviations: CMV, cytomegalovirus; aCMV, asymptomatic CMV; sCMV, symptomatic CMV; n-csCMV, non-clinically significant CMV; csCMV, clinically significant CMV*

**Week 78 onwards**

To estimate utility values for SOT and HSCT patients in the Stage 2 alive/dead Markov (from 78 week onwards), a two-step approach was applied. First, the difference between the mean Danish general population utility score at age 53 (starting age of the model cohort) and the week 20 SOT and HSCT utilities (0.81 and 0.71, respectively) from the Study 303 IPD analysis was calculated (42). Secondly, this disutility value was then applied to the mean Danish population utility values in every model cycle. The annual general population utility values used in the model are based on the age-specific Danish general population values found in Jensen et al. (2021) (67). The approach used in line with UK NICE precedence (NICE 2019) (43), where the long-term disutility associated with HSCT patients was based on the difference between the mean utility value of patients from the trial endpoint and the mean utility values from the UK general population.

**Graft loss**

As there were limited graft losses in Study 303, the graft loss utility decrement is informed by the asymptomatic csCMV (cs-aCMV), symptomatic csCMV (cs-sCMV) and n-csCMV categories in the vignette study (see supplementary documentation). The disutility value has been calculated for each health state by taking the difference between the utility of no graft loss, and the utility of either the graft loss from a kidney or lung transplant. Then, the average has been taken of the decrements from the three categories (cs-aCMV, cs-sCMV and n-csCMV) using a 1:1:1 ratio. Due to limited data on heart, lung and other graft loss, the average disutility of a lung graft loss is used as a proxy to inform the utility decrement for these graft losses. The utility decrement is applied for a lifetime after a graft loss event has occurred which allows the model to capture the long-term impact of a graft loss event and not just the immediate impact of a graft loss event. The utility decrements for each health state and transplant type are shown Table 70. The model also has the option to apply disutility from the literature.

Dialysis disutility was taken from the literature. A study by Liem et al. (2008) (68) estimated the disutility of dialysis as the difference between the utility of haemodialysis and renal transplantation, with a disutility value of -0.25. This value is referred to in a NICE guideline on the cost-effectiveness of hemodiafiltration versus high flux standard haemodialysis.

**Table 70: Graft loss disutility**

| Baseline transplant type | Utility decrement Mean (SE) | Source |
|---|---|---|
| Heart | [redacted] | Vignette Study (Takeda Pharmaceuticals Company Limited 2021), see supplementary documentation) |
| Kidney | | |
| Lung | | |
| Liver | | |
| Other | | |
| Dialysis disutility | -0.25 | Liem, Bosch et al. (2008)(68)[a] (used in NICE NG107) |

*Source: Vignette Study (Takeda Pharmaceuticals Company Limited 2021), Liem, Bosch et al. (2008)*
[a]*: The disutility of dialysis is the difference between the utilty of hemodialysis and renal transplantation SE: standard error – assumed to be 10% of the mean value*



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### GvHD

GvHD events are not included in the base case analysis. If these events are included in a scenario analysis, the utility decrement applied to each event in the model is -0.09. This value was used in a recent technology appraisal for an anti-CMV agent (NICE 2019) (43), with the utility decrement calculated by converting SF-36 from a paper exploring the quality of life of different severities of GvHD (Pidala, Kurland et al. 2011) (69) using an algorithm developed by Ara and Brazier (2008) (70).

### Adverse events

**Mean disutility values for AEs were estimated from published literature on UK-based disutility (**

Table 71). The primary source of information for the disutility values was the Catalogue of EQ-5D Scores for UK (Sullivan, Slejko et al. 2011) (51), with other sources for UK disutility values used if there was no suitable condition in Sullivan, Slejko et al. (2011). The articles were identified through desk research and by searching NICE submissions in similar indications to identify previously used disutility values. If the article specified that the disutility value had a duration for greater than 1-year, the disutility was adjusted to a 1-year value. For example, the disutility value for vomiting from Nafees et al (2017) was -0.25 over 10-years. This was divided by 10 to get a yearly disutility value of -0.025 which was then used in the model. If the article did not specify a time period, it was assumed that the disutility was a yearly disutility value. It should be further noted that the final utility decrement applied is adjusted for the duration of the AE event (i.e., the model does not apply a full annual utility decrement per event and instead adjusts the utility decrement for the expected duration of the event). For example, the 1-year disutility of anemia is -0.25 however a patient only experiences anemia for a mean of 10.8 days. The model therefore adjusts the disutility value to -0.0074 per anemia event ($-0.25 * \frac{10.8}{365.25} = -0.0074$).

It was assumed all disutility values were annual utility decrements. However, in cases where the time period for a disutility was explicitly reported, the values have been adjusted to create a one-year disutility value. The disutility associated with each AE is adjusted for duration of the event (reported in the IPD analysis report (Takeda Pharmaceuticals Company Limited 2021) (42)) using the following formula: $\frac{Duration\ of\ AE}{365.25}$.

**Table 71: Duration and disutility of clinically important and treatment emergent adverse events**

| AE Type | Duration of AE (days) | Mean AE Disutility (SE) | Source of disutility | Description in source |
|---|---|---|---|---|
| Acute kidney injury | 25.9 | -0.10 (0.0091) [a] | (Sullivan, Slejko et al. 2011) (51) | ICD-9 593 Oth Renal & Ureteral Disorders |
| Anaemia | 36.9 | -0.25 (0.03) [b] | (Ossa, Briggs et al. 2007) (52) | Difference between no anaemia and moderate anaemia |
| Diarrhoea | 15.92 | -0.07 (0.02) [a] | (Sullivan, Slejko et al. 2011) (51) | 154 Non-infectious Gastroenteritis |
| Dysgeusia | N/A | N/A | Assumed no care required and therefore no duration and zero disutility | N/A |
| Fatigue | 77.69 | -0.04‡ (0.0041) [b] | (Nafees, Lloyd et al. 2017)† (53) | Fatigue |
| Febrile neutropenia | 10.80 | -0.09 (0.02) [a] | (Nafees, Stafford et al. 2008) (71) | Febrile neutropenia |
| Headache | 21.22 | -0.03 (0.0065) [a] | (Sullivan, Slejko et al. 2011) (51) | 084 Headaches, Including Migraine |
| Leukopenia | 21.50 | -0.09 (0.02) [c] | (Bullement, Nathan et al. 2019) (54) | Leukopenia |
| Nausea | 19.36 | -0.03‡ (0.0025) [b] | (Nafees, Lloyd et al. 2017)† (53) | Nausea and vomiting |

| AE Type | Duration of AE (days) | Mean AE Disutility (SE) | Source of disutility | Description in source |
|---|---|---|---|---|
| Neutropenia | 14.80 | -0.09 (0.02) [a] | (Nafees, Stafford et al. 2008) (71) | Neutropenia |
| Pyrexia | 11.77 | -0.11 (0.01) [b] | (Beusterien, Davies et al. 2010) (55) | Based on no change in lymphocytic leukaemia with pyrexia |
| Renal impairment | 29.50 | -0.10 (0.01) [a] | (Sullivan, Slejko et al. 2011) (51) | ICD-9 593 Oth Renal & Ureteral Disorders |
| Thrombocytopenia | 48.90 | -0.11 (0.02) [c] | (Tolley, Goad et al. 2013) (56) | Difference between a patient with PFS response with thrombocytopenia and PFS responder mean |
| Vomiting | 14.72 | -0.03‡ (0.0025) [b] | (Nafees, Lloyd et al. 2017) † (53) | Nausea and vomiting |

*Source: Sullivan, Slejko et al. (2011), Nafees, Lloyd et al. (2017), Tolley, Goad et al. (2013), Bullement, Nathan et al. (2019), Beusterien, Davies et al. (2010), (Nafees, Stafford et al. 2008), Ossa, Briggs et al. (2007)*
*AE: Adverse Event*
*^ Adjustment from 10 year to 1 year disutility value*
*‡ All changes are compared to baseline state of patients with small-cell lung cancer who are stable and have no side effects*
*[a] standard error is provided in the paper*
*[b] standard error is assumed to be 10% of the mean value*
*[c] standard error calculated using the upper and lower 95% confidence interval with the formula* $\frac{Lower\ C.I. - Upper\ C.I.}{3.92}$

## 8.5 Resource use and costs

All costs are estimated in Danish Croner (DKK) at 2022 currency levels.

**Treatment costs**

Treatment costs in the model are a combination of acquisition, administration, and monitoring costs. Drug acquisitions cost for maribavir has been provided by Takeda while costs for the individual IAT drugs have been sourced from Medicinpriser.dk. In the case of foscarnet, the Danish Medicines Council has provided the price since foscarnet since it is not publicly available. Further, it should be noted that the price of foscarnet is equivalent to wholesaler price and not pharmacy purchase price as are for the other products in the analysis. The cost of IAT implemented in the model is a weighted average cost of the four anti-CMV agents, with the distribution across these drugs estimated using the treatment patterns observed in the IAT arm in Study 303. In Study 303, 7 out of 116 patients in the IAT arm were on a treatment mix between foscarnet/valganciclovir (3 patients) and foscarnet/ganciclovir (4 patients). An assumption has been made that in these cases, patients are distributed evenly across the two drugs, the readjusted percentages taken from the CSR is presented in Table 72 (23,39).

**Table 72: IAT treatment distribution**

| Drug | Study 303 distribution n (%) | Readjusted distribution n (%) |
|---|---|---|
| Ganciclovir | [redacted] | |
| Valganciclovir | | |
| Foscarnet | | |
| Cidofovir | | |
| Foscarnet / valganciclovir | | |

| | |
|---|---|
| Foscarnet / ganciclovir | [redacted] |

*Sources: Study 303 CSR (Takeda Pharmaceuticals Company Limited 2021)*

**Time on treatment**

In the Study 303 CSR (Takeda Pharmaceuticals Company Limited 2021) the total time exposure (exposure duration) to IAT, its constituent drugs, and maribavir has been reported (Table 73). These durations are used to adjust costs per cycle in the Stage 1 CMV Markov (weeks 0 to 78) by multiplying the relevant costs by time on treatment in weeks divided by 8 weeks. An 8-week period was chosen as that is the duration of the study treatment Stage (see section 8), with patients not completing the entire 8-week phase assumed to discontinue from treatment.

In the base case, for the intervention, the maribavir exposure duration value is used, whilst for the comparator the IAT exposure duration value is applied, regardless of the IAT drug. This approach was considered the most appropriate method because it keeps the approach to costs consistent with the treatment efficacy data (clearance and recurrence) which uses treatment specific values (i.e., maribavir and IAT). For retreatment, time on treatment is assumed to be the same as the initial time on treatment value for all drugs.

**Table 73: Average time on treatment per 8-week treatment cycle from Study 303**

| | Maribavir Mean (SE) | IAT Mean (SE) | Ganciclovir Mean (SE) | Valganciclovir Mean (SE) | Foscarnet Mean (SE) | Cidofovir Mean (SE) |
|---|---|---|---|---|---|---|
| **Time on treatment (weeks)** | [redacted] | | | | | |

*Source: Study 303 CSR (Takeda Pharmaceuticals Company Limited 2021)*
*SE: standard error – assumed to be 10% of the mean value; TEAE: treatment emergent adverse events*

**Drug acquisition costs**

Drug acquisition costs have been calculated using the drug monographs (Table 74) their respective SmPCs (i.e. mg/kg and frequency of dose). The cost per pack, cost per oral solution, and cost per 4-week cycle for the indication dose are calculated based on input from Danish physicians. It should be noted that although the SmPC indicates there is an induction dose and maintenance dose, in practice, Danish clinicians (participants at the Danish maribavir advisory board (Takeda Pharma A/S in 2022)) explained patients receive a single dosing regimen until the CMV has cleared (i.e. there is no maintenance dose).

**Table 74: Drug monographs**

| Drug | Indication dose* | Assumed indication dose for a 4-week period^ | IV days per 4 -week period |
|---|---|---|---|
| **Maribavir** | 400 mg twice daily (BID) for 8 weeks (assumes fixed price for an 8-week dose, irrespective of weight or dose frequency) † | | NA (oral drug) |
| **Ganciclovir** | Initially 5 mg/kg every 12 hours for 14–21 days, then maintenance 6 mg/kg once daily, on 5 days of the week, alternatively maintenance 5 mg/kg once daily, maintenance only for patients at risk of relapse; if disease | 5 mg/kg every 12 hours for 28 days | 28 days |

| Drug | Indication dose* | Assumed indication dose for a 4-week period^ | IV days per 4 -week period |
|---|---|---|---|
| | progresses initial induction treatment may be repeated. | | |
| **Valganciclovir** | Initially 900 mg twice daily for 21 days, then maintenance 900 mg daily, induction regimen may be repeated if retinitis progresses. | 900 mg twice daily for 28 days | NA (oral drug) |
| **Foscarnet** | Initially 60 mg/kg every 8 hours for 2–3 weeks, alternatively initially 90 mg/kg every 12 hours for 2–3 weeks, then maintenance 60 mg/kg daily, then increased if tolerated to 90–120 mg/kg daily, if disease progresses on maintenance dose, repeat induction regimen. | 60 mg/kg every 8 hours 28 days | 28 days |
| **Cidofovir** | Initially 5 mg/kg once weekly for 2 weeks, then maintenance 5 mg/kg every 2 weeks, maintenance treatment to be started 2 weeks after completion of induction treatment. | 5 mg/kg once weekly for 4 weeks | 4 days |

*Sources: Advisory board (Takeda Pharma A/S in 2022)*
*† Indication dose not provided on the SmPC. Used in Study 303.*
**Indication dose is provided in the SmPC*
*^The assumed dose is from the advisory board which stated that in Denmark the induction dose is used to treat CMV until clearance*

Table 75 shows the drug acquisition costs acquired primarily through medicinpriser.dk. Note that comma statements are based on Danish formats and are therefore using a period sign as thousands separator.

**Table 75: Drug acquisition costs**

| Drug | Cost per pack | Cost per 4-week cycle | Source |
|---|---|---|---|
| **Maribavir** | [redacted] | [redacted] | Provided by Takeda |
| **Ganciclovir** | [redacted] | [redacted] | Medicinpriser.dk |
| **Valganciclovir** | [redacted] | [redacted] | Medicinpriser.dk |
| **Foscarnet** | [redacted] | [redacted] | Provided by Danish Medicines Council |
| **Cidofovir** | [redacted] | [redacted] | Medicinpriser.dk |

*Maribavir cost is provided by Takeda. The cost of foscarnet is provided by the Danish Medicines Council. All other costs are taken from Medicinpriser.dk* (57).

Drug acquisition costs have been adjusted for the time on treatment. For example, the cost per 4-week cycle o[redacted] for maribavir has been multiplied by the actual time on treatment (7.5 weeks) divided by the treatment duration in Study 303 (8-weeks).

Week 0 to 8

The cost of maribavir for an 8-week treatment cycle is [redacted]. This cost is incurred by all patients in cycle 0 and then adjusted to account for the time on treatment observed in Study 303 (costs multiplied by [redacted] to account for a 7.5-week treatment duration, see section 8. The cost of IAT (weighted average of the individual IAT drugs) is applied to all patients in cycle 0. To calculate an 8-week cost, two 4-weekly costs are summed together. This cost is then multiplied by the time on treatment observed in Study 303 in the IAT arm (costs multiplied by [redacted]



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treatment duration). As the treatment costs are incurred by all patients in cycle 0, no further acquisitions costs are incurred by patients in cycle 1 (week 4) or cycle 2 (week 8) of the model.

Week 8 to 78

In the base case, from week 8 onwards, for both the maribavir and IAT arm, patients who occupy the csCMV health state are assumed to receive IAT (i.e., no patients are on maribavir). The 4-week cyclical costs are adjusted to account for time on treatment in each cycle, as explained above, the costs are multiplied by [redacted]

Week 78 onwards

The model transitions to the Stage 2 Alive/Dead Markov from week 78, where there are no CMV-related costs applied to any patients in the model.

**Monitoring costs**

The summary of product characteristics (SmPC) has been used to estimate the 4-week monitoring frequency (Table 76 and Table 77) for each anti-CMV agent considered in this economic model. In the case of maribavir, the relevant monitoring frequencies have been assumed to equal to the monitoring requirements of valganciclovir as this was the only oral IAT drug. The frequencies reported in Table 76 were then multiplied by the relevant unit cost for each monitoring type to derive a 4-week monitoring cost (Table 77). Similar to methods described in the section about time on treatment (see above), for week 0 to 78, the monitoring costs were adjusted for time on treatment. From week 78 onwards, it was assumed no patients were on treatment, so monitoring costs were not included.

**Table 76: Summary of product characteristics (SmPC)**

| Drug | SmPC summary |
|---|---|
| **Maribavir** | Assumed same as valganciclovir |
| **Ganciclovir** | It is recommended that complete blood counts including platelet counts be monitored during therapy. |
| **Valganciclovir** | It is recommended that complete blood counts and platelet counts should be monitored regularly during therapy. |
| **Foscarnet** | Serum creatinine should be monitored every second day during induction therapy and once weekly during maintenance therapy.<br>Seizures, related to alterations in plasma minerals and electrolytes, have been associated with foscarnet treatment. Therefore, patients must be carefully monitored for such changes and their potential sequelae. |
| **Cidofovir** | Renal function (serum creatinine and urine protein) must be monitored within 48 hours prior to each dose of cidofovir.<br>Neutropenia may occur during cidofovir therapy. Neutrophil count should be monitored while receiving cidofovir therapy |

*Source: (NICE 2021), Gilead Sciences Inc., 2010*

**Table 77: Monitoring frequency**

| Drug | Complete blood count | Renal function (serum creatine) | Electrolytes | Neutrophils |
|---|---|---|---|---|
| **Maribavir** | 1.00 | 0 | 0 | 0 |
| **Ganciclovir** | 3.50 | 0 | 0 | 0 |



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| | | | | |
|---|---|---|---|---|
| **Valganciclovir** | 1.00 | 0 | 0 | 0 |
| **Foscarnet** | 0 | 3.50 | 3.50 | 0 |
| **Cidofovir** | 0 | 3.50 | 0 | 3.50 |

*Source: For ganciclovir, valganciclovir, and foscarnet:(Medicines.org 2020); cidofovir: (Gilead Sciences Inc. 2010) (72); maribavir is assumed to be the same as valganciclovir*

The costs of monitoring listed in Table 78 has been acquired through Righospitalets labportal.

**Table 78: Monitoring costs**

| Drug | Unit costs, DKK (SE) | Rigshospitalet Labportal |
|---|---|---|
| **Complete blood count** | 720 (144) | Code GRH00983 |
| **Renal function (serum creatine)** | 13 (3) | Code NPU04998 |
| **Electrolytes** | 18 (4) | Code NPU04144 |
| **Neutrophils** | 13 (3) | Code NPU02902 |

*Source: Rigshospitalets Labportal 2022* (59)

† *The total unit cost has been used.*
*SE: standard error – assumed to be 10% of the cost*

**Administration costs**

It is assumed that no administration costs would be incurred to provide the oral drugs (maribavir and valganciclovir). For drugs delivered intravenously (IV), a cost derived from the Danish DRG-system (2.513 DKK – DRG 2022: 18MA98 - MDC18 1-dagsgruppe, pat. Mindst 7 år, Diagnose: DB259 - Cytomegaloviral sygdom). For drugs delivered intravenously, the cost of a single infusion is applied once per day of treatment, regardless of the setting and number of IV doses requires. For example, though patients on ganciclovir require 5 mg/kg every 12 hours (twice per day), this is costed as a single IV infusion rather than two separate infusions. As stated, the cost of infusion, 2.513 DKK, is derived from the Danish DRG-system 2022 code 18MA98. The total number of IV days required has been calculated using the drug monograph from
Table 74. This is a conservative assumption, as patients require more than one infusion per day when treated with ganciclovir and foscarnet; therefore, the cost burden may be even higher than what is proposed in the model. A scenario investigating the cost when applying cost at every dose of IV treatment is presented in the scenario analysis.

**Health state unit costs and resource use**

The model leverages health-state specific healthcare resource utilization (HRU) rather than treatment-specific HRU. In the base case, the frequency of HRU is taken from the IPD analysis of Study 303 (Table 79). Whilst the frequency of hospitaliation is taken from the figures observed in the study, it is assumed that the emergency room (ER) visits captured in Study 303 are indirectly captured through hospitalisation visits in the model. The assumption being that a patient requiring an ER visit would have a serious enough condition to warrant hospitalisation. Therefore, including both ER visits and hospitalisation would overestimate the true cost of health resource utilisation. Additionally, outpatient visits were excluded as HRU data from Study 303 represent protocol driven care, which does not reflect real-world healthcare usage in a non-trial environment. It should be noted the model incorporates transplant specific HRU incident rates, this decision has been made as clinicians indicated that the underlying disease states are likely to have an impact on HRU.

Healthcare costs for each health state were sourced from the Danish DRG-system (shown in Table 80). In Study 303, patients with CMV were required to have viral load tests twice per week to monitor the progression of disease. Therefore, in the model, patients in the csCMV health state have eight tests every 4-week cycle (twice every week for a four-week cycle) with the unit cost per test of 720 DKK. The cost is derived from Rigshospitalets Labportal and based on code RGH00983, which related to the procedure full blood count. Originally the code NPU28653 was meant to be used since it relates to quantifying CMV in blood, but no cost has been present in the portal relating to this code. As an alternative measure the code RGH00983 has been used since the sample material, blood, is the same for both tests,

and because the procedure RGH00983 is associated with a relatively high cost compared to other procedures listed in the database. It is therefore viewed as an conservative input.

**Table 79: Healthcare resource use (4-week probability)**

| Health resource | 4-week probability of HRU (SOT): Mean (SE) | 4-week probability of HRU (HSCT): Mean (SE) |
|---|---|---|
| Hospitalisation (csCMV) | [redacted] | [redacted] |
| Hospitalisation (n-csCMV) | | |

*Sources: Study 303 IPD Analysis (Takeda Pharmaceuticals Company Limited 2021)*
*HRU: healthcase resource use; SOT: solid organ transplant; HSCT: haemopoietic stem cell transplant; SE: standard error –calculated using the formula:* $\sqrt{\frac{p*(1-p)}{n}}$*, where p is the incidence percentage and n is the number of individuals in the trial arm.*

Table 80 uses the DRG code 18MA98 with have been derived from the interactive DRG databased by searching for CMV infection as diagnose code and hospitalisation as procedure, it is assumed that a hospitalisation lasts more than 12 hours, and thus the reflective tariff has been selected. It should be noted that the same code is used for IV infusion since the interactive DRG database does not differentiate between the procedures of hospitalisation or IV infusion. Further, it should be noted that the model does not differentiate between hospitalisation (csCMV) or hospitalisation (n-csCMV), since the cost is expected to be the same since they both result in hospitalisation.

**Table 80: Healthcare resource costs**

| Health resource | Cost, DKK | DRG 2022 |
|---|---|---|
| Hospitalisation (csCMV) | 29.940 | 18MA98 DRG 2022, 18MA06 – Virussygdomme, pat. Mindst 18 år, u. Kompl. Faktorer, Diagnose: DB259 – Cytomegaloviral sygdom UNS |
| Hospitalisation (n-csCMV) | 29.940 | 18MA98 DRG 2022, 18MA06 – Virussygdomme, pat. Mindst 18 år, u. Kompl. Faktorer, Diagnose: DB259 – Cytomegaloviral sygdom UNS |

*Source: DRG 2022* (58)

**Disease complications**

As the DRG-system costs does not provide a breakdown of the costs associated with re-transplantation compared to a first transplant, it is assumed that the cost of a particular organ transplant from DRG-system is equal to the cost of a second transplant due to graft loss. The costs associated with re-transplantation due to graft loss are summarised in Table 81 and applied for each graft loss event. In addition, there is a cost of dialysis which is taken from DRG-system (11PR10), with patients receiving dialysis for 1.79 years in accordance to the average length of dialysis based on data from Scandiatransplant.org requested by Takeda Pharma A/S.

**Table 81: Graft loss costs**

| Transplant type | Re-transplant Cost, DKK | |
|---|---|---|
| Heart | 807.724 | 05MP04 DRG 2022, 05MP04 – Hjertetransplantation, Diagnose: DZ941 - Hjertetransplanteret |
| Kidney | 546.270 | 11MP01 DRG 2022, 11MP01 – Nyretransplantation, kompliceret: Diagnose: DZ940 - Nyretransplanteret |
| Lung | 861.566 | 26MP07 DRG 2022, 26MP07 – Lungetransplantation, Diagnose: DZ942 – Lungetransplanteret |



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| | | |
|---|---|---|
| Liver | 552.000 | 26MP06 DRG 2022, 26MP06 – Levertransplantation, Diagnose: DZ944 - Levertransplanteret |
| Other | 679.862 | There are no Danish DRG codes for transplant of pancreas and intestines which the item labeled others consists of. the median cost of heart, kidney, lung, and liver transplants has therefore been used as a substitute. |
| Annual cost of dialysis | 479.544 (3.074 kr. * 3 time a week * 52 weeks per year) | 11PR10 is used as DRG code with a cost of 3.074 DKK. The patient is expected to receive dialysis 3 times a week all year (73) . |

*Transplant cost and dialysis cost source: DRG 2022* (58)

**GvHD**

GvHD events are not included in the base case analysis due to limited clinical evidence that CMV has a causal relationship on GvHD (see section 8). If these events are included in scenario analysis, the cost applied in the model will be 25.419 DKK. This cost is sourced from DRG 2022 code 16MA10 - Øvrige sygdomme i blod og bloddannende organer, Diagnose: DT860A - Graft-versus-host reaktion.

**AE unit costs and resource use**

The costs of each AE were sourced from DRG 2022, as summarised in Table 82. The costs associated with each AE are multiplied by the proportion of each AE outlined in Table 63, and applied for each respective event per cycle.

**Table 82: Cost of clinically important and treatment emergent adverse events**

| AE Type | Cost, DKK | DRG 2022 |
|---|---|---|
| Acute kidney injury | 41.886 kr. | DRG 2022: 11MA01 - Akutte medicinske nyresygdomme uden dialyse og uden plasmaferese, Diagnose: DN179 - Akut nyreinsufficiens UNS |
| Anaemia | 25.419 kr. | DRG 2022: 16MA10 - Øvrige sygdomme i blod og bloddannende organer, Diagnose: DD649 - Anæmi UNS |
| Diarrhoea | 6.756 kr. | DRG 2022: 06MA11 - Malabsorption og betændelse i spiserør, mave og tarm, pat. Mindst 18 år, u. Kompl. Bidiag., Diagnose: DK529B - Ikke-infektiøs diaré UNS |
| Dysgeusia | 24.168 kr. | DRG 2022: 01MA17 - Andre uspecifikke sygdomme i nervesystemet, Diagnose: DR438B - Smagsforstyrrelse UNS |
| Fatigue | 4.460 kr. | DRG 2022: 23MA03 - Symptomer og fund. U, kompl. Bidiag., Diagnose: DR539A - Udmattelse |
| Febrile neutropenia | 38.408 kr. | DRG 2022: 16MA03 - Granulo- og trombocytopeni, Diagnose: DD709 - Neutropeni UNS |
| Headache | 4.460 kr. | DRG 2022: 23MA03 - Symptomer og fund. U, kompl. Bidiag., Diagnose: DR519 - Hovedpine UNS |
| Leukopenia | 25.419 kr. | DRG 2022: 16MA10 - Øvrige sygdomme i blod og bloddannende organer, Diagnose: DD728H - Leukopeni |
| Nausea | 6.756 kr. | DRG 2022: 06MA11 - Malabsorption og betændelse i spiserør, mave og tarm, pat. Mindst 18 år, u. Kompl. Bidiag., Diagnose: DR119B - Kvalme |
| Neutropenia | 3.176 kr. | DRG 2022: 16MA98 - MDC16 1-dagsgruppe, pat. Mindst 7 år, Diagnose: DD709 - Neutropeni UNS |
| Pyrexia | 18.647 kr. | DRG 2022: 18MA04 - Feber af ukendt årsag, pat. Mindst 18 år, uden biopsi og/eller scopi, Diagnose: DR509 - Feber UNS |
| Renal impairment | 33.289 kr. | DRG 2022: 11MA02 - Andre primære eller sekundære medicinske nyresygdomme uden dialyse, Diagnose: DN199 - Nyreinsufficiens UNS |
| Thrombocytopenia | 38.408 kr. | DRG 2022: 16MA03 - Granulo- og trombocytopeni, Diagnose: DD696 - Trombocytopeni UNS |



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| | | |
|---|---|---|
| Vomiting | 6.756 kr. | DRG 2022: 06MA11 - Malabsorption og betændelse i spiserør, mave og tarm, pat. Mindst 18 år, . Kompl. Bidiag., Diagnose: DR119C - Opkastning |

*Sources: DRG 2022* (58)

**Patient cost**

Patient costs in the form of hourly pay and transportation costs are not included in the model base case due to uncertainty surrounding transportation time to and from the hospital. Based on the Danish advisory board held by Takeda Pharma A/S in 2022, physicians stated that the heterogeneity of the patient population makes it impossible to determine the proportion of patients who travels to and from the hospital to receive IV infusions and what proportion is hospitalised as part of the treatment. Naturally, only patients receiving IV infusions as part of their treatments would travel to and from hospitals to receive treatment. To account for potential patient costs associated with IV infusions a scenario analysis attributing transportation costs and hourly pay to the frequency of infusions and time on treatment has been included in the model. Further, the analysis has the option to include proportion of patients already hospitalised. However, in the scenario presented in section 8.7.1 Deterministic sensitivity analyses) the proportion is set to 0 to show the extremes of the analysis. The costs have been based on the Danish Medicines Councils document concerning valuation of unit costs. The costs, hours of IV infusions per cycle, and number of IV trips to the hospital is listed in Table 83.

**Table 83: Patient cost scenario**

| Unit costs | Mean | Source |
|---|---|---|
| **Patient time cost (per hour)** | 181 kr. | Danish Medicine Councils document concerning valuation of unit costs (74) |
| **Cost of transportation** | 140 kr. | Danish Medicine Councils document concerning valuation of unit costs (74) |

| Hours of IV infusions per cycle | Mean | Source |
|---|---|---|
| **Maribavir** | 0 | Assumed equal to the number of IV days |
| **IAT** | 0 | Assumed equal to the number of IV days |
| **Ganciclovir** | 28 | Assumed equal to the number of IV days |
| **Valganciclovir** | 0 | Assumed equal to the number of IV days |
| **Foscarnet** | 28 | Assumed equal to the number of IV days |
| **Cidofovir** | 4 | Assumed equal to the number of IV days |

| Number of IV trips to hospital | Mean | Source |
|---|---|---|
| **Proportion of patients already hospitalised** | 0,00 | Assumption |
| **Maribavir** | 0 | Assumed equal to the number of IV days |
| **IAT** | 0 | Assumed equal to the number of IV days |
| **Ganciclovir** | 28 | Assumed equal to the number of IV days |
| **Valganciclovir** | 0 | Assumed equal to the number of IV days |
| **Foscarnet** | 28 | Assumed equal to the number of IV days |
| **Cidofovir** | 4 | Assumed equal to the number of IV days |



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## 8.6 Results

### 8.6.1 Base case overview

For the base case overview, see Appendix J Deterministic base case) (Table 142 and Table 143)

### 8.6.2 Base case results

Table 84 below shows the base case result based on the input values listed in Appendix J Deterministic base case. Results stratified based on populations consistent only of SOT or HSCT patients are available in Appendix P Results stratified based on transplant type).

**Table 84: Base case results**

| Per patient | Maribavir | IAT | Incremental |
|---|---|---|---|
| **Effect** | | | |
| Total life years gained | [redacted] | | |
| Total QALYs | | | |
| **Costs** | | | |
| Total costs | | | |
| Drug costs | | | |
| Administrative costs | | | |
| Monitoring cost | | | |
| Hospital admissions costs | | | |
| Adverse reactions costs | | | |
| Patient time and transport costs | | | |
| Re-treatment costs | | | |
| Graft loss costs | | | |
| **Incremental results** | | | |
| **ICER (per QALY)** | | | |



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## 8.7 Sensitivity analyses

### 8.7.1 Deterministic sensitivity analyses

Several deterministic sensitivity analyses (DSA) were conducted to identify parameters that were influential to the base case outputs and to assess the relative impact of changes to individual, or groups of, parameter values on results. The changes that have been made can be found in the DSA control sheet of the model. A summary of the parameters, their variation type, and variation value is presented in Appendix K Deterministic sensitivity analyses). Parameters were varied by their 95% confidence interval when possible (see Table 144 for the distributions used for each parameter), otherwise the parameter was varied by 20% in both the upper and lower direction, or an assumed upper and lower value as appropriate.

For the results of the deterministic sensitivity analysis, see Table 145 in Appendix K Deterministic sensitivity analyses). The top 25 parameters from the deterministic sensitivity analysis are also presented in the tornado diagram below (Figure 16). Moreover, Figure 17 shows the max PRP to where the ICER become negative. The results are also shown in Table 85.



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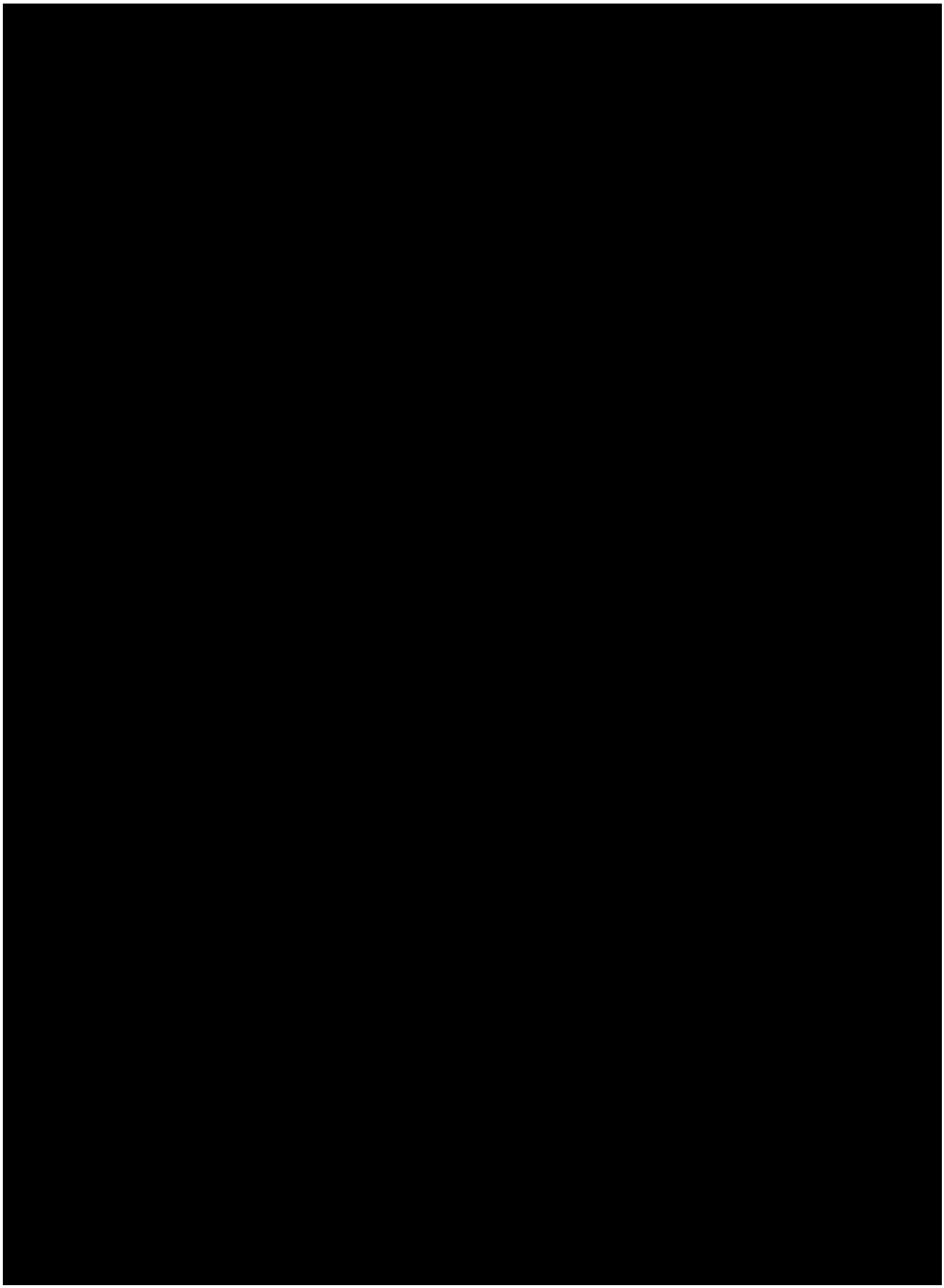



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[redacted]

**Scenario analysis**

Scenario analyses representing alternative base case outputs are presented in Table 87. The purpose of the scenarios are outlined in Table 86.

[redacted]



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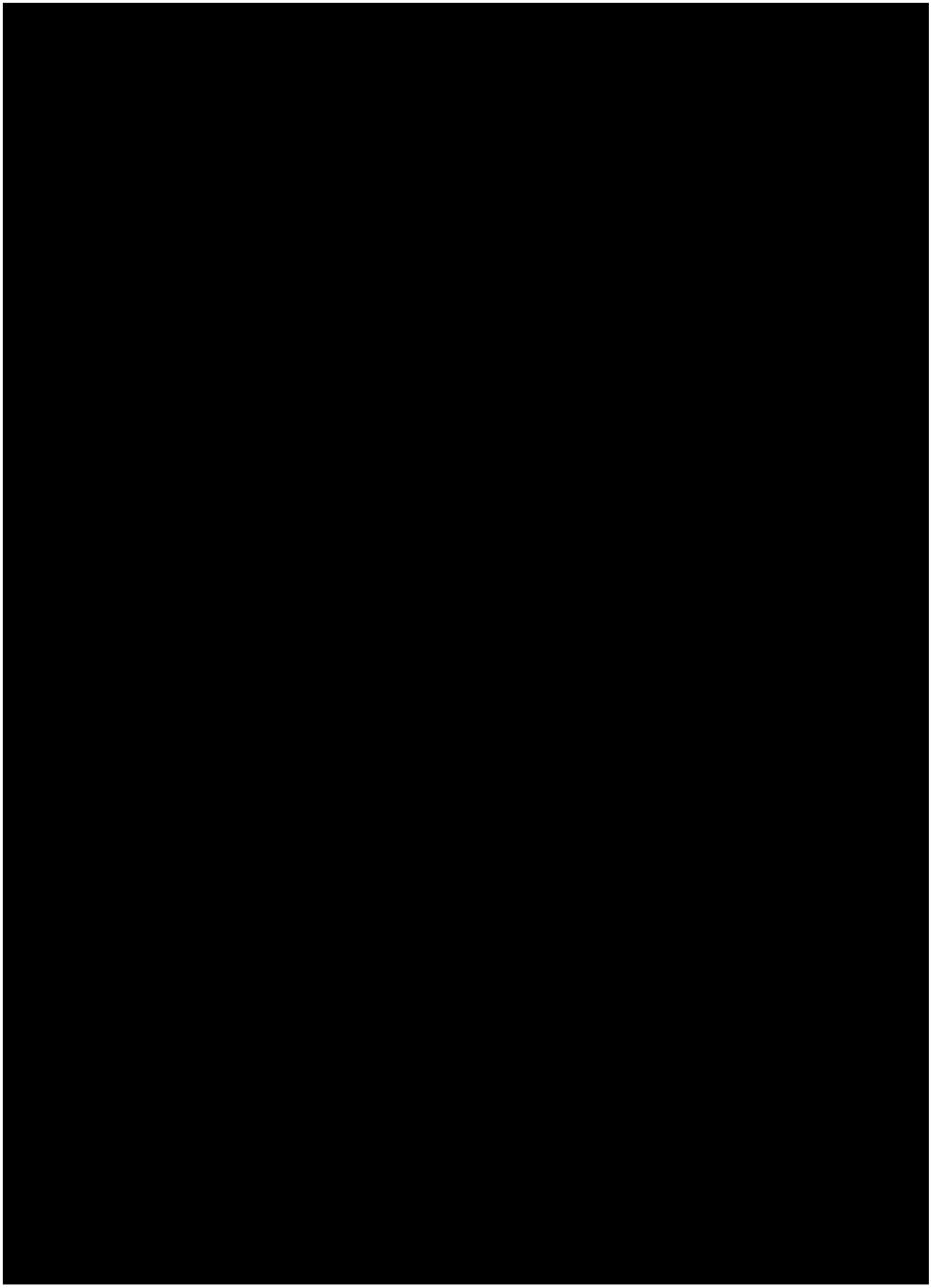



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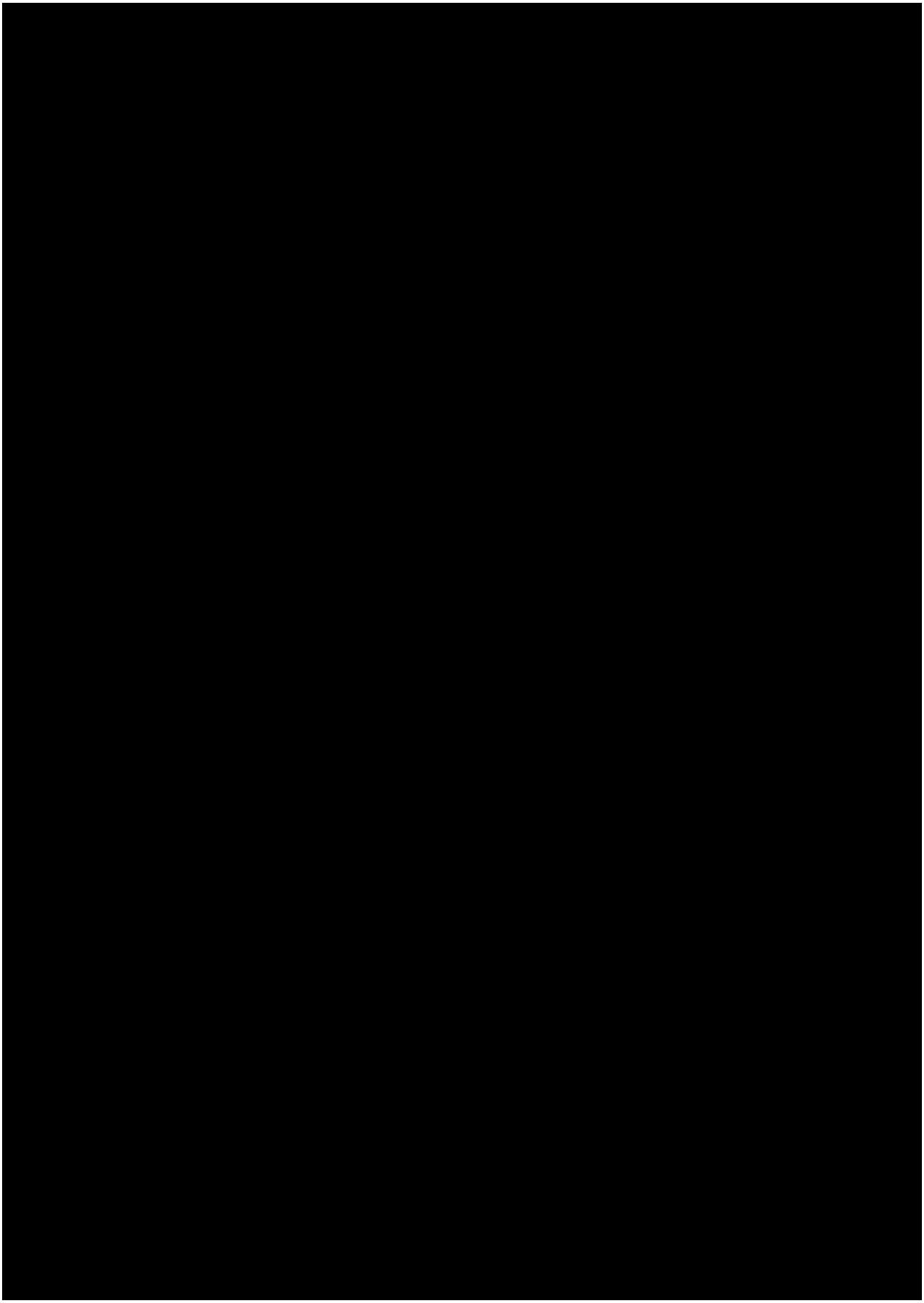



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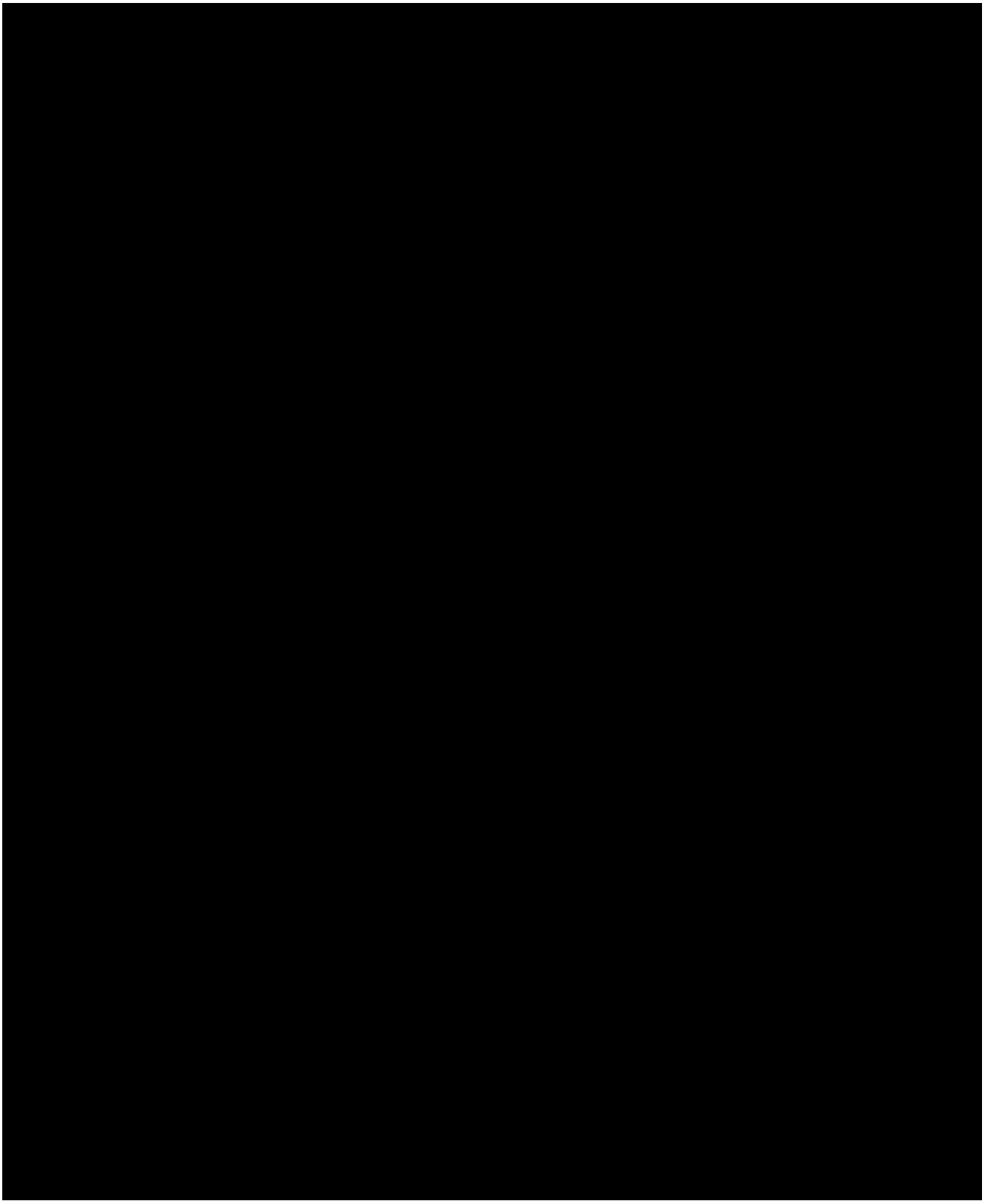

### 8.7.2 Probabilistic sensitivity analyses

Table 89 shows the cost-effectiveness result per patient while Figure 18 shows the results of each iteration of the PSA (blue dot), with the grey line showing the cost-effectiveness threshold. The majority of iterations fall in the north-east



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quadrant indicating maribavir provides more QALYs at a higher cost than IAT. The result of the probabilistic sensitivity analysis stratified on transplant type can be found in Appendix L Probabilistic sensitivity analyses) showing both tables, scatter pots, and CEAC (Table 147, Table 148, Figure 26, **Figure 27**, Figure 28, Figure 29).

**Table 89: PSA cost-effectiveness result per patient**

| Outcome | Maribavir | IAT | Incremental |
|---|---|---|---|
| Costs | [redacted] | | |
| QALYs total | | | |
| ICER (DKK/QALY) | | | |

[redacted]

**Cost-effectiveness acceptability curve (CEAC)**

The CEAC (Figure 19) shows the probability that maribavir is cost-effective compared to IAT at a range of WTP thresholds. Maribavir has approximately 60% probability of being cost-effective at a WTP threshold of [redacted] Maribavir has a higher probability (>50%) of being cost-effective than IAT at a WTP threshold above [redacted]



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# 9. Budget impact analysis

The budget impact analysis is developed to estimate the expected budget impact of recommending maribavir as possible standard treatment in Denmark. The budget impact analysis is embedded in the Markov model, consequently any changes made related to the cost per patient is reflected in the budget impact analysis. All costs included in the budget impact analysis are undiscounted, further patient costs, including transportation costs, are excluded from the analysis as per the guidelines by the Danish Medicine Council (44).

The analysis compares the costs for the Danish regions per year over a five-year timeframe, in the scenario where maribavir is recommended as possible standard treatment and the second scenario where maribavir is not recommended as possible standard treatment. The total budget impact per year is the difference between the two scenarios.

## 9.1 Patient population

The number of patients, including the proportions of SOT and HSCT patients, incorporated in the budget impact analysis is determined in section 5. The patient population, the intervention and choice of comparator(s)). The distribution of patients in the two scenarios are presented in Table 90 and Table 91, and represents the assumption, that in the scenario where maribavir is recommended as standard treatment, it will be used for all new patients from year 2 and onwards. In year 1 approximately only a third of patients will be treated with maribavir as it is a novel treatment that physicians will need to become familiar with.



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**Table 90: Number of patients expected to be treated over the next five-year period - if maribavir is introduced**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Maribavir (total)** | | | | | |
| *SOT* | | | | | |
| *HSCT* | | | | | |
| **IAT (total)** | | | | | |
| *SOT* | | | | | |
| *HSCT* | | | | | |
| **Total number of patients** | | | | | |

Abbreviation: HSCT, hematopoietic stem cell transplantation; IAT, investigator assigned treatment; SOT, solid organ transplantation

**Table 91: Number of patients expected to be treated over the next five-year period - if maribavir is NOT introduced**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Maribavir (total)** | | | | | |
| **IAT (total)** | | | | | |
| *SOT* | | | | | |
| *HSCT* | | | | | |
| **Total number of patients** | | | | | |

Abbreviation: HSCT, hematopoietic stem cell transplantation; IAT, investigator assigned treatment; SOT, solid organ transplantation

### Expenditure per patient

**Table 92: Costs per patient per year**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Maribavir - SOT | | | | | |
| Maribavir - HSCT | | | | | |
| IAT - SOT | | | | | |
| IAT - HSCT | | | | | |

Abbreviation: HSCT, hematopoietic stem cell transplantation; IAT, investigator assigned treatment; SOT, solid organ transplantation

### Budget impact

**Table 93: Expected budget impact of recommending maribavir for SOT patients with R/R CMV**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| The pharmaceutical under consideration is recommended | | | | | |



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| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Of which: Drug costs** | | | | | |
| **Of which: Administrative costs** | | | | | |
| **Of which: Hospital costs** | | | | | |
| **Of which: Adverse reaction costs** | | | | | |
| Minus:<br>The pharmaceutical under consideration is NOT recommended | | | | | |
| **Of which: Drug costs** | | | | | |
| **Of which: Administrative costs** | | | | | |
| **Of which: Hospital costs** | | | | | |
| **Of which: Adverse reaction costs** | | | | | |
| Budget impact of the recommendation | | | | | |

**Table 94: Expected budget impact of recommending maribavir for HSCT patients with R/R CMV**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| The pharmaceutical under consideration is recommended | | | | | |
| **Of which: Drug costs** | | | | | |
| **Of which: Administrative costs** | | | | | |
| **Of which: Hospital costs** | | | | | |
| **Of which: Adverse reaction costs** | | | | | |
| Minus:<br>The pharmaceutical under consideration is NOT recommended | | | | | |
| **Of which: Drug costs** | | | | | |
| **Of which: Administrative costs** | | | | | |
| **Of which: Hospital costs** | | | | | |
| **Of which: Adverse reaction costs** | | | | | |
| Budget impact of the recommendation | | | | | |



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Abbreviation: CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; R/R, refractory with or without resistance

# 10. Discussion on the submitted documentation

**Clinical data from the SOLSTICE study**

The approval of maribavir is based on one pivotal trial (SOLSTICE) that enrolled 352 post-transplant HSCT or SOT recipients with CMV infection refractory with or without resistance to ganciclovir, valganciclovir, foscarnet, and/or cidofovir. This was a study comparing maribavir with ganciclovir, valganciclovir, foscarnet, and/or cidofovir [IAT arm] – which represents the standard of care in Denmark. The reported data from the SOLSTICE study reflects the same patient population as maribavir is intended to treat in Denmark. According to the Danish experts, the characteristics of the study population are overall comparable to the Danish setting, thus considered to be transferable. In SOLSTICE the primary endpoint was clearance of CMV viraemia after 8 weeks, which is recognized as clinically relevant to prevent CMV disease and mortality in transplant recipients and was further supported by secondary endpoints; maintenance of CMV clearance through week 16, clinically relevant recurrence of CMV viraemia, all-cause mortality, graft outcomes, and AEs. The chosen and presented outcomes herein are based on input from the Danish clinical experts and are thus considered to be critical or important outcomes. The distribution of the CMV therapies within SOLSTICE was also validated by the Danish clinical experts and was considered reflective of Danish clinical practice for difficult-to-treat infections with refractory or resistant CMV. In conclusion, it is considered a strength that the SOLSTICE study, reflecting the relevant patient population and relevant comparators in Denmark, is used in this submission.

In SOLSTICE, treatment was administered for a maximum of 8 weeks, with 12 weeks of follow-up. The acute nature of the disease means that 20 weeks is more than sufficient for evaluation of CMV clearance and recurrence; however, evaluation of important long-term outcomes, such as graft loss and mortality, are difficult within this time frame. SOLSTICE was conducted with an open-label design, a necessity because of the need for the physician to individualize drug selection for treatment-refractory patients in the IAT arm, choosing the appropriate therapy based on clinical data and judgment and institutional guidelines. Furthermore, genetic testing for antiviral resistance in SOLSTICE may have resulted in the identification of the most appropriate treatment for patients in the IAT arm. Consequently, the maribavir results may be conservative, given that genetic testing is not part of routine Danish practice for the management of CMV infections.

**Adjustments to Danish setting**

The data used for estimating the overall R/R CMV patient population and patients eligible for treatment is associated with uncertainties. Number of transplants and incidence rates for R/R CMV is based on data from Scandiatransplant.org and the internal epidemiology SLR (Takeda Pharmaceutical Company Limited 2021). The results have been presented to Danish clinical experts, and the incidence rate is assessed to be significantly lower in Danish clinical practice than what is found in the internal epidemiology SLR (Takeda Pharmaceutical Company Limited 2021). Based on the assessment by the clinical experts, the incidence rate has been lowered to their assumptions.

**Health economic analysis**

In patients with CMV, maribavir demonstrated a statistically significant and clinically relevant improvement in CMV clearance compared with IAT. The economic model utilized this primary endpoint, alongside important secondary endpoints from SOLSTICE, and outputs from an IPD analysis of SOLSTICE data to establish the cost-effectiveness of maribavir compared with IAT. The superior clearance observed in Study 303 for maribavir compared with IAT has been utilised in the model to inform the transition probabilities between the csCMV and n-csCMV health state. As a result of this superior clearance, patients in the IAT arm spend longer durations in the csCMV health state (0.56 life years in the IAT arm versus 0.41 life years in the maribavir arm). This impacts the cost-effectiveness results because the csCMV

health state is associated with higher costs, greater mortality and lower quality of life compared with the n-csCMV health state. The key driver of costs in the maribavir arm are the acquisition costs for maribavir and the IAT administration costs (driven by the requirement of IV infusions for ganciclovir, cidofovir and foscarnet) for patients receiving retreatment. In the IAT arm the key cost driver is the treatment administration costs for the IAT drugs.

Certainty around the deterministic results were assessed as part of the DSA. In the Stage 1 Markov, clearance probabilities, drug acquisition costs for maribavir and IV costs were the parameters affecting the ICER the most. As the duration of the Stage 1 Markov had the greatest impact in the DSA, this input parameter was extensively validated with clinicians and further confirmed by data from OTUS. The validation exercise found that 78 weeks was a reasonably pragmatic duration for the Stage 1 Markov. While there was evidence that the Stage 1 Markov could be extended beyond 78 weeks, this extension would only favour the maribavir arm, therefore the decision to transition to the Stage 2 Markov at 78 weeks reflects a conservative estimate. Another important driver of the results are the assumptions around the IV costs for the relevant IAT drugs (ganciclovir, cidofovir, and foscarnet). Patients in the IAT arm occupy the csCMV health state for longer, resulting in greater exposure to the high IV costs. The assumptions adopted in this model reflect the most robust estimates for the Danish perspective. It should be noted that the IV costs in the model are conservative because a pragmatic assumption has been made that even if patients were to require more than one IV infusion per 24 hours, only one IV infusion cost will be applied during this 24-hour period. Therefore, it could be argued that the IV costs could be even higher in this model and therefore the incremental costs between maribavir and IAT would decrease and the ICER would improve. Finally, despite the DSA identifying the clearance transition probability (estimated from Study 303) as an important parameter for further consideration, the deterministic analysis and PSA are of greater importance to assess this uncertainty.

Beyond the results, two important aspects of the model should be noted. First, the definition of clinically significant CMV assumes that patients are on treatment with an anti-CMV agent. Therefore, when the Study 303 and OTUS data were used to inform risk of CMV recurrence, the requirement of treatment was included as part of the definition for recurrence. This definition was discussed with clinicians and health economists who all agreed that recurrences requiring treatment are those CMV events that have clinical and economic significance. Another important aspect to note is that the model has simplified the assumptions around disease complications, this includes graft loss events for SOT patients and GvHD and relapse in the underlying condition for HSCT patients. A more robust model would have further explored in detail the consequence of these events from a cost and health perspective. However, the exploration of these events was limited due to two reasons: 1) intentionally keeping the focus of the model on CMV was of greater importance than modelling individual disease pathways for these events; 2) as there are a greater number of these events in the IAT arm a more granular approach would only further favour maribavir so the limited approach reflects a conservative assumption.

In conclusion, the economic model described in this report has translated the important clinical value drivers for maribavir into a robust economic model.

## 11. List of experts

None of the involved clinical experts wanted to be mentioned by name as part of the application process.

## 12. References

1. Livtencity: Pending EC decision | European Medicines Agency [Internet]. [cited 2022 Sep 29]. Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/livtencity
2. Avery RK, Alain S, Alexander BD, Blumberg EA, Chemaly RF, Cordonnier C, et al. Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized



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Clinical Trial. Clin Infect Dis. 2022 Sep 10;75(4):690–701.
3. Crough T, Khanna R. Immunobiology of human cytomegalovirus: from bench to bedside. Clin Microbiol Rev. 2009 Jan;22(1):76–98.
4. Cytomegalovirus [Internet]. [cited 2021 Jul 26]. Available from: https://www.ssi.dk/sygdomme-beredskab-og-forskning/sygdomsleksikon/c/cytomegalovirus
5. Crough T, Khanna R. Immunobiology of human cytomegalovirus: from bench to bedside. Clin Microbiol Rev [Internet]. 2009 Jan [cited 2022 Mar 3];22(1):76–98. Available from: https://pubmed.ncbi.nlm.nih.gov/19136435/
6. Grigoleit GU, Kapp M, Einsele H. Indirect Effects of Cytomegalovirus Infection. Eur Oncol Haematol. 2009;03(01):41.
7. Ljungman P, Styczynski J, Einsele H. Viral Infections. EBMT Handb Hematop Stem Cell Transplant Cell Ther [Internet]. 2019 Dec 12 [cited 2022 Mar 3];281–90. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553936/
8. Fishman JA. Infection in Solid-Organ Transplant Recipients. http://dx.doi.org/101056/NEJMra064928 [Internet]. 2009 Oct 9 [cited 2022 Mar 3];357(25):2601–14. Available from: https://www.nejm.org/doi/full/10.1056/nejmra064928
9. Letermovir (Prevymis) [Internet]. [cited 2022 Mar 3]. Available from: https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/i-l/letermovir-prevymis-forebyggelse-af-cytomegalovirus-cmv-reaktivering-og-sygdom
10. Fisher CE, Knudsen JL, Lease ED, Jerome KR, Rakita RM, Boeckh M, et al. Risk Factors and Outcomes of Ganciclovir-Resistant Cytomegalovirus Infection in Solid Organ Transplant Recipients. Clin Infect Dis. 2017 Jul;65(1):57–63.
11. Liu J, Kong J, Chang YJ, Chen H, Chen YH, Han W, et al. Patients with refractory cytomegalovirus (CMV) infection following allogeneic haematopoietic stem cell transplantation are at high risk for CMV disease and non-relapse mortality. Clin Microbiol Infect [Internet]. 2015 [cited 2022 Nov 29];21(12):1121.e9-1121.e15. Available from: https://pubmed.ncbi.nlm.nih.gov/26093077/
12. Robin C, Hémery F, Dindorf C, Thillard J, Cabanne L, Redjoul R, et al. Economic burden of preemptive treatment of CMV infection after allogeneic stem cell transplantation: a retrospective study of 208 consecutive patients. BMC Infect Dis [Internet]. 2017 Dec 5 [cited 2022 Nov 29];17(1). Available from: https://pubmed.ncbi.nlm.nih.gov/29207952/
13. Hakimi Z, Aballéa S, Ferchichi S, Scharn M, Odeyemi IA, Toumi M, et al. Burden of cytomegalovirus disease in solid organ transplant recipients: a national matched cohort study in an inpatient setting. Transpl Infect Dis. 2017 Oct;19(5).
14. Hakimi Z, Ferchichi S, Aballea S, Odeyemi I, Toumi M, English M, et al. Burden of cytomegalovirus disease in allogeneic hematopoietic cell transplant recipients: a national, matched cohort study in an inpatient setting. Curr Res Transl Med [Internet]. 2018 Nov 1 [cited 2022 Nov 29];66(4):95–101. Available from: https://pubmed.ncbi.nlm.nih.gov/30274738/
15. Selvey LA, Lim WH, Boan P, Swaminathan R, Slimings C, Harrison AE, et al. Cytomegalovirus viraemia and mortality in renal transplant recipients in the era of antiviral prophylaxis. Lessons from the western Australian experience. BMC Infect Dis [Internet]. 2017 Jul 17 [cited 2022 Nov 29];17(1). Available from: https://pubmed.ncbi.nlm.nih.gov/28716027/
16. Green ML, Leisenring W, Xie H, Mast TC, Cui Y, Sandmaier BM, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. Lancet Haematol [Internet]. 2016 Mar 1 [cited 2022 Nov 29];3(3):e119–27. Available from: https://pubmed.ncbi.nlm.nih.gov/26947200/
17. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. Clin Infect Dis [Internet]. 2002 Apr 15 [cited 2022 Nov 29];34(8):1094–7. Available from: https://pubmed.ncbi.nlm.nih.gov/11914998/
18. Ramanan P, Razonable RR. Cytomegalovirus infections in solid organ transplantation: a review. Infect Chemother [Internet]. 2013 May [cited 2022 Nov 29];45(3):260–71. Available from: https://pubmed.ncbi.nlm.nih.gov/24396627/
19. Takeda. Epidemiology of Cytomegalovirus Patient Populations following Solid Organ Transplant or Hematopoietic Stem Cell Transplant : A Systematic Literature Review. 2021. [Data on file].
20. Takeda. Updated Epi estimates - CMV patient segments 2021. [Data on file].
21. Scandiatransplant figures — Site [Internet]. [cited 2022 Sep 26]. Available from: http://www.scandiatransplant.org/data/scandiatransplant-figures

22. Metode ved stamcelletransplantation - Kræftens Bekæmpelse [Internet]. [cited 2022 Sep 26]. Available from: https://www.cancer.dk/hjaelp-viden/kraeftbehandling/behandlingsformer/stamcelletransplantation/metode-ved-stamcelletransplantation/
23. Takeda. SHP620-303 Clinical Study Report. 2021. [Data on file].
24. Stamcelletransplantation - Kræftens Bekæmpelse [Internet]. [cited 2022 Sep 26]. Available from: https://www.cancer.dk/hjaelp-viden/kraeftbehandling/behandlingsformer/stamcelletransplantation/
25. Gjærde LK, Rank CU, Andersen MK, Jakobsen LH, Sengeløv H, Olesen G, et al. Improved survival after allogeneic transplantation for acute lymphoblastic leukemia in adults: a Danish population-based study. Leuk Lymphoma [Internet]. 2022 [cited 2022 Sep 26];63(2):416–25. Available from: https://pubmed.ncbi.nlm.nih.gov/34672245/
26. Isatuximab (Sarclisa) i kombination med carfilzomib og dexamethason [Internet]. [cited 2022 Sep 26]. Available from: https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/i-l/isatuximab-sarclisa-i-komb-med-carfilzomib-og-dexamethason-til-2-linjebehandling-af-knoglemarvskraeft
27. Malignt Lymfom og CLL National årsrapport 2020. 2020 [cited 2022 Sep 26]; Available from: www.rkkp.dk
28. Non-Hodgkins lymfom - Lægehåndbogen på sundhed.dk [Internet]. [cited 2022 Sep 26]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/blod/tilstande-og-sygdomme/lymfomer/non-hodgkins-lymfom/
29. British Transplantation Society. The prevention and management of CMV disease after solid organ transplantation. 2015.
30. Emery V, Zuckerman M, Jackson G, Aitken C, Osman H, Pagliuca A, et al. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. Br J Haematol. 2013 Jul;162(1):25–39.
31. Abbott realtime CMV [Internet]. [cited 2022 Sep 29]. Available from: https://www.molecular.abbott/sal/RealTime-CMV-Package-Insert-US-51-608290.pdf
32. COBAS® AmpliPrep/COBASO TaqMan® CMV Test.
33. artus CMV PCR Kits CE - QIAGEN [Internet]. [cited 2022 Sep 29]. Available from: https://www.qiagen.com/es/spotlight-pages/ias/automated-qpcr-workflow/detection/artus-cmv-pcr-kits-ce/#productdetails
34. Cymevene 500mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2022 Sep 26]. Available from: https://www.medicines.org.uk/emc/product/10242/smpc#gref
35. Cidofovir 75 mg/ml Concentrate for Solution for Infusion - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2022 Sep 26]. Available from: https://www.medicines.org.uk/emc/product/11151
36. Foscavir 24 mg/ml Solution for Infusion - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2022 Sep 26]. Available from: https://www.medicines.org.uk/emc/product/874/smpc
37. Valcyte 450 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2022 Sep 26]. Available from: https://www.medicines.org.uk/emc/product/1641/smpc
38. Papanicolaou GA, Silveira FP, Langston AA, Pereira MR, Avery RK, Uknis M, et al. Maribavir for Refractory or Resistant Cytomegalovirus Infections in Hematopoietic-cell or Solid-organ Transplant Recipients: A Randomized, Dose-ranging, Double-blind, Phase 2 Study. Clin Infect Dis [Internet]. 2019 Apr 8 [cited 2022 Sep 26];68(8):1255–64. Available from: https://pubmed.ncbi.nlm.nih.gov/30329038/
39. Avery RK, Alain S, Alexander BD, Blumberg EA, Chemaly RF, Cordonnier C, et al. Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial - Supplementary Data. Clin Infect Dis [Internet]. 2022 Sep 10 [cited 2022 Sep 26];75(4). Available from: https://pubmed.ncbi.nlm.nih.gov/34864943/
40. Takeda. Data on file. Healthcare resource utilization in transplant recipients with cytomegalovirus infection refractory/resistant to treatment receiving maribavir versus investigator assigned therapy: Exploratory analysis of a Phase 3 trial. 2021.
41. Pescovitz MD, Bloom R, Pirsch J, Johnson J, Gelone S, Villano SA. A randomized, double-blind, pharmacokinetic study of oral maribavir with tacrolimus in stable renal transplant recipients. Am J Transplant [Internet]. 2009 Oct [cited 2022 Sep 26];9(10):2324–30. Available from: https://pubmed.ncbi.nlm.nih.gov/19663892/
42. Takeda. Data on File. SHP620-303 Individual Patient Data Analysis. 2021.
43. NICE. Letermovir for preventing cytomegalovirus disease after a stem cell transplant: Technology appraisal guidance [TA591]. 2019 TA591.
44. Medicinrådet. Medicinrådets metodevejledning for vurdering af nye laegemidler.
45. Finansministeriet. Dokumentationsnotat for den samfundsøkonomiske diskonteringsrente.




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46. Organ and Tissue Donation and Transplantation. [cited 2022 Sep 27]; Available from: http://www.odt.nhs.uk.
47. Danmarks Statistik [Internet]. [cited 2022 Sep 27]. Available from: https://www.dst.dk/da/
48. Hahn T, McCarthy PL, Zhang M-J, Wang D, Arora M, Frangoul H, et al. Risk factors for acute graft-versus-host disease after human leukocyte antigen-identical sibling transplants for adults with leukemia. J Clin Oncol. 2008 Dec 10;26(35):5728–34.
49. Cantoni N, Hirsch HH, Khanna N, Gerull S, Buser A, Bucher C, et al. Evidence for a bidirectional relationship between cytomegalovirus replication and acute graft-versus-host disease. Biol Blood Marrow Transplant. 2010 Sep;16(9):1309–14.
50. HMRN - Survival [Internet]. [cited 2022 Sep 27]. Available from: https://hmrn.org/statistics/survival
51. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 31(6):800–4.
52. Ossa DF, Briggs A, McIntosh E, Cowell W, Littlewood T, Sculpher M. Recombinant erythropoietin for chemotherapy-related anaemia: economic value and health-related quality-of-life assessment using direct utility elicitation and discrete choice experiment methods. Pharmacoeconomics [Internet]. 2007 [cited 2022 Sep 27];25(3):223–37. Available from: https://pubmed.ncbi.nlm.nih.gov/17335308/
53. Nafees B, Lloyd AJ, Dewilde S, Rajan N, Lorenzo M. Health state utilities in non-small cell lung cancer: An international study. Asia Pac J Clin Oncol. 2017 Oct;13(5):e195–203.
54. Bullement A, Nathan P, Willis A, Amin A, Lilley C, Stapelkamp C, et al. Cost Effectiveness of Avelumab for Metastatic Merkel Cell Carcinoma. PharmacoEconomics - open [Internet]. 2019 Sep 1 [cited 2022 Sep 27];3(3):377–90. Available from: https://pubmed.ncbi.nlm.nih.gov/30680676/
55. Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes. 2010 May 18;8:50.
56. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. Eur J Health Econ [Internet]. 2013 Oct 1 [cited 2022 Sep 27];14(5):749–59. Available from: https://pubmed.ncbi.nlm.nih.gov/22941034/
57. Forside - www.medicinpriser.dk [Internet]. [cited 2022 Sep 27]. Available from: https://medicinpriser.dk/
58. DRG-takster 2022 - Sundhedsdatastyrelsen [Internet]. [cited 2022 Sep 27]. Available from: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2022
59. RH Laboratorieundersøgelse [Internet]. [cited 2022 Sep 27]. Available from: https://labportal.rh.dk/
60. Camargo JF, Kimble E, Rosa R, Shimose LA, Bueno MX, Jeyakumar N, et al. Impact of Cytomegalovirus Viral Load on Probability of Spontaneous Clearance and Response to Preemptive Therapy in Allogeneic Stem Cell Transplantation Recipients. Biol Blood Marrow Transplant [Internet]. 2018 Apr 1 [cited 2022 Sep 27];24(4):806–14. Available from: https://pubmed.ncbi.nlm.nih.gov/29217388/
61. Martin PJ, Counts GW, Appelbaum FR, Lee SJ, Sanders JE, Deeg HJ, et al. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. J Clin Oncol [Internet]. 2010 Feb 20 [cited 2022 Sep 27];28(6):1011–6. Available from: https://pubmed.ncbi.nlm.nih.gov/20065176/
62. Miller RJH, Clarke BA, Howlett JG, Khush KK, Teuteberg JJ, Haddad F. Outcomes in patients undergoing cardiac retransplantation: A propensity matched cohort analysis of the UNOS Registry. J Heart Lung Transplant [Internet]. 2019 Oct 1 [cited 2022 Sep 27];38(10):1067–74. Available from: https://pubmed.ncbi.nlm.nih.gov/31378576/
63. Panchal H, Muskovich J, Patterson J, Schroder PM, Ortiz J. Expanded criteria donor kidneys for retransplantation United Network for Organ Sharing update: proceed with caution. Transpl Int [Internet]. 2015 Aug 1 [cited 2022 Sep 27];28(8):990–9. Available from: https://pubmed.ncbi.nlm.nih.gov/25864733/
64. Kawut SM, Lederer DJ, Keshavjee S, Wilt JS, Daly T, D'Ovidio F, et al. Outcomes after lung retransplantation in the modern era. Am J Respir Crit Care Med. 2008 Jan 1;177(1):114–20.
65. Kim HJ, Larson JJ, Lim YS, Kim WR, Pedersen RA, Therneau TM, et al. Impact of MELD on waitlist outcome of retransplant candidates. Am J Transplant [Internet]. 2010 Dec [cited 2022 Sep 27];10(12):2652–7. Available from: https://pubmed.ncbi.nlm.nih.gov/21070603/
66. Rayner HC, Pisoni RL, Bommer J, Canaud B, Hecking E, Locatelli F, et al. Mortality and hospitalization in haemodialysis patients in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant [Internet]. 2004 Jan [cited 2022 Sep 27];19(1):108–20. Available from: https://pubmed.ncbi.nlm.nih.gov/14671046/
67. Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Appl Health Econ Health Policy [Internet]. 2021 Jul 1 [cited 2022 Sep 27];19(4):579–91. Available from: https://pubmed.ncbi.nlm.nih.gov/33527304/




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68. Liem YS, Bosch JL, Myriam Hunink MG. Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta-analysis. Value Health [Internet]. 2008 [cited 2022 Sep 27];11(4):733–41. Available from: https://pubmed.ncbi.nlm.nih.gov/18194399/
69. Pidala J, Kurland B, Chai X, Majhail N, Weisdorf DJ, Pavletic S, et al. Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. Blood. 2011 Apr 28;117(17):4651–7.
70. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health. 2011 Jun;14(4):539–45.
71. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes [Internet]. 2008 Oct 21 [cited 2022 Sep 27];6. Available from: https://pubmed.ncbi.nlm.nih.gov/18939982/
72. Gilead Sciences Inc. (2010). "Vistide®(cidofovir injection) [Internet]. [cited 2022 Sep 29]. Available from: https://www.gilead.com/~/media/Files/pdfs/medicines/other/vistide/vistide.pdf
73. Dialyse - Lægehåndbogen på sundhed.dk [Internet]. [cited 2022 Sep 27]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/nyrer-og-urinveje/tilstande-og-sygdomme/behandlinger/dialyse/
74. Vaerdisaetning af enhedsomkostninger. [cited 2022 Sep 27]; Available from: www.medicinraadet.dk
75. Natori Y, Alghamdi A, Tazari M, Miller V, Husain S, Komatsu T, et al. Use of Viral Load as a Surrogate Marker in Clinical Studies of Cytomegalovirus in Solid Organ Transplantation: A Systematic Review and Meta-analysis. Clin Infect Dis [Internet]. 2018 Feb 15 [cited 2022 Sep 28];66(4):617–31. Available from: https://pubmed.ncbi.nlm.nih.gov/29020339/
76. Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S, Danziger-Isakov L, et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation [Internet]. 2018 Jun 1 [cited 2022 Sep 28];102(6):900–31. Available from: https://pubmed.ncbi.nlm.nih.gov/29596116/
77. Jang JE, Hyun SY, Kim YD, Yoon SH, Hwang DY, Kim SJ, et al. Risk factors for progression from cytomegalovirus viremia to cytomegalovirus disease after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant [Internet]. 2012 Jun [cited 2022 Sep 28];18(6):881–6. Available from: https://pubmed.ncbi.nlm.nih.gov/22062802/
78. Emery VC, Cope A V, Bowen EF, Gor D, Griffiths PD. The dynamics of human cytomegalovirus replication in vivo. J Exp Med. 1999 Jul 19;190(2):177–82.
79. Simons CL, Rivero-Arias O, Yu LM, Simon J. Multiple imputation to deal with missing EQ-5D-3L data: Should we impute individual domains or the actual index? Qual Life Res [Internet]. 2015 Mar 20 [cited 2022 Nov 29];24(4):805–15. Available from: https://pubmed.ncbi.nlm.nih.gov/25471286/
80. Ware JE. KM. BJB. T-BDM. GB& MME 2008. S-36v2® HS. Administration guide for clinical trial investigators. 2008;
81. Babigumira JB, Lubinga SJ, Castro E, Custer B. Cost-utility and budget impact of methylene blue-treated plasma compared to quarantine plasma. Blood Transfus. 2018;16(2):154–62.
82. Freedberg KA, Scharfstein JA, Seage GR, Losina E, Weinstein MC, Craven DE, et al. The cost-effectiveness of preventing AIDS-related opportunistic infections. JAMA. 1998 Jan 14;279(2):130–6.
83. Custer B, Busch MP, Marfin AA, Petersen LR. The cost-effectiveness of screening the U.S. blood supply for West Nile virus. Ann Intern Med. 2005 Oct 4;143(7):486–92.
84. Buti M, Casado MA, Fosbrook L, Wong JB, Esteban R. Cost-effectiveness of combination therapy for naive patients with chronic hepatitis C. J Hepatol. 2000 Oct;33(4):651–8.
85. Puttarajappa CM, Hariharan S, Smith KJ. A Markov Analysis of Screening for Late-Onset Cytomegalovirus Disease in Cytomegalovirus High-Risk Kidney Transplant Recipients. Clin J Am Soc Nephrol. 2018;13(2):290–8.
86. Laupacis A, Keown P, Pus N, Krueger H, Ferguson B, Wong C, et al. A study of the quality of life and cost-utility of renal transplantation. Kidney Int. 1996 Jul;50(1):235–42.
87. Restelli U, Croce D, Pacelli V, Ciceri F, Girmenia C. Cost-effectiveness analysis of the use of letermovir for the prophylaxis of cytomegalovirus in adult cytomegalovirus seropositive recipients undergoing allogenic hematopoietic stem cell transplantation in Italy. Infect Drug Resist. 2019;12:1127–38.
88. Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. N Engl J Med. 2017;377(25):2433–44.
89. Merck. Merck. MK-8828 (Letermovir) CSR preliminary dry-run - ePRO. Data on file. February 21, 2017. . CSR 2017.
90. Castejón N, Cappelleri JC, Cuervo J, Lang K, Mehta P, Mokgokong R, et al. Social preferences for health states




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associated with acute myeloid leukemia for patients undergoing treatment in the United Kingdom. Health Qual Life Outcomes. 2018 Apr 18;16(1):66.
91. Brown C, Mayes A, Schelfhout J, Jiang Y, Glover M, Taymor E. PSY93 - COST EFFECTIVENESS OF LETERMOVIR AS PROPHYLAXIS OF CLINICALLY SIGNIFICANT CYTOMEGALOVIRUS REACTIVATION AND DISEASE IN ADULT CMV-SEROPOSITIVE ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANT: AN ENGLISH PAYER PERSPECTIVE. Value Heal. 2018 Oct;21:S451–2.
92. Schelfhout J, Jiang Y, Miles L, Merchant S, Graham J. Cost Effectiveness of Letermovir as Cytomegalovirus Prophylaxis in in Allogeneic Hematopoietic Stem Cell Transplant Recipients. Biol Blood Marrow Transplant. 2018 Mar;24(3):S384.
93. CADTH. Pharmacoeconomic Review Report: Letermovir. 2018 Letermovir.
94. van Agthoven M, Segeren CM, Buijt I, Uyl-de Groot CA, van der Holt B, Lokhorst HM, et al. A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma; a prospective randomised phase III study. Eur J Cancer. 2004 May;40(8):1159–69.
95. Leunis A, Redekop WK, Uyl-de Groot CA, Löwenberg B. Impaired health-related quality of life in acute myeloid leukemia survivors: a single-center study. Eur J Haematol. 2014 Sep;93(3):198–206.
96. Blumberg EA, Hauser IA, Stanisic S, Mueller E, Berenson K, Gahlemann CG, et al. Prolonged prophylaxis with valganciclovir is cost effective in reducing posttransplant cytomegalovirus disease within the United States. Transplantation. 2010 Dec 27;90(12):1420–6.
97. Howard K, Salkeld G, White S, McDonald S, Chadban S, Craig JC, et al. The cost-effectiveness of increasing kidney transplantation and home-based dialysis. Nephrology (Carlton). 2009 Feb;14(1):123–32.
98. Luan FL, Stuckey LJ, Park JM, Kaul D, Cibrik D, Ojo A. Six-month prophylaxis is cost effective in transplant patients at high risk for cytomegalovirus infection. J Am Soc Nephrol. 2009 Nov;20(11):2449–58.
99. Narayan R, Perkins RM, Berbano EP, Yuan CM, Neff RT, Sawyers ES, et al. Parathyroidectomy versus cinacalcet hydrochloride-based medical therapy in the management of hyperparathyroidism in ESRD: a cost utility analysis. Am J Kidney Dis. 2007 Jun;49(6):801–13.
100. Luan FL, Kommareddi M, Ojo AO. Universal prophylaxis is cost effective in cytomegalovirus serology-positive kidney transplant patients. Transplantation. 2011 Jan 27;91(2):237–44.
101. Alsumali A, Chemaly RF, Graham J, Jiang Y, Merchant S, Miles L, et al. Cost-effectiveness analysis of cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplant recipients from a US payer perspective. J Med Virol. 2021;93(6):3786–94.
102. Chan TS-Y, Cheng SS-Y, Chen W-T, Hsu DC, Chau RW-Y, Kang SH, et al. Cost-effectiveness of letermovir as cytomegalovirus prophylaxis in adult recipients of allogeneic hematopoietic stem cell transplantation in Hong Kong. J Med Econ. 2020 Dec;23(12):1485–92.
103. Muduma G, Odeyemi I, Pollock RF. A cost-utility analysis of prolonged-release tacrolimus relative to immediate-release tacrolimus and ciclosporin in liver transplant recipients in the UK. J Med Econ. 2016 Oct;19(10):995–1002.
104. Ratcliffe J, Longworth L, Young T, Bryan S, Burroughs A, Buxton M, et al. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. Liver Transpl. 2002 Mar;8(3):263–70.
105. Tilden DP, Chapman J, Davey PJ, Solly ML, Crowley S. A decision-analytic economic evaluation of valaciclovir prophylaxis for the prevention of cytomegalovirus infection and disease in renal transplantation. Clin Transplant. 2004 Jun;18(3):312–20.
106. Das A. Cost-effectiveness of different strategies of cytomegalovirus prophylaxis in orthotopic liver transplant recipients. Hepatology. 2000 Feb;31(2):311–7.
107. CADTH. CDR Pharmacoeconomic Review Report For Tolvaptan (Jinarc). 2018 Tolvaptan.
108. McFarlane PA, Bayoumi AM, Pierratos A, Redelmeier DA. The quality of life and cost utility of home nocturnal and conventional in-center hemodialysis. Kidney Int. 2003 Sep;64(3):1004–11.
109. NICE. Everolimus for preventing organ rejection in liver transplantation-Technology appraisal guidance. 2015 TA348.
110. Neri L, McEwan P, Sennfält K, Baboolal K. Characterizing the relationship between health utility and renal function after kidney transplantation in UK and US: a cross-sectional study. Health Qual Life Outcomes. 2012 Nov 23;10:139.
111. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ [Internet]. 1996 [cited 2022 Sep 29];313(7052):275–83. Available from: https://pubmed.ncbi.nlm.nih.gov/8704542/
112. Drummond MF. Measuring and valuing effects : consumption benefits of health care. Consum Benefits Healthc



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[Internet]. 4th ed. 2015 [cited 2022 Sep 29];181–217. Available from: https://www.saxo.com/dk/methods-for-the-economic-evaluation-of-health-care-programmes_michael-f-drummond-mark-j-sculpher-karl-claxton_paperback_9780199665884
113. Molenberghs G, Verbeke G. Linear Mixed Models for Longitudinal Data. 2000 [cited 2022 Sep 29]; Available from: http://link.springer.com/10.1007/978-1-4419-0300-6
114. Home - electronic medicines compendium (emc) [Internet]. [cited 2022 Sep 29]. Available from: https://www.medicines.org.uk/emc#gref
115. Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). Value Health [Internet]. 2008 [cited 2022 Sep 27];11(7):1131–43. Available from: https://pubmed.ncbi.nlm.nih.gov/18489495/
116. Overview | Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia | Guidance | NICE [Internet]. [cited 2022 Sep 29]. Available from: https://www.nice.org.uk/guidance/ta451



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

A clinical systematic literature review (SLR) was conducted to identify relevant publications to address the following research question: "What is the clinical evidence for the efficacy and safety of anti-CMV agents (namely maribavir, ganciclovir, valganciclovir, foscarnet and cidofovir) for the treatment of R/R CMV infection/disease in SOT or HSCT recipients?" Electronic database searches of MEDLINE® (via PubMed) and CENTRAL (via Cochrane Library) were performed on 5 July 2022.

The eligibility criteria used for the SLR are defined in terms of the Population, Interventions, Comparators, Outcomes, (PICO) and study design framework as well as language and timeframe. Potentially relevant clinical studies were reviewed and assessed individually by two reviewers for relevance. Disagreements between reviewers were resolved during a consensus meeting.

## A.1 Databases

The key biomedical databases, including Medical Literature Analysis and Retrieval System Online (MEDLINE®) and the Cochrane Library, were searched to identify efficacy and safety data of maribavir, ganciclovir, valganciclovir, foscarnet, and cidofovir for the treatment of R/R CMV infection/disease in SOT or HSCT recipients.

**Table 95: Databases included in the literature search**

| Database | Platform | Relevant period for the search | Date of search completion |
|---|---|---|---|
| **MEDLINE®** | Pubmed.com | January 2000 – July 2022 | 5 July 2022 |
| **CENTRAL** | Cochrane Library | January 2000 – July 2022 | 5 July 2022 |

Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; MEDLINE®, Medical Literature Analysis and Retrieval System Online

**Table 96: Registers included in the search**

| Database | Platform | Search strategy | Date of search |
|---|---|---|---|
| **US NIH registry & results database** | https://clinicaltrials.gov | CMV and drug terms | 15 August 2022 |
| **EU Clinical Trials Register** | EU Clinical Trials Register | CMV and drug terms | 15 August 2022 |

Abbreviations: CMV, cytomegalovirus; EU, European Union; NIH, national institutes of health; US, United States



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## A.2 Search strategy

### A.2.1 PubMed search strategy

**Table 97: PubMed search for clinical SLR, 5 July 2022**

| # | Query | Results |
|---|---|---|
| 1 | transplant[tiab] OR transplants[tiab] OR transplantation[tiab] OR graft[tiab] OR grafts[tiab] | 673,462 |
| 2 | organ[tiab] OR solid[tiab] OR lung[tiab] OR heart[tiab] OR pancreas[tiab] OR kidney[tiab] OR liver[tiab] | 3,425,115 |
| 3 | hemopoetic[tiab] OR haemopoetic[tiab] OR hemopoietic[tiab] OR haemopoietic[tiab] OR hematopoietic[tiab] OR haematopoietic[tiab] OR allogeneic[tiab] OR 'stem cell' [tiab] | 307,604 |
| 4 | (#1 AND #2) OR (#1 AND #3) | 354,663 |
| 5 | cytomegalovirus[mh] | 22,524 |
| 6 | CMV[tiab] OR cytomegalovirus[tiab] | 54,730 |
| 7 | #5 OR #6 | 57,077 |
| 8 | resistant[tiab] OR refractory[tiab] OR resistance[tiab] | 1,285,633 |
| 9 | #4 AND #7 AND #8 | 1,022 |
| 10 | foscarnet[mh] | 1,613 |
| 11 | foscavir[mh] | 1,613 |
| 12 | foscarnet*[tiab] OR Foscavir*[tiab] | 1,873 |
| 13 | #10 OR #11 OR #12 | 2,488 |
| 14 | ganciclovir[mh] | 6,505 |
| 15 | ganciclovir[tiab] OR Cytovene*[tiab] OR Cymevene*[tiab] | 7,190 |
| 16 | #14 OR #15 | 8,293 |
| 17 | valganciclovir[mh] | 881 |
| 18 | valganciclovir[tiab] OR Cymeval*[tiab] OR Valcyt*[tiab] OR Valcyte*[tiab] OR Valixa*[tiab] OR Darilin*[tiab] OR Rovalcyte*[tiab] | 1,358 |
| 19 | #17 OR #18 | 1,562 |
| 20 | maribavir[nm] | 102 |
| 21 | maribavir[tiab] OR benzimidavir[tiab] OR 1263w94[tiab] OR camvia[tiab] OR 'shp 620'[tiab] OR shp620[tiab] OR shp-620[tiab] OR tak620[tiab] OR 'tak 620'[tiab] OR tak-620[tiab] OR vp41263[tiab] OR 'gw 1263'[tiab] | 194 |
| 22 | #20 OR #21 | 203 |
| 23 | cidofovir[mh] | 1,297 |
| 24 | brincidofovir[nm] | 105 |
| 25 | cidofovir[tiab] OR brincidofovir[tiab] OR Vistide*[tiab] | 1,955 |
| 26 | #23 OR #25 | 2,216 |
| 27 | #13 OR #16 OR #19 OR #22 OR #26 | 12,571 |
| 28 | #9 AND #27 | 446 |
| 29 | Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Practice Guideline[pt] OR (Review[pt] NOT (Systematic Review[pt] OR Meta-Analysis[pt])) | 7,082,405 |



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| # | Query | Results |
|---|---|---|
| 30 | #28 NOT #29 | 227 |
| 31 | English[la] OR Danish[la] AND (2000/1/1:2022/7/5[pdat]) | 19,641,333 |
| 32 | #30 AND #31 | 189 |

Abbreviations: ab, abstract; CMV, cytomegalovirus; la, language; Mh, MeSH term; nm, supplementary concept; pdat, publication date; pt, publication type; SLR, systematic literature review; ti, title;

### A.2.2 CENTRAL search strategy

**Table 98: CENTRAL search for clinical SLR, 5 July 2022**

| # | Query | Results |
|---|---|---|
| 1 | (transplant OR transplants OR transplantation OR graft OR grafts):ti,ab,kw | 55,894 |
| 2 | (organ OR solid OR lung OR heart OR pancreas OR kidney OR liver):ti,ab,kw | 349,913 |
| 3 | (hemopoetic OR haemopoetic OR hemopoietic OR haemopoietic OR hematopoietic OR haematopoietic OR allogeneic OR "stem cell"):ti,ab,kw | 18,196 |
| 4 | (#1 AND #2) OR (#1 AND #3) | 36,380 |
| 5 | [mh cytomegalovirus] | 332 |
| 6 | (CMV OR cytomegalovirus):ti,ab,kw | 3,151 |
| 7 | #5 OR #6 | 3,151 |
| 8 | (resistant OR refractory OR resistance):ti,ab,kw | 98,506 |
| 9 | #4 AND #7 AND #8 | 195 |
| 10 | [mh foscarnet] | 86 |
| 11 | [mh foscavir] | 86 |
| 12 | (foscarnet* OR Foscavir*):ti,ab,kw | 178 |
| 13 | #10 OR #11 OR #12 | 178 |
| 14 | [mh ganciclovir] | 406 |
| 15 | (ganciclovir OR Cytovene* OR Cymevene*):ti,ab,kw | 795 |
| 16 | #14 OR #15 | 810 |
| 17 | [mh valganciclovir] | 132 |
| 18 | (valganciclovir OR Cymeval* OR Valcyt* OR Valcyte* OR Valixa* OR Darilin* OR Rovalcyte*):ti,ab,kw | 390 |
| 19 | #17 OR #18 | 390 |
| 20 | (maribavir OR benzimidavir OR 1263w94 OR camvia OR "shp 620" OR shp620 OR shp-620 OR tak620 OR "tak 620" OR tak-620 OR vp41263 OR "gw 1263"):ti,ab,kw | 54 |
| 21 | [mh cidofovir] | 47 |
| 22 | (cidofovir OR brincidofovir OR Vistide*):ti,ab,kw | 155 |
| 23 | #21 OR #22 | 155 |
| 24 | #13 OR #16 OR #19 OR #20 OR #23 | 1163 |
| 25 | #9 AND #24 | 73 |



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| # | Query | Results |
|---|---|---|
| 26 | ("conference abstract" OR review):pt OR NCT*:au | 444.144 |
| 27 | (clinicaltrials.gov OR trialsearch OR meeting):so | 426,318 |
| 28 | abstract:ti | 7,917 |
| 29 | #26 OR #27 OR #28 | 641,252 |
| 30 | #25 NOT #29 with Cochrane Library publication date from Jan 2000 to Jul 2022, in Trials | 32 |

Abbreviations: ab, abstract; CMV, cytomegalovirus; la, language; kw, keyword; Mh, MeSH term; nm, supplementary concept; pdat, publication date; pt, publication type; ; SLR, systematic literature review; so, source; ti, title.

### A.2.3 Study selection criteria

The search strategy developed to meet the objective of the SLR was defined using the PICOs framework by the inclusion and exclusion criteria specified in Table 99.

**Table 99: Inclusion and exclusion criteria for the clinical systematic literature review**

| Category | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population (P)** | ▪ CMV infection/disease in SOT or HSCT recipients that are refractory or resistant to treatments<br>▪ Adolescents and Adults (≥12 years)<br>▪ Race: No restriction<br>▪ Gender: No restriction | ▪ SOT or HSCT recipients who received prophylactic treatment for CMV or patients with other infections or coinfections<br>▪ Studies evaluating children (<12 years) |
| **Interventions (I)** | ▪ Cidofovir<br>▪ Ganciclovir<br>▪ Foscarnet<br>▪ Maribavir<br>▪ Valganciclovir | ▪ Any other intervention other than the interventions provided in the inclusion list |
| **Comparator (C)** | ▪ Any therapy above | ▪ Any therapy other than the mentioned therapies |
| **Outcomes (O)** | ▪ No restrictions | n/a |
| **Study design** | ▪ RCTs<br>▪ Clinical trials (non-RCTs and single arm)<br>▪ Observational (prospective or retrospective) studies<br>▪ Systematic reviews and meta-analysis | ▪ Case studies and case series |
| **Timeframe** | ▪ January 2000 – July 2022 | ▪ Studies published prior to 2000 |



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| Category | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Language** | ▪ Articles in English<br>▪ Articles in Danish | ▪ Any other language than English, Danish |
| **Publication type** | ▪ Peer-reviewed published full-text articles | ▪ Case reports<br>▪ Letters, comments, editorials and news<br>▪ Preclinical trials and animal experiments<br>▪ Narrative (non-systematic) reviews<br>▪ Guidelines<br>▪ Conference abstracts |

Abbreviations: CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplant; n/a, not applicable; RCT, randomized controlled trial; SOT, solid organ transplant



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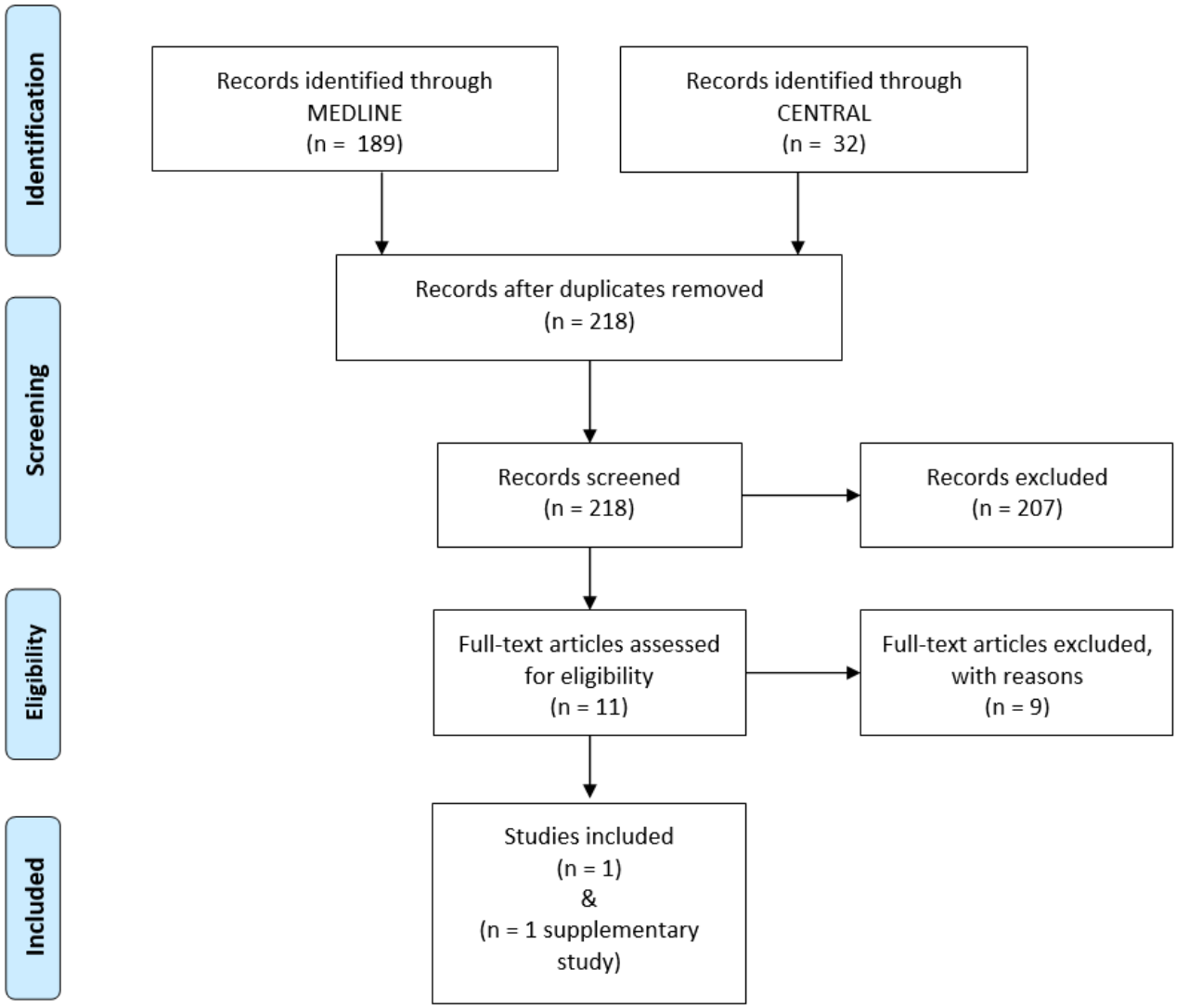
### A.2.4 Systematic selection of studies

**Figure 20: PRISMA flow diagram**




Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; MEDLINE, Medical Literature Analysis and Retrieval System Online

For a list of included studies and publications see Table 14 in Section 6.2.



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Table 100 shows a detailed list of excluded studies upon full-text screening.

**Table 100: Overview of studies excluded upon full-text screening**

| Full reference | Reason for exclusion |
|---|---|
| Drug-resistant cytomegalovirus in transplant recipients: a French cohort study. Hantz S, Garnier-Geoffroy F, Mazeron MC, Garrigue I, Merville P, Mengelle C, Rostaing L, Saint Marcoux F, Essig M, Rerolle JP, Cotin S, Germi R, Pillet S, Lebranchu Y, Turlure P, Alain S; French CMV Resistance Survey Study Group. *J Antimicrob Chemother*. 2010;65(12):2628-40. | No comparator and relevant endpoint(s) |
| Incidence and outcomes of ganciclovir-resistant cytomegalovirus infections in 1244 kidney transplant recipients. Myhre HA, Haug Dorenberg D, Kristiansen KI, Rollag H, Leivestad T, Asberg A, Hartmann A. *Transplantation*. 2011;92(2):217-23. | Study design not relevant for this application |
| Ganciclovir-resistant cytomegalovirus infections among lung transplant recipients are associated with poor outcomes despite treatment with foscarnet-containing regimens. Minces LR, Nguyen MH, Mitsani D, Shields RK, Kwak EJ, Silveira FP, Abdel-Massih R, Pilewski JM, Crespo MM, Bermudez C, Bhama JK, Toyoda Y, Clancy CJ. *Antimicrob Agents Chemother*. 2014;58(1):128-35. | No relevant endpoint(s) for this application |
| Maribavir use in practice for cytomegalovirus infection in French transplantation centers. Alain S, Revest M, Veyer D, Essig M, Rerolles JP, Rawlinson W, Mengelle C, Huynh A, Kamar N, Garrigue I, Kaminski H, Segard C, Presne C, Mazeron MC, Avettant-Fenoël V, Lecuit M, Lortholary O, Coaquette A, Hantz S, Leruez-Ville M, Ploy MC. *Transplant Proc*. 2013;45(4):1603-7. | Study design not relevant for this application |
| Outcomes in transplant recipients treated with foscarnet for ganciclovir-resistant or refractory cytomegalovirus infection. Avery RK, Arav-Boger R, Marr KA, Kraus E, Shoham S, Lees L, Trollinger B, Shah P, Ambinder R, Neofytos D, Ostrander D, Forman M, Valsamakis A. *Transplantation*. 2016;100(10):e74-80. | Study design not relevant for this application |
| Outcomes of transplant recipients treated with cidofovir for resistant or refractory cytomegalovirus infection. Mehta Steinke SA, Alfares M, Valsamakis A, Shoham S, Arav-Boger R, Lees L, Ostrander D, Forman MS, Shedeck A, Ambinder RF, Jones RJ, Avery RK. *Transpl Infect Dis*. 2021;23(3):e13521. | Study design not relevant for this application |
| Safety and efficacy of foscarnet for the management of ganciclovir-resistant or refractory cytomegalovirus infections: A single-center study. Pierce B, Richardson CL, Lacloche L, Allen A, Ison MG. *Transpl Infect Dis*. 2018;20(2):e12852. | Study design not relevant for this application |
| Use of cidofovir for cytomegalovirus disease refractory to ganciclovir in solid organ recipients. Bonatti H, Sifri CD, Larcher C, Schneeberger S, Kotton C, Geltner C. *Surg Infect (Larchmt)*. 2017;18(2):128-136. | Study design not relevant for this application |
| Oral maribavir for treatment of refractory or resistant cytomegalovirus infections in transplant recipients. Avery RK, Marty FM, Strasfeld L, Lee I, Arrieta A, Chou S, Tatarowicz W, Villano S. *Transpl Infect Dis*. 2010;12(6):489-96. | Study design not relevant for this application |

The studies listed in the table above have been excluded either due to study design incl. too few patients or have no specified endpoints. Moreover, some of the studies have been excluded as they are out of scope for this application.

### Quality assessment

The literature search has been performed and documented in accordance with the methodology recommended by the Danish Medicines Council. Quality assessment of the studies identified are provided in Table 101.



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**Table 101: Quality assessment of studies identified by SLR**

| Trial | SOLSTICE (TAK-620-303; NCT02931539) |
|---|---|
| Was randomization carried out appropriately? | Yes |
| Was the concealment of treatment allocation adequate? | Yes |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Yes |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | No |
| Were there any unexpected imbalances in dropouts between groups? | No |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | No |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Yes |

## Unpublished data

N/A



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# Appendix B Main characteristics of included studies

| Trial name: SOLSTICE (TAK-620-303) | NCT number: NCT02931539 |
|---|---|
| **Objective** | To evaluate the efficacy and safety of maribavir compared to IAT in SOT and HSCT recipients with CMV infections refractory or resistant (R/R) to ganciclovir, valganciclovir, foscarnet or cidofovir. |
| **Publications – title, author, journal, year** | Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial. Avery RK, Alain S, Alexander BD, Blumberg EA, Chemaly RF, Cordonnier C, Duarte RF, Florescu DF, Kamar N, Kumar D, Maertens J, Marty FM, Papanicolaou GA, Silveira FP, Witzke O, Wu J, Sundberg AK, Fournier M; SOLSTICE Trial Investigators. *Clin Infect Dis.* 2022;75:690-701<br><br>doi: 10.1093/cid/ciab988 |
| **Study type and design** | A randomized, open-label, active-controlled, multicenter, phase 3 trial. Eligible patients were randomized 2:1 to receive open-label maribavir (400 mg orally twice daily) or investigator-assigned therapy (IAT) (ganciclovir, valganciclovir, foscarnet, and/or cidofovir), as per the investigator's prescribed dosing for 8 weeks. Randomization was done through a centralized interactive response technology system and stratified by transplant type (SOT/HSCT) and CMV DNA level. The choice of specific IAT was at investigators' discretion and could include mono- or combination therapy (≤2 drugs) with any of the four approved IATs except combination therapy with cidofovir and foscarnet. For patients in the IAT group, changes to dose or dosing schedule of anti-CMV therapies were permitted, as well as discontinuation of one therapy, if combination therapy were originally selected. Addition of another anti-CMV therapy was not permitted and only switches between ganciclovir and valganciclovir were allowed. No change to dose or dosing schedule was allowed for patients in the maribavir group. A maribavir rescue arm was an option for patients originally assigned IAT after ≥3 weeks of treatment. After 3 weeks, patients in the IAT group could stop treatment (at the discretion of the investigator) for lack of confirmed viraemia clearance and/or intolerance to the assigned treatment, and enter into the rescue arm. Rescue treatment consisted of maribavir 400 mg BID for 8 weeks for patients in the IAT arm. Reduction or modifying of immunosuppressant drug use was permitted.<br><br>The treatment phase was followed by 12 weeks of follow-up, in which patients were off study-assigned therapy. Patients were evaluated weekly until week 12, then every 2 weeks through to week 20. |
| **Sample size (n)** | N = 352 randomized patients; n = 235 assigned maribavir, n = 117 assigned IAT |



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**Main inclusion and exclusion criteria**

**Main inclusion criteria:**

- Recipients of HSCT or SOT aged ≥12 years at the time of consent
- Recipients must weight ≥ 35 kg
- Documented CMV infection in whole blood or plasma, with a screening value of ≥2,730 IU/mL in whole blood or ≥910 IU/mL in plasma in two consecutive assessments separated by at least 1 day. Both samples should be taken within 14 days prior to randomization with second sample obtained within 5 days prior to randomization. The same laboratory and same sample type (whole blood or plasma) must be used for these assessments.
- Current CMV infection that is refractory to the most recently administered of the four anti-CMV treatment agents (defined as documented failure to achieve >1 $\log_{10}$ decrease in CMV DNA level in whole blood or plasma after a 14-day or longer treatment period with IV ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir.
- Screening laboratory assessments (results from either the central laboratory or a local laboratory):
    - Absolute neutrophil count (ANC) ≥1,000/$mm^3$ (1.0 × $10^9$/L)
    - Platelet count ≥25,000/$mm^3$ (25 × $10^9$/L)
    - Haemoglobin ≥8 g/dL
    - Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 $m^2$
- Negative serum β-human chorionic gonadotropin pregnancy test at screening, if a female childbearing potential. Sexually active females of child bearing potential must agree to comply with any applicable contraceptive requirements of the protocol. If male, must agree to use an acceptable method of birth control, as defined in the protocol, during the study treatment administration period and for 90 days afterward if treated with maribavir, ganciclovir, valganciclovir, or cidofovir and for 180 days afterward if treated with foscarnet.
- Patients who can swallow tablets, or receive tablets crushed and/or dispensed in water via nasogastric or orogastric tube.
- Patients who is willing and have an understanding and ability to fully comply with study procedures and restrictions defined in the protocol.
- Patients who is willing to provide necessary samples (e.g., biopsy) for the diagnosis of tissue invasive CMV disease at baseline as determined by the Investigator.
- Life expectancy of ≥8 weeks.

**Main exclusion criteria:**

- Current CMV infection considered R/R due to inadequate adherence to prior anti-CMV treatment (to the best knowledge of the Investigator)
- Require ganciclovir, valganciclovir, foscarnet, or cidofovir administration for conditions other than CMV when study treatment is initiated or would need a coadministration with maribavir for CMV infection. A patient who is not continuing with the same antiviral drug(s) (ganciclovir, valganciclovir, or foscarnet) for the study treatment (if randomized to the IAT arm), must discontinue their use before the first dose of study drug. If the patient is currently being treated with cidofovir and is assigned by the investigator to another anti-CMV therapy as IAT, the patient must discontinue its use of cidofovir at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment
- Receiving leflunomide, letermovir, or artesunate when study treatment is initiated (leflunomide must discontinue ≥14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment; letermovir must discontinue ≥3 days prior to the first dose of study treatment; artesunate must discontinue prior to the first dose of study treatment)



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| Trial name: SOLSTICE (TAK-620-303) | NCT number: NCT02931539 |
|---|---|

- Have severe vomiting, diarrhea, or other severe gastrointestinal illness within 24 hours prior to the first dose of study treatment that would preclude administration of oral/enteral medication.
- Known hypersensitivity to the active substance or to an excipient for a study treatment.
- Tissue invasive CMV disease with central nervous system involvement including the retina (example, CMV retinitis).
- Serum aspartate aminotransferase (AST) > 5 times upper limit of normal (ULN) at screening, or serum alanine aminotransferase (ALT) > 5 times ULN at screening, or total bilirubin >= 3.0 x ULN at screening (except for documented Gilbert's syndrome), by local or central lab. Participants with biopsy confirmed CMV hepatitis will not be excluded from study participation despite AST or ALT > 5 times ULN at screening.
- Known positive results for human immunodeficiency virus (HIV). Participants must have a confirmed negative HIV test result within 3 months of study entry or, if unavailable, be tested by a local laboratory during the screening period.
- Require mechanical ventilation or vasopressors for hemodynamic support at the time of enrollment.
- Pregnant or breast feeding.
- Previously received maribavir.
- Received any investigational agent with known anti-CMV activity within 30 days before initiation of study treatment or investigational CMV vaccine at any time.
- Received any unapproved agent or device within 30 days before initiation of study treatment.
- Active malignancy with the exception of nonmelanoma skin cancer. Participants who have had a HSCT and who experience relapse or progression of the malignancy as per investigator's opinion are not to be enrolled.
- Undergoing treatment for acute or chronic hepatitis C.
- Any clinically significant medical or surgical condition that, in the investigator's opinion, could interfere with the interpretation of study results, contraindicate the administration of the assigned study treatment, or compromise the safety or well-being of the participant.

| | |
|---|---|
| **Intervention** | Maribavir 400 mg (2 × 200 mg oral tablets) twice daily for 8 weeks (n = 235) |
| **Comparator(s)** | IAT (ganciclovir [IV], valganciclovir [oral], foscarnet [IV], or cidofovir [IV]) (n = 117) |
| **Follow-up time** | 12 weeks |
| **Is the study used in the health economic model?** | Yes |



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**Primary, secondary and exploratory endpoints**

A list of the primary, secondary, exploratory and safety endpoints are listed below. Endpoints highlighted in bold are reported in this application and/or included within the economic model.

**Primary endpoint:**

- **Confirmed CMV viraemia clearance at the end of study week 8**

**Key secondary endpoint:**

- **Confirmed CMV viraemia clearance and CMV infection symptom control at the end of study week 8 with the benefit maintained through study week 16**

**Additional secondary endpoints:**

- Achievement of confirmed CMV viraemia clearance after 8 weeks of receiving study-assigned treatment
- Achievement of confirmed CMV viraemia clearance and CMV infection symptom control after 8 weeks of receiving study-assigned treatment
- The maintenance of the CMV viraemia clearance and CMV infection symptom control achieved at the end of study week 8 through weeks 12 and 20
- **Recurrence of CMV viraemia**
- Recurrence of CMV viraemia during and off study-assigned treatment
- Maribavir resistance profile
- **All-cause mortality**
- Endpoints assessed for maribavir rescue treatment:
    - Confirmed clearance of plasma CMV DNA at the end of 8 weeks of maribavir rescue treatment phase
    - Achievement of viraemia clearance and CMV infection symptom control for maribavir rescue treatment

**Exploratory endpoints:**

- CMV viral load change over time
- Time to first CMV viraemia clearance
- Time from first CMV viraemia clearance to CMV viraemia recurrence
- **Graft outcomes (rejection or graft loss)**
- Specific T-cell response over time

**Safety endpoints:**

- Extent of exposure and compliance
- Prior and concomitant medications
- **AEs**
- AE of special interest
- AE by medical concept
- Clinical laboratory variables
- Vital signs
- Electrocardiogram
- Treatment with hemopoietic growth factors, blood, and blood product transfusions



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| Trial name: SOLSTICE (TAK-620-303) | NCT number: NCT02931539 |
|---|---|

**Method of analysis**

The intention-to-treat (ITT) population was the primary population for all efficacy parameters. For both the primary and key secondary endpoints, the difference in proportion of responders between treatment groups were obtained using Cochran-Mantel-Haenszel (CMH) weighted average across all strata, and tested using CMH method, with transplant type (SOT, HSCT) and baseline plasma CMV DNA concentration (low, <9100 IU/mL; intermediate/high, ≥9100 IU/mL) as two stratification factors. All statistical tests and CIs were 2-sided at $\alpha$=0.05 and the 95% confidence limits of the weighted average of difference across strata were provided using the normal approximation. Hypothesis testing of the primary and key secondary endpoint was adjusted for multiple comparisons using a fixed sequence testing procedure to control the family-wise Type 1 error rate at a 5% level. Only after the primary efficacy endpoint was deemed statistically significant, the key secondary endpoint was assessed at $\alpha$=0.05 (2-sided). The phrase 'statistically significant' is applied only to analyses of the primary and key secondary efficacy endpoints with adjustment for multiplicity. If indicated, the other secondary endpoints and exploratory endpoints were analyzed statistically at $\alpha$=0.05 (2-sided), without adjustment for multiple comparisons. Safety data were analyzed descriptively in all patients who received a dose of study drug (safety population).

Sensitivity analyses of the primary endpoint were conducted using similar methods to those described for the primary endpoint, but without adjustment for multiple comparisons. Efficacy in the rescue arm was conducted in the rescue population (all patients who entered the rescue arm and received any dose of maribavir as rescue therapy). Time-to-event endpoints were summarized using Kaplan–Meier estimation.

**Subgroup analyses**

Subgroup analyses were performed for the primary efficacy endpoint for the following prespecified subgroups and summarized in a forest plot:

- Transplant type (SOT, HSCT)
- CMV DNA viral load (low, intermediate/high)
- Symptom CMV infection at baseline as adjudicated by Endpoint Adjudication Committee (EAC)
- Presence of CMV mutation resistant to ganciclovir, foscarnet, and/or cidofovir per central laboratory results (yes, no)
- Age group
  - ≥18 to <45 years of age
  - ≥45 to <65 years of age
  - ≥65 years of age
- Enrolling region (North America, Europe, Asia)
- Sex (male, female)
- Prior antilymphocyte use (yes, no)
- Maribavir vs. individual IAT type (if sample size was adequate)

**Other relevant information** None

Abbreviations: AE, adverse event; ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CMH, Cochran-Mantel-Haenszel; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; EAC, endpoint adjudication committee; eGFR, estimated glomerular filtration rate; HSCT, hematopoietic stem cell transplant; IAT, investigator assigned treatment; ITT, intention-to-treat; IU, international unit; IV, intravenous; R/R, refractory and/or resistant; SOT, solid organ transplant; ULN, upper limit of normal

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

**Table 102: Baseline demographics and characteristics of patients included in the SOLSTICE trial in the ITT population.**

| Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety | | |
|---|---|---|
| | SOLSTICE (TAK-620-303) | |
| | Maribavir (n = 235) | IAT (n = 117) |
| **Age, years** | | |
| Median (range) | 57.0 (19-79) | 54.0 (19-77) |
| **Male sex, n (%)** | 148 (63.0) | 65 (55.6) |
| **Race, n (%)** | | |
| White | 179 (76.2) | 87 (74.4) |
| Black or African American | 29 (12.3) | 18 (15.4) |
| Asian | 9 (3.8) | 7 (6.0) |
| Other | 16 (6.8) | 5 (4.3) |
| Missing | 2 (0.9) | 0 |
| **Region, n (%)** | | |
| North America | 134 (57.0) | 71 (60.7) |
| Europe | 97 (41.3) | 39 (33.3) |
| Asia | 4 (1.7) | 7 (6.0) |
| **SOT, n (%)** | 142 (60.4) | 69 (59.0) |
| Kidney | 74 (52.1) | 32 (46.4) |
| Lung | 40 (28.2) | 22 (31.9) |
| Heart | 14 (9.9) | 9 (13.0) |
| Multiple | 5 (3.5) | 5 (7.2) |
| Liver | 6 (4.2) | 1 (1.4) |
| Pancreas | 2 (1.4) | 0 |
| Intestine | 1 (0.7) | 0 |



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| | | |
|---|---|---|
| **HSCT, n (%)** | 93 (39.6) | 48 (41.0) |
| **Allogeneic** | 92 (98.9) | 48 (100.0) |
| **Donor type** | | |
| HLA identical sibling | 13 (14.1) | 2 (4.2) |
| HLA matched other relative | 12 (13.0) | 10 (20.8) |
| HLA mismatched relative | 11 (12.0) | 7 (14.6) |
| Unrelated donor | 56 (60.9) | 29 (60.4) |
| **Stem cell source** | | |
| Peripheral blood stem cell | 71 (77.2) | 30 (62.5) |
| Bone marrow | 16 (17.4) | 13 (27.1) |
| Cord blood | 5 (5.4) | 5 (10.4) |
| Presence of acute GvHD confirmed for HSCT recipients | 23 (25.0) | 8 (17.0) |
| Presence of chronic GvHD confirmed for HSCT recipients | 6 (6.5) | 5 (10.6) |
| **CMV DNA levels by central laboratory at baseline, IU/mL** | | |
| Median (IQR) | 3377.0 (1036–12,544) | 2869.0 (927–11,636) |
| **CMV DNA levels category as reported by central laboratory at baseline, n (%)** | | |
| Low (<9100 IU/mL) | 153 (65.1) | 85 (72.6) |
| Intermediate (≥9100 and <91 000 IU/mL) | 68 (28.9) | 25 (21.4) |
| High (≥91 000 IU/mL) | 14 (6.0) | 7 (6.0) |
| **Symptomatic CMV infection by Endpoint Adjudication Committee, n (%)** | 21 (8.9) | 8 (6.8) |
| CMV syndrome in SOT recipients | 10 (47.6) | 7 (87.5) |
| CMV disease | 12 (57.1) | 1 (12.5) |
| **CMV serostatus for SOT recipients, n (%)** | n = 142 | n = 69 |
| Donor +/recipient + | 11 (7.7) | 8 (11.6) |
| Donor −/recipient + | 3 (2.1) | 1 (1.4) |
| Donor +/recipient − | 120 (84.5) | 56 (81.2) |
| Donor −/recipient − | 7 (4.9) | 3 (4.3) |



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| | | |
|---|---|---|
| Missing | 1 (0.7) | 1 (1.4) |
| **CMV serostatus for HSCT recipients, n (%)** | n = 93 | n = 48 |
| Donor +/recipient + | 42 (45.2) | 17 (35.4) |
| Donor −/recipient + | 39 (41.9) | 26 (54.2) |
| Donor +/recipient − | 6 (6.5) | 3 (6.3) |
| Donor −/recipient − | 5 (5.4) | 1 (2.1) |
| Missing | 1 (1.1) | 1 (2.1) |
| **Patients with or without CMV mutations known to confer resistance to ganciclovir, foscarnet, and/or cidofovir, n (%)** | | |
| Refractory CMV infection with resistance | 121 (51.5) | 69 (59.0) |
| Refractory CMV infection without resistance | 96 (40.9) | 34 (29.1) |
| Missing resistance results | 18 (7.7) | 14 (12.0) |
| **Prior use of CMV prophylaxis, n (%)** | 100 (42.6) | 45 (38.5) |
| **Current CMV infection is the first episode post-transplant, n (%)** | 162 (68.9) | 78 (66.7) |
| **Most recent anti-CMV agent prior to randomization, n (%)** | | |
| Ganciclovir/Valganciclovir | 204 (86.8) | 98 (83.8) |
| Foscarnet | 27 (11.5) | 18 (15.4) |
| Cidofovir | 4 (1.7) | 1 (0.9) |
| **Prior direct-acting anti-CMV agents at any time, n (%)** | n = 234 | n = 116 |
| Valganciclovir | 178 (76.1) | 96 (82.8) |
| Ganciclovir | 147 (62.8) | 82 (70.7) |
| Foscarnet | 49 (20.9) | 37 (31.9) |
| Cidofovir | 7 (3.0) | 5 (4.3) |

Abbreviations: CMV, cytomegalovirus; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; HLA, human leukocyte antigen; IAT, investigator-assigned therapy; IQR, interquartile range; IU, international unit; LLOQ, lower limit of quantification; SOT, solid organ transplant.
Ref. (2) and supplementary documentation



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**Table 103: Baseline demographics and characteristics by treatment group and transplant type.**

| | HSCT | | | SOT | | |
|---|---|---|---|---|---|---|
| | Maribavir (n=93) | IAT (n=48) | Total (n=141) | Maribavir (n=93) | IAT (n=48) | Total (n=141) |
| **Age (years)** | | | | | | |
| Mean (SD) | | | | | | |
| **Age category (years), n (%)** | | | | | | |
| 12-17 | | | | | | |
| 18-44 | | | | | | |
| 45-64 | | | | | | |
| ≥65 | | | | | | |
| **Sex, n (%)** | | | | | | |
| Male | | | | | | |
| Female | | | | | | |
| **Ethnicity, n (%)** | | | | | | |
| Hispanic or Latino | | | | | | |
| Not Hispanic or Latino | | | | | | |
| Not reported | | | | | | |
| Unknown | | | | | | |
| **Race, n (%)** | | | | | | |
| White | | | | | | |
| Black or African American | | | | | | |
| Asian | | | | | | |
| Other | | | | | | |
| Missing | | | | | | |
| **Enrolling regions, n (%)** | | | | | | |
| North America | | | | | | |
| Europe | | | | | | |



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| | HSCT | | | SOT | | |
|---|---|---|---|---|---|---|
| | Maribavir (n=93) | IAT (n=48) | Total (n=141) | Maribavir (n=93) | IAT (n=48) | Total (n=141) |
| Asia | | | | | | |
| **Current transplant type** | | | | | | |
| **SOT, n (%)** | | | | | | |
| Heart | | | | | | |
| Lung | | | | | | |
| Liver | | | | | | |
| Pancreas | | | | | | |
| Intestine | | | | | | |
| Kidney | | | | | | |
| Multiple | | | | | | |
| **HSCT, n (%)** | | | | | | |
| Autologous | | | | | | |
| Allogeneic | | | | | | |
| **Underlying disease, n (%)** | | | | | | |
| Leukaemia (acute myeloid) | | | | | | |
| Leukaemia (chronic myeloid) | | | | | | |
| Leukaemia (acute lymphocytic) | | | | | | |
| Lymphoma (non-Hodgkin's) | | | | | | |
| Myelodysplastic syndrome | | | | | | |
| Other myeloid malignancy | | | | | | |
| Other | | | | | | |
| **Current graft status at baseline** | | | | | | |
| **SOT, n (%)** | | | | | | |
| Functioning with complications | | | | | | |
| Functioning | | | | | | |



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| | HSCT | | | SOT | | |
|---|---|---|---|---|---|---|
| | Maribavir (n=93) | IAT (n=48) | Total (n=141) | Maribavir (n=93) | IAT (n=48) | Total (n=141) |
| Other | | | | | | |
| **HSCT, n (%)** | | | | | | |
| Partially engrafted | | | | | | |
| Functioning with complications | | | | | | |
| Functioning | | | | | | |
| **Acute GvHD confirmed, n (%)** | | | | | | |
| No | | | | | | |
| Yes | | | | | | |
| **Chronic GvHD confirmed, n (%)** | | | | | | |
| No | | | | | | |
| Yes | | | | | | |
| **Type of preparative conditioning regimen, n (%)** | | | | | | |
| Myeloablative | | | | | | |
| Non-myeloablative | | | | | | |
| Reduced intensity conditioning regimen | | | | | | |
| NA | | | | | | |
| Missing | | | | | | |
| **Net immunosuppression use changed prior to the study, n (%)** | | | | | | |
| No | | | | | | |
| Yes | | | | | | |
| Missing | | | | | | |
| **Antilymphocyte use, n (%)** | | | | | | |
| No | | | | | | |



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| | HSCT | | | SOT | | |
|---|---|---|---|---|---|---|
| | Maribavir (n=93) | IAT (n=48) | Total (n=141) | Maribavir (n=93) | IAT (n=48) | Total (n=141) |
| Yes | | | | | | |
| **Renal impairment, n (%)** | | | | | | |
| No impairment | | | | | | |
| Mild | | | | | | |
| Moderate | | | | | | |
| Severe | | | | | | |
| Missing | | | | | | |
| **Hepatic impairment, n (%)** | | | | | | |
| No impairment | | | | | | |
| Grade 1 | | | | | | |
| Grade 2 | | | | | | |
| Missing | | | | | | |

Abbreviations: CMV, cytomegalovirus; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; IAT, investigator-assigned therapy; SOT, solid organ transplant.
Ref. (23)

### Comparability of patients across studies

Not applicable as only the SOLSTICE (TAK-620-303) study is relevant and included in the assessment.

### Comparability of the study populations with Danish patients eligible for treatment

SOLSTICE was conducted with an open-label design (2), principally because of the need for the physician to individualize drug selection for treatment-refractory patients in the IAT arm, choosing the appropriate therapy based on clinical data and judgment, institutional guidelines, and published guidance documents. Furthermore, genetic testing for antiviral resistance in SOLSTICE may have resulted in the identification of the most appropriate treatment for patients in the IAT arm. Therefore, the maribavir results may be conservative given that genetic testing is not part of routine Danish practice for the management of CMV infection as stated in section 5. For patients in the IAT arm, the protocol allowed investigators flexibility to choose a combination of two antiviral drugs, to cycle between oral valganciclovir and IV ganciclovir during the study, and to modify dose as necessary. This was specifically to limit the impact of toxicity on the ability of the patients to complete therapy due to the well characterized toxicities associated with the anti-CMV agents used as IAT.

The comparability of the study population of the SOLSTICE 303 trial has been discussed with the Danish experts at the advisory board held in Denmark and has been confirmed to be transferable to the Danish population. Please see section 5 and 10 for additional information.

# Appendix D Efficacy and safety results per study

## Definition, validity and clinical relevance of included outcome measures

**Table 104: Outcome measures**

| Outcome measure | Definition | Validity | Clinical relevance |
|---|---|---|---|
| **Confirmed CMV viraemia clearance at the end of study week 8** | Defined as plasma CMV DNA concentrations <LLOQ (i.e., <137 IU/mL) at the end of study week 8, when assessed by central specialty laboratory, in two consecutive post-baseline samples separated by at least 5 days.<br><br>Subjects who received alternative or rescue anti-CMV treatment by study week 8 were considered as non-responders. | The choice of the primary endpoint is supported by the accumulated clinical literature, which confirms the premise that CMV viremia predicts development of CMV disease in transplant recipients (75–77) | CMV viraemia is predictive of CMV disease and mortality in transplant recipients and suppression or clearance of CMV viraemia is associated with clinical resolution of CMV infection/disease as well as improved patient outcomes. |
| **Confirmed CMV viraemia clearance and CMV infection symptom control at week 8 with the benefit maintained through week 16** | Patients were required to meet the following criteria:<br><br>• Primary endpoint responder (i.e., CMV viraemia clearance at end of study week 8)<br><br>• CMV infection symptom control at week 8 (for patients who were symptomatic at baseline) or no new symptoms of tissue invasive disease or CMV syndrome at week 8 (for patients who were asymptomatic at baseline)<br><br>• Maintenance of CMV viraemia clearance and CMV infection symptom control through week 16, where maintenance of CMV viraemia clearance through week 16 is determined by the absence of two consecutive positive CMV DNA viral load assessments through week 16 | The choice of the primary endpoint is supported by the accumulated clinical literature, which confirms the premise that CMV viremia predicts development of CMV disease in transplant recipients (30,75–78). Therefore, use of viremia clearance is considered a validated surrogate endpoint for use in clinical trials investigating the treatment of CMV.<br><br>Observations of off-treatment effect and symptom control are clinically valid assessments of durability of CMV infection/disease control. | CMV viraemia is predictive of CMV disease and mortality in transplant recipients and suppression or clearance of CMV viraemia is associated with clinical resolution of CMV infection/disease as well as improved patient outcomes. |

| Outcome measure | Definition | Validity | Clinical relevance |
|---|---|---|---|
| | Subjects were NOT required to complete the stipulated 8 weeks of study-assigned treatment; however, subjects who initiated alternative (non-study) anti-CMV treatment or maribavir rescue therapy before week 16 were non-responders. | | |
| **Recurrence of CMV viraemia** | Defined as plasma CMV DNA concentrations ≥LLOQ, when assessed by central specialty laboratory, in 2 consecutive plasma samples separated by at least 5 days after achieving confirmed viraemia clearance.<br><br>All CMV DNA measurements after achieving confirmed CMV viremia clearance regardless of rescue or alternative treatment were included in the assessment. | Because CMV—like all herpes viruses—is a latent virus, recurrence is inevitable unless the host immune system +/- effective antiviral therapy is able to suppress viral replication. Since low level viral loads may fluctuate near LLOQ it may not be considered clinically relevant. | CMV viraemia is predictive of CMV disease and mortality in transplant recipients. Minimizing the occurrence of recurrence of CMV viraemia is associated with clinical resolution of CMV infection/disease as well as improved patient outcomes. |
| **Clinically relevant recurrence of CMV viraemia** | Recurrence of CMV infection that required anti-CMV treatment initiation.<br><br>Recurrence was evaluated in patients with CMV viremia clearance at Week 8 (ie, who fulfilled the requirement for the primary efficacy endpoint) and who received alternative treatment after Week 8. | Because CMV—like all herpes viruses—is a latent virus, recurrence is inevitable unless the host immune system +/- effective antiviral therapy is able to suppress viral replication. Since low level viral loads may fluctuate near LLOQ it may not be considered clinically relevant. | CMV viraemia is predictive of CMV disease and mortality in transplant recipients. Minimizing the occurrence of clinically relevant recurrence of CMV viraemia is associated with clinical resolution of CMV infection/disease as well as improved patient outcomes. |
| **All-cause mortality** | Evaluated as time to event<br><br>Included ALL deaths reported on study regardless of receipt of alternative anti-CMV treatment or maribavir rescue therapy. | All-cause mortality assesses a hard clinical endpoint commonly utilized in clinical trials, in addition to assessment of relatedness of these events to the treatment received. | Minimizing all-cause mortality is an aim of treatment and is a generally utilized efficacy outcomes. |



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| Outcome measure | Definition | Validity | Clinical relevance |
|---|---|---|---|
| **Graft outcomes** | Graft outcomes were evaluated for all randomized patients. | Assessment of graft outcomes are a hard clinical endpoint commonly utilized in post-transplant clinical trials, in addition to assessment of relatedness of these events to the treatment received. | Minimizing poor graft outcomes is an aim of treatment post-transplant and is a generally utilized efficacy outcomes. |
| **HRQoL** | Assessed by both EQ-5D-5L and SF-36v2 questionnaires.<br><br>Responses to the questionnaires were collected on study (ITT population) after receiving study-assigned treatment, but before initiation of alternative anti-CMV treatment or maribavir rescue therapy. The HRQoL responses after receiving rescue therapy were summarized separately as well as the reason for not completing the questionnaires. Baseline was defined as the last response on or before the first dose date of study-assigned treatment for evaluations and the last response on or before the first dose of maribavir rescue therapy for evaluations using the rescue set.<br><br>Missing data were handled in accordance with the instrument developer's recommendation (79,80). | EQ-5D-5L and SF-36v2 questionnaires are standardized validated instruments for measuring generic health status and related QoL. | Assessing HRQoL is a requirement of many HTA bodies including DMC and is being used to measure utilities in the economic model. |
| **Hospitalization*** | Data on hospital admissions were collected at each study visit and analyzed by treatment during the treatment and follow-up phases. Analyses included the number of pts with ≥1 hospitalization and length of hospital stay (LOS). Hospitalization rates and LOS (per person/year) were estimated using negative binomial models adjusting for exposure time.<br><br>Analyses describing hospitalizations and LOS for the rescue arm and individual IAT groups were conducted separately. | The collection of hospitalization data has been based on simple observations as described in the definition section. | Reducing hospitalizations is critical for alleviating disease burden to healthcare systems. |



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| Outcome measure | Definition | Validity | Clinical relevance |
|---|---|---|---|
| AEs | The primary analysis of safety was based on the "treatment-emergent" principle. An AE that had a start date on or after the first dose of study-assigned treatment or that had a start date before the date of first dose of study-assigned treatment but increased in severity after the first dose of study-assigned treatment was considered a treatment-emergent AE (TEAE) for the observation period. Any AE that occurred from the time of informed consent form signature to date of first dose was listed as a pretreatment AE and was not evaluated in the safety analyses. If an AE onset date was incomplete, an imputation algorithm was used to classify the AE as pretreatment or treatment emergent.<br><br>The on-treatment observation period starts at the date of study treatment initiation through 7 days after the last dose of study treatment, or through 21 days after the last dose of cidofovir (if cidofovir is the IAT). Safety analyses for the maribavir rescue arm were analyzed separately using the Rescue Set. | Use of AEs reporting as measures of drug safety has been accepted as reliable and valid endpoint measures. AE reporting is standard in clinical trials. TEAEs and their relatedness, have been accepted as reliable and valid endpoint measures, monitoring, and assessment of these are commonly conducted in clinical trials. | Safety assessments are clinically relevant to understand the overall AE profile of a treatment.<br><br>Assessment of treatment limiting toxicities such as myelosuppression and nephrotoxicity are clinically relevant, as they can lead to premature treatment discontinuation leading to treatment failure and potentially poor patient outcomes. |

Abbreviations: AE, adverse event; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; EAC, endpoint adjudication committee; IAT, investigator-assigned treatment; IU, international unit; LLOQ, lower limit of quantification

* included by request of the DMC

## Results per study

**Table 105: Results of included outcome measures from the SOLSTICE trial**

| | | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome | Study arm | N total | n event | Result % (CI) | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| Confirmed CMV viraemia clearance at week 8 | maribavir | 235 | 131 | 55.7 (49.4–62.1) | 32.8 | 22.8–42.7 | <0.001 | OR: 4.00 | 2.44–6.58 | <0.001 | See table footnote* | Avery RK et al 2022 & SOLSTICE CSR |
| | IAT | 117 | 28 | 23.9 (16.2–31.7) | | | | | | | | |
| Confirmed CMV viraemia clearance and CMV infection symptom control at week 8 with the benefit maintained through week 16 | maribavir | 235 | 44 | 18.7 (13.7–23.7) | 9.5 | 2.0–16.9 | 0.013 | OR: 2.02 | 1.02–3.98 | 0.045 | See table footnote* | Avery RK et al 2022 & SOLSTICE CSR |
| | IAT | 117 | 12 | 10.3 (4.8–15.8) | | | | | | | | |
| Clinically relevant recurrence of CMV viremia after achieving clearance at week 8 | maribavir | 131 | 34 | 26.0 (18.4–33.5) | - 9.7 | -29.0 to 9.5 | 0.295 | OR: 0.63 | 0.27–1.50 | 0.352 | See table footnote† | Avery RK et al 2022 & SOLSTICE CSR |
| | IAT | 28 | 10 | 35.7 (18.0–53.5) | | | | | | | | |



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| | | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Outcome** | **Study arm** | **N total** | **n event** | **Result % (CI)** | **Difference** | **95% CI** | ***P* value** | **Difference** | **95% CI** | ***P* value** | | |
| All-cause mortality (in days) | [redacted] | | | | | | | | | | | Avery RK et al 2022 & SOLSTICE CSR |
| Graft loss | maribavir | 235 | 1 | 0.4 (0.01–2.3) | 0.4 | -0.4 to 1.26 | 0.480 | - | - | - | See table footnote† | Avery RK et al 2022 & SOLSTICE CSR |
| | IAT | 117 | 0 | 0 (0–0.03) | | | | | | | | |
| Acute graft rejection | [redacted] | | | | | | | | | | | Avery RK et al 2022 & SOLSTICE CSR |
| Chronic graft rejection | [redacted] | | | | | | | | | | | Avery RK et al 2022 & SOLSTICE CSR |



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| | | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome | Study arm | N total | n event | Result % (CI) | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| EQ-5D-5L Single Index Utility Score | [redacted] | | | | | | | | | | | SOLSTICE CSR |

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; CSR, clinical study report; HR, Hazard ratio; HSCT, hematopoietic stem cell transplant; IAT, investigator-assigned therapy; NA, not applicable; NR, not reached; OR, Odds ratio; SOT, solid organ transplant.

*Cochran-Mantel-Haenszel (CMH) weighted average approach is used for the adjusted difference in proportion, the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration. Odds ratio obtained by Unconditional MLE & 95% CI obtained by normal approximation and p-value is obtained from Fisher's exact test.

**Absolute difference and the corresponding 95% CI is computed by the normal approximation method and p-value obtained from the CI for an estimate of effect

†Unadjusted difference in proportion and the corresponding 95% CI is computed by the normal approximation method and p-value obtained from two-sample test for proportion. Odds ratio obtained by Unconditional MLE & 95% CI obtained by normal approximation and p-value is obtained from Fisher's exact test.

ǂThe median survival is based on the Kaplan–Meier estimator and the p-value is obtained by log-rank test. The HR and corresponding p-value is based on a Cox proportional hazards model with adjustment for stratification, and study arm

Ref. (2,23)



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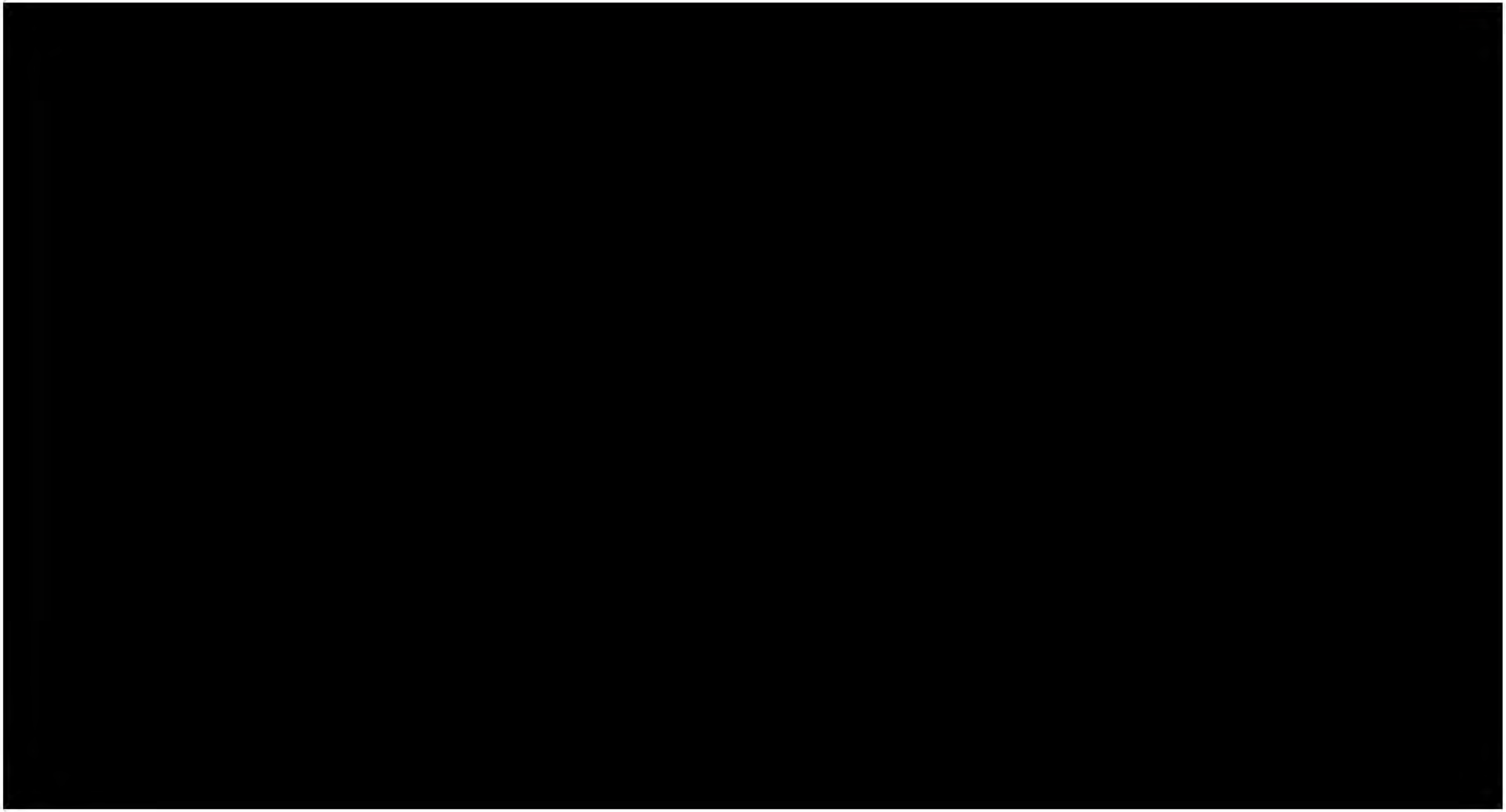



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*Cochran-Mantel-Haenszel (CMH) weighted average approach is used for the adjusted difference in proportion, the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration. Odds ratio obtained by Unconditional MLE & 95% CI obtained by normal approximation and p-value is obtained from Fisher's exact test.

**Unadjusted difference in proportion and the corresponding 95% CI is computed by the normal approximation method and p-value obtained from two-sample test for proportion. Odds ratio obtained by Unconditional MLE & 95% CI obtained by normal approximation and p-value is obtained from Fisher's exact test.

#The median survival is based on the Kaplan–Meier estimator and the p-value is obtained by log-rank test. The HR and corresponding p-value is based on a Cox proportional hazards model with adjustment for stratification, and study arm

Additional reported sensitivity analyses on CMV viraemia clearance analysis were also consistent with the primary analysis (Table 107).

**Table 107: Additional sensitivity analyses on CMV viraemia clearance (ITT population)**

| CMV viraemia clearance at end of week 8 (response) | Maribavir (n = 235) | IAT (n = 117) | Adjusted difference in proportion of responders (95% CIs) |
|---|---|---|---|
| **Based on stratification used at randomization** | | | |
| Patients with response, n (%) | 131 (55.7) | 28 (23.9) | 31.8 (21.9–41.8) |
| **Patients who received 8 weeks of study-assigned treatment** | n = 183 | n = 37 | |
| Patients with response, n (%) | 129 (70.5) | 22 (59.5) | 10.2 (–7.0 to 27.4) |
| **Patients on treatment 72 hours after treatment initiation** | n = 233 | n = 116 | |
| Patients with response, n (%) | 131 (56.2) | 28 (24.1) | 33.1 (23.1–43.1) |
| **Patients on treatment 7 days after treatment initiation** | n = 232 | n = 113 | |



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| CMV viraemia clearance at end of week 8 (response) | Maribavir (n = 235) | IAT (n = 117) | Adjusted difference in proportion of responders (95% CIs) |
|---|---|---|---|
| Patients with response, n (%) | 131 (56.5) | 28 (24.8) | 32.6 (22.5–42.8) |
| **Patients on treatment 14 days after treatment initiation** | n = 224 | n = 98 | |
| Patients with response, n (%) | 131 (58.5) | 28 (28.6) | 30.8 (19.9–41.8) |
| **Patients on treatment 21 days after treatment initiation** | n = 217 | n = 80 | |
| Patients with response, n (%) | 131 (60.4) | 27 (33.8) | 27.5 (15.3–39.8) |
| **Patients on treatment 28 days after treatment initiation** | n = 214 | n = 65 | |
| Patients with response, n (%) | 131 (61.2) | 25 (38.5) | 23.4 (9.9–36.9) |
| **Randomized patients with baseline CMV DNA >LLOQ per the central laboratory** | n = 225 | n = 109 | |
| Patients with response, n (%) | 124 (55.1) | 27 (24.8) | 31.2 (20.9–41.5) |
| **Randomized patients with baseline CMV DNA ≥910 IU/mL per the central laboratory** | n = 182 | n = 88 | |
| Patients with response, n (%) | 94 (51.6) | 22 (25.0) | 27.4 (15.9–39.0) |

Abbreviations: CI, confidence interval; CM, cytomegalovirus; DNA, deoxyribonucleic acid; IAT, investigator-assigned treatment; ITT, intention-to-treat;

IU, international unit; mL, millilitres; n, number of patients
Adjusted for transplant type and baseline plasma CMV DNA concentration.
Ref. (2) and supplementary documentation

## Appendix E Safety data for intervention and comparator(s)

The safety population (N=350) was used for safety analyses in the SOLSTICE (TAK-620-303) trial and consisted of all randomized patients who received at least one dose of study medication. For this analysis, patients were included in the treatment group corresponding to the study medication they actually received.

All safety data for the intervention and the comparators from the main study SOLSTICE are presented and described in the main body of this application in Section 7. Additional safety data are, however, provided here.

**Table 108: Treatment-emergent adverse events (TEAEs), serious TEAEs, TEAE leading to study or treatment discontinuation (safety population)**

| | | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome | Study arm | N total | n event | Result % (CI) | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| Any TEAE | maribavir | 234 | 228 | 97.4 (95.4–99.5) | 6.0 | 0.6–11.6 | 0.011 | OR: 3.59 | 1.27–10.12 | 0.015 | See table footnote* | Avery RK et al 2022 & SOLSTICE CSR |
| | IAT | 116 | 106 | 91.4 (86.3–96.5) | | | | | | | | |



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| | | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome | Study arm | N total | n event | Result % (CI) | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| Serious TEAE | maribavir | 234 | 90 | 38.5 (32.2–44.7) | 1.4 | -9.4 to 12.2 | 0.801 | OR: 1.06 | 0.67–1.68 | 0.816 | See table footnote* | Avery RK et al 2022 & SOLSTICE CSR |
| | IAT | 116 | 43 | 37.1 (28.3–45.9) | | | | | | | | |
| Any TEAE leading to study discontinuation | maribavir | 234 | 17 | 7.3 (3.9–10.6) | -0.5 | -6.4 to 5.4 | 0.868 | OR: 0.93 | 0.40–2.16 | 0.832 | See table footnote* | Avery RK et al 2022 & SOLSTICE CSR |
| | IAT | 116 | 9 | 7.8 (2.9–12.6) | | | | | | | | |
| Any TEAE leading to discontinuation of treatment | maribavir | 234 | 31 | 13.2 (8.9–17.6) | -18.7 | -28.2 to -9.1 | <0.001 | OR: 0.33 | 0.19–0.56 | <0.001 | See table footnote* | Avery RK et al 2022 & SOLSTICE CSR |
| | IAT | 116 | 37 | 31.9 (23.4–40.4) | | | | | | | | |

Abbreviations: CI, confidence interval; OR, Odds ratio; TEAE, treatment emergent adverse event

*Unadjusted difference in proportion and the corresponding 95% CI is computed by the normal approximation method and p-value obtained from two-sample test for proportion. Odds ratio obtained by Unconditional MLE & 95% CI obtained by normal approximation and p-value is obtained from Fisher's exact test.

Ref. (2,23)



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The majority of patients in both treatment groups had at least one treatment-emergent adverse events (TEAE) in the on-treatment observation period, reflecting the medical complexity of this patient population (Table 109).

**Table 109: Summary of TEAEs during the on-treatment observation period by treatment group (safety population).**

| | | | IAT type | | | |
|---|---|---|---|---|---|---|
| Category, n (%) | Maribavir (n = 234) | IAT (n = 116) | Ganciclovir/ valganciclovir (n = 56) | Foscarnet (n = 47) | Cidofovir (n = 6) | > 1 IAT (n = 7) |
| Any TEAE | 228 (97.4) | 106 (91.4) | [redacted] | | | |
| Any treatment-related TEAE | 141 (60.3) | 57 (49.1) | | | | |
| Any serious TEAE | 90 (38.5) | 43 (37.1) | | | | |
| Any treatment-related serious TEAE | 12 (5.1) | 17 (14.7) | | | | |
| Any TEAE leading to discontinuation of study-assigned treatment | 31 (13.2) | 37 (31.9) | | | | |
| Any treatment-related TEAE leading to discontinuation of study-assigned treatment | 11 (4.7) | 27 (23.3) | | | | |
| Any serious TEAE leading to discontinuation of study-assigned treatment | 20 (8.5) | 17 (14.7) | | | | |
| Any treatment-related serious TEAE leading to discontinuation of study-assigned treatment | 5 (2.1) | 9 (7.8) | | | | |
| Any TEAE leading to study discontinuation | 17 (7.3) | 9 (7.8) | | | | |
| Any treatment-related TEAE leading to study discontinuation | 3 (1.3) | 2 (1.7) | | | | |

| Category, n (%) | Maribavir (n = 234) | IAT (n = 116) | IAT type | | | |
|---|---|---|---|---|---|---|
| | | | Ganciclovir/ valganciclovir (n = 56) | Foscarnet (n = 47) | Cidofovir (n = 6) | > 1 IAT (n = 7) |
| Any serious TEAE leading to death | 16 (6.8) | 6 (5.2) | [redacted] | | | |
| Any treatment-related serious TEAE leading to death | 1 (0.4) | 1 (0.9) | | | | |
| Any TEAE of special interest | [redacted] | | | | | |
| Any treatment-related TEAE of special interest | | | | | | |

Abbreviations: IAT, investigator-assigned treatment; TEAE, treatment-emergent adverse event

Data are presented as n (%). The on-treatment observation period started at the time of study-assigned treatment initiation through 7 days after the last dose of study-assigned treatment or through 21 days if cidofovir was used, or until the maribavir rescue treatment initiation or until the non-study CMV treatment initiation, whichever was earlier.

TEAEs were coded using MedDRA, Version 23.0.

Ref. (2,23)

**Table 110: Frequently occurring (in ≥5% of patients in the maribavir or IAT group) TEAE during the on-treatment observation period considered related to study assigned treatment by the investigator (safety population).**

| System organ class preferred term, n (%) | Maribavir (n = 234) | IAT (n = 116) | IAT type | | |
|---|---|---|---|---|---|
| | | | Ganciclovir/ valganciclovir (n = 56) | Foscarnet (n = 47) | Cidofovir (n = 6) |
| **Any related TEAE** | 141 (60.3) | 57 (49.1) | 23 (41.1) | 29 (61.7) | 2 (33.3) |

| System organ class preferred term, n (%) | Maribavir (n = 234) | IAT (n = 116) | IAT type | | |
|---|---|---|---|---|---|
| | | | Ganciclovir/ valganciclovir (n = 56) | Foscarnet (n = 47) | Cidofovir (n = 6) |
| **Blood and lymphatic system disorders** | | | | | |
| Anemia | 3 (1.3) | 9 (7.8) | 3 (5.4) | 6 (12.8) | 0 |
| Febrile neutropenia | 0 | 4 (3.4) | 4 (7.1) | 0 | 0 |
| Leukopenia | 0 | 5 (4.3) | 4 (7.1) | 1 (2.1) | 0 |
| Neutropenia | 4 (1.7) | 16 (13.8) | 14 (25.0) | 2 (4.3) | 0 |
| Thrombocytopenia | 0 | 6 (5.2) | 4 (7.1) | 2 (4.3) | 0 |
| **Gastrointestinal disorders** | | | | | |
| Diarrhoea | 9 (3.8) | 6 (5.2) | 1 (1.8) | 4 (8.5) | 1 (16.7) |
| Nausea | 20 (8.5) | 11 (9.5) | 1 (1.8) | 8 (17.0) | 1 (16.7) |
| Vomiting | 18 (7.7) | 5 (4.3) | 0 | 4 (8.5) | 1 (16.7) |
| **General disorders and administration site conditions** | | | | | |
| Oedema peripheral | 0 | 4 (3.4) | 0 | 4 (8.5) | 0 |
| **Investigations** | 20 (8.5) | 9 (7.8) | 2 (3.6) | 6 (12.8) | 0 |



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| System organ class preferred term, n (%) | Maribavir (n = 234) | IAT (n = 116) | IAT type | | |
|---|---|---|---|---|---|
| | | | Ganciclovir/ valganciclovir (n = 56) | Foscarnet (n = 47) | Cidofovir (n = 6) |
| Immunosuppressant drug level increased | 14 (6.0) | 0 | 0 | 0 | 0 |
| **Metabolism and nutrition disorders** | | | | | |
| Hypocalcaemia | 0 | 5 (4.3) | 1 (1.8) | 4 (8.5) | 0 |
| Hypokalaemia | 1 (0.4) | 5 (4.3) | 0 | 4 (8.5) | 1 (16.7) |
| Hypomagnesaemia | 0 | 5 (4.3) | 1 (1.8) | 4 (8.5) | 0 |
| **Nervous system disorders** | | | | | |
| Dysgeusia | 84 (35.9) | 1 (0.9) | 1 (1.8) | 0 | 0 |
| Headache | 2 (0.9) | 4 (3.4) | 0 | 4 (8.5) | 0 |
| Taste disorder | 20 (8.5) | 1 (0.9) | 0 | 1 (2.1) | 0 |
| **Renal and urinary disorders** | | | | | |
| Acute kidney injury | 4 (1.7) | 9 (7.8) | 0 | 9 (19.1) | 0 |
| Renal impairment | 0 | 3 (2.6) | 0 | 3 (6.4) | 0 |
| Proteinuria | 1 (0.4) | 2 (1.7) | 0 | 1 (2.1) | 1 (16.7) |



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| System organ class preferred term, n (%) | Maribavir (n = 234) | IAT (n = 116) | IAT type | | |
|---|---|---|---|---|---|
| | | | Ganciclovir/ valganciclovir (n = 56) | Foscarnet (n = 47) | Cidofovir (n = 6) |
| Renal failure | 0 | 2 (1.7) | 0 | 0 | 1 (16.7) |

Abbreviations: IAT, investigator-assigned treatment; TEAE, treatment-emergent adverse event

Data are presented as n (%). The cidofovir group was not considered in the application of the 5% cutoff due to low patient numbers (n = 6).

The on-treatment observation period started at the time of study-assigned treatment initiation through 7 days after the last dose of study-assigned treatment or through 21 days if cidofovir was used, or until the maribavir rescue treatment initiation or until the non-study CMV treatment initiation, whichever was earlier.

TEAEs were coded using MedDRA, Version 23.0.

Ref. (2) and supplementary documentation

Deaths due to TEAEs was reported from a total of 40 patients deaths. The specific TEAE is listed per treatment group in Table 111.

**Table 111: Causes of all deaths (safety population).**

| Fatal TEAE | Maribavir (n = 234) | IAT (n = 116) |
|---|---|---|
| CMV encephalitis | 2 | 2[a] |
| Multiple organ dysfunction syndrome | 3 | 0 |
| Respiratory failure | 2 | 1 |
| Septic shock | 2 | 0 |
| Respiratory tract infection | 2 | 0 |

| Fatal TEAE | Maribavir (n = 234) | IAT (n = 116) |
|---|---|---|
| Recurrence of leukaemia | 1 | 1 |
| Recurrence of acute myeloid leukaemia | 1 | 1 |
| Recurrence of Hodgkin's disease | 1[b] | 0 |
| Recurrence of diffuse B-cell lymphoma | 1 | 0 |
| Recurrence of acute lymphocytic leukaemia | 1 | 0 |
| Deep vein thrombosis | 1 | 0 |
| Venous thrombosis | 1 | 0 |
| Hypoxia | 1 | 0 |
| Drug interaction | 1[c] | 0 |
| CMV syndrome and dyspnoea | 1 | 0 |
| Pulmonary embolism | 1 | 0 |
| General physical health deterioration | 1 | 0 |
| CMV enterocolitis | 0 | 1 |
| Myocardial infarction | 1 | 0 |



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| Fatal TEAE | Maribavir (n = 234) | IAT (n = 116) |
|---|---|---|
| Acute GvHD | 1 | 0 |
| Cardiac arrest | 1 | 0 |
| Acute respiratory distress syndrome | 0 | 2 |
| CMV colitis | 1 | 0 |
| CMV pneumonia | 0 | 1 |
| Febrile neutropenia, pneumonia, and tuberculosis | 0 | 1 |
| Pneumonia due to fungus and respiratory syncytial virus | 0 | 1 |
| Neutropenic sepsis | 0 | 1 |
| Post-transplant lymphoproliferative disorder | 0 | 1 |

Abbreviations: CMV, cytomegalovirus; GvHD, graft-versus host disease; IAT, investigator-assigned treatment; TEAE, treatment-emergent adverse event

Data are presented as n (%). The cidofovir group was not considered in the application of the 5% cutoff due to low patient numbers (n = 6).

[a]Includes one patient who had onset of fatal TEAE on Day 3 of maribavir rescue therapy.

[b]Relapse of Hodgkin's disease occurred 3 days prior to initiation of study treatment.

[c]TEAE was considered related to study-assigned treatment.

Ref. (2) and supplementary documentation



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# Appendix F Comparative analysis of efficacy and safety

As SOLSTICE (TAK-620-303) is the only relevant trial, a comparative analysis is not applicable.



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# Appendix G Extrapolation

Extrapolation of efficacy data and mortality data is explained in detail in section 8.

Figure 21: Markov Trace phase 1

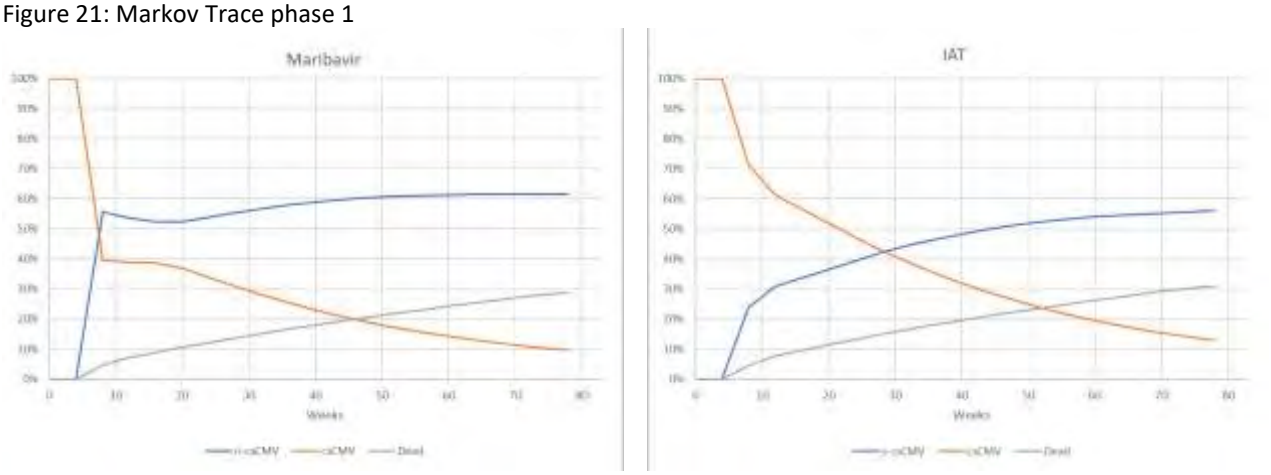
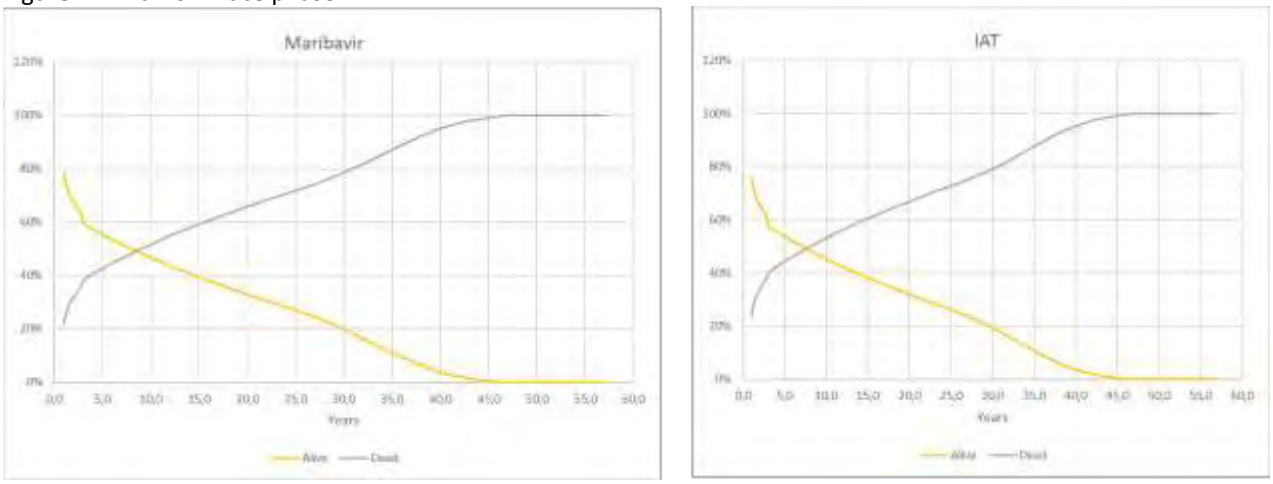



Figure 22: Markov Trace phase 1



# Appendix H – Literature search for HRQoL data

A health-related quality-of-life (HRQoL) SLR was conducted to identify the studies reporting the health-related utility values associated with CMV infection/disease in SOT or HSCT recipients. Takeda has during the last few years conducted several HRQoL SLRs and the latest updated HRQoL was conducted by Paraxel in September 2021. Therefore the HRQoL SLR in this application is a compilation of one original SLR and three sets of updates conducted across multiple timeframes from 2017-2022, with the most recent update conducted in July 2022 by Takeda Pharma A/S for this application. A summary of the timeframes covered for the original HRQoL SLR and its subsequent updates is presented in Table 112 and Table 113. The results obtained from the included studies identified across all reviews were compiled and are presented in this section.

**Table 112: Summary of the SLRs conducted for health-related utility review**

| Years of search | 2017 | 2020 | 2021 | 2022 |
|---|---|---|---|---|
| **Version** | Original SLR | Update 1 | Update 2 | Final update |
| **Health-related utility SLR search dates** | Data inception to 14th November 2017 | 15th November 2017 to 28th April 2020 | 29th April 2020 to 21st September 2021 | 21st September 2021 to 5th July 2022 |

Abbreviations: SLR, systematic literature review

## H.1 Databases

The key biomedical databases, including MEDLINE®, and the Cochrane Library, were searched for this literature review. Table 113 presents the platforms used to search these databases across the four SLRs.

**Table 113: Databases searched for the literature review and the search platform for health-related utility review**

| | Platform | | | |
|---|---|---|---|---|
| **Database** | Original SLR (Database inception to 14th November 2017) | First update (15th November 2017 to 28th April 2017) | Second update (29th April to 21th September 2021) | Final update (21th September 2021 to 5th July 2022) |
| **MEDLINE®** | Ovid SP® | Ovid SP® | Pubmed.com | Pubmed.com |
| **CENTRAL** | Not searched | Not searched | Cochrane library | Cochrane library |
| **Embase®** | Ovid SP® | Ovid SP® | Embase.com | Not searched |
| **EconLit** | Ovid SP® | Ovid SP® | AEAweb.org | Not searched |
| **NHS EED** | Ovid SP® | Not searched | Not searched | Not searched |

Abbreviations: Embase®: Excerpta Medica Database; CENTRAL, Cochrane Central Register of Controlled Trials; MEDLINE®, Medical Literature Analysis and Retrieval System; NHS EED: Cochrane National Health Service Economic Evaluation Database; SLR, systematic literature review

## H.2 Search strategy

The key biomedical databases, including MEDLINE®, and the Cochrane Library, were searched for this literature review. Table 113 presents the platform used to search these databases across the four SLRs. There were minor

differences in the search terms across the four SLRs, any missing evidence (from the original SLR and its first update) was identified in the second update undertaken by Parexel.

The search strategies used for retrieving records from the published literature are provided in Table 114 to Table 126.

***Original SLR: Database inception to 14th November 2017***

**Table 114: Summary of the search hits retrieved from Embase (searched via Ovid SP®, search timeframe: Data inception to 14th November 2017)**

| # | Query | Results |
|---|---|---|
| 1 | exp Cytomegalovirus/ | 36513 |
| 2 | exp cytomegalovirus infection/ | 31767 |
| 3 | exp human cytomegalovirus/ | 6435 |
| 4 | (cytomegal* or CMV or HCMV or salivary gland virus* or hhv 5 or (herpesvirus 5 adj human)).tw. | 65015 |
| 5 | or/1-4 | 81339 |
| 6 | Quality of life.tw. or exp "Quality of Life"/ | 468089 |
| 7 | (Utilit* or disutilit*).tw. | 230558 |
| 8 | 6 and 7 | 16014 |
| 9 | (health state* or HSUV).tw. | 8865 |
| 10 | (EQ5D or EQ 5D or EuroQoL).tw. | 14098 |
| 11 | (health utility index or HUI2 or HUI3 or HUI 2 or HUI 3).tw. | 752 |
| 12 | (medical outcome study or short-form or shortform or mos sf or sf6d or sf 6d or sf 6 d or sf 6 dimension or sf six or shortform six).tw. | 35676 |
| 13 | patient preference.tw. or exp Patient Preference/ | 15784 |
| 14 | (Time Trade Off or Standard Gamble or rating$ scale).tw. | 62430 |
| 15 | ((mapping or crosswalk*) and (utilit* or qol or quality or patient or pro)).tw. | 25456 |
| 16 | or/8-15 | 163856 |
| 17 | 5 and 16 | 98 |

**Table 115: Summary of the search hits retrieved from MEDLINE® (searched via Ovid SP®, search timeframe: Data inception to 14th November 2017)**

| # | Query | Results |
|---|---|---|
| 1 | Cytomegalovirus/ | 20600 |
| 2 | exp cytomegalovirus infection/ | 25446 |
| 3 | (cytomegal* or CMV or HCMV or salivary gland virus* or hhv 5 or (herpesvirus 5 adj human)).ti,ab. | 50834 |
| 4 | or/1-3 | 55774 |
| 5 | Quality of life.tw. or exp "Quality of Life"/ | 292980 |
| 6 | (Utilit* or disutilit*).tw. | 181983 |
| 7 | 5 and 6 | 10083 |
| 8 | (health state* or HSUV).tw. | 5730 |
| 9 | (EQ5D or EQ 5D or EuroQoL).tw. | 8512 |
| 10 | (health utility index or HUI2 or HUI3 or HUI 2 or HUI 3).tw. | 578 |

| # | Query | Results |
|---|---|---|
| 11 | (medical outcome study or short-form or shortform or mos sf or sf6d or sf 6d or sf 6 d or sf 6 dimension or sf six or shortform six).tw. | 28789 |
| 12 | patient preference.mp. | 9777 |
| 13 | (Time Trade Off or Standard Gamble or rating$ scale).tw. | 46042 |
| 14 | ((mapping or crosswalk*) and (utilit* or qol or quality or patient or pro)).tw. | 18978 |
| 15 | or/7-14 | 118209 |
| 16 | 4 and 15 | 47 |

**Table 116: Summary of the search hits retrieved from EconLit (searched via Ovid SP®, search timeframe: Data inception to 14th November 2017)**

| # | Query | Results |
|---|---|---|
| 1 | (cytomegal* or CMV or HCMV or salivary gland virus* or hhv 5 or (herpesvirus 5 adj human)).ti,ab. | 9 |

**Table 117: Summary of the search hits retrieved from NHS EED (searched via Ovid SP®, search timeframe: Data inception 2007 to 14th November 2017)**

| # | Query | Results |
|---|---|---|
| 1 | Cytomegalovirus/ | 11 |
| 2 | exp cytomegalovirus infection/ | 42 |
| 3 | (cytomegal* or CMV or HCMV or salivary gland virus* or hhv 5 or (herpesvirus 5 adj human)).ti,ab. | 75 |
| 4 | or/1-3 | 75 |

***Update one: 15th November 2017 to 28th April 2020***

**Table 118: Summary of the search hits retrieved from Embase (searched via Ovid SP®, search timeframe: 15th November 2017 to 28th April 2020)**

| # | Query | Results |
|---|---|---|
| 1 | exp Cytomegalovirus/ | 39790 |
| 2 | exp cytomegalovirus infection/ | 35631 |
| 3 | exp human cytomegalovirus/ | 7090 |
| 4 | (cytomegal* or CMV or HCMV or salivary gland virus* or hhv 5 or (herpesvirus 5 adj human)).tw. | 72308 |
| 5 | or/1-4 | 90353 |
| 6 | Quality of life.tw. or exp "Quality of Life"/ | 578778 |
| 7 | (Utilit* or disutilit*).tw. | 286057 |
| 8 | 6 and 7 | 20533 |
| 9 | (health state* or HSUV).tw. | 11064 |
| 10 | (EQ5D or EQ 5D or EuroQoL).tw. | 19952 |
| 11 | (health utility index or HUI2 or HUI3 or HUI 2 or HUI 3).tw. | 917 |
| 12 | (medical outcome study or short-form or shortform or mos sf or sf6d or sf 6d or sf 6 d or sf 6 dimension or sf six or shortform six).tw. | 45154 |
| 13 | patient preference.tw. or exp Patient Preference/ | 21236 |

| # | Query | Results |
|---|---|---|
| 14 | (Time Trade Off or Standard Gamble or rating$ scale).tw. | 77273 |
| 15 | ((mapping or crosswalk*) and (utilit* or qol or quality or patient or pro)).tw. | 33165 |
| 16 | or/8-15 | 209629 |
| 17 | 5 and 16 | 134 |
| 18 | limit 17 to yr="2017 -Current" | 43 |

**Table 119: Summary of the search hits retrieved from MEDLINE® (searched via Ovid SP®, search timeframe: 15th November 2017 to 28th April 2020)**

| # | Query | Results |
|---|---|---|
| 1 | Cytomegalovirus/ | 20698 |
| 2 | exp Cytomegalovirus Infections/ | 25523 |
| 3 | exp human cytomegalovirus/ | 0 |
| 4 | (cytomegal* or CMV or HCMV or salivary gland virus* or hhv 5 or (herpesvirus 5 adj human)).tw. | 51877 |
| 5 | or/1-4 | 56700 |
| 6 | Quality of life.tw. or exp "Quality of Life"/ | 331721 |
| 7 | (Utilit* or disutilit*).tw. | 205444 |
| 8 | 6 and 7 | 11643 |
| 9 | (health state* or HSUV).tw. | 6357 |
| 10 | (EQ5D or EQ 5D or EuroQoL).tw. | 10707 |
| 11 | (health utility index or HUI2 or HUI3 or HUI 2 or HUI 3).tw. | 609 |
| 12 | (medical outcome study or short-form or shortform or mos sf or sf6d or sf 6d or sf 6 d or sf 6 dimension or sf six or shortform six).tw. | 32924 |
| 13 | patient preference.tw. or exp Patient Preference/ | 11655 |
| 14 | (Time Trade Off or Standard Gamble or rating$ scale).tw. | 51501 |
| 15 | ((mapping or crosswalk*) and (utilit* or qol or quality or patient or pro)).tw. | 21346 |
| 16 | or/8-15 | 134959 |
| 17 | 5 and 16 | 48 |
| 18 | limit 17 to yr="2017 -Current" | 8 |

**Table 120: Summary of the search hits retrieved from EconLit (searched via Ovid SP®, search timeframe: 15th November 2017 to 28th April 2020)**

| # | Query | Results |
|---|---|---|
| 1 | (cytomegal* or CMV or HCMV or salivary gland virus* or hhv 5 or (herpesvirus 5 adj human)).ti,ab. | 10 |
| 2 | limit 1 to yr="2017 -Current" | 1 |

***Update two: 29th April 2020 to 21st September 2021***



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**Table 121: Summary of the search hits retrieved from Embase (searched via Embase.com, search timeframe: 29th April November 2020 to 21st September 2021)**

| # | Query | Results |
|---|---|---|
| 1 | 'cytomegalovirus'/syn OR 'cytomegalovirus infection'/syn | 85732 |
| 2 | 'organ transplantation'/syn OR 'hematopoietic stem cell transplantation'/syn OR (organ NEAR/2 transplant*) OR (hematopoietic NEAR/2 stem NEAR/2 cell NEAR/2 transplant*) OR SOT OR 'Solid organ transplant' OR Solid NEAR/3 transplant OR 'solid organ transplantation'/syn | 546187 |
| 3 | #1 AND #2 | 22341 |
| 4 | ((utilit* NEAR/2 (measure* OR outcome* OR state* OR health OR score* OR weight* OR analysis)):ab,ti) OR 'health utility index' OR hui OR (utilit* NEXT/1 (score* OR value* OR evaluation*)) OR (health NEXT/2 utilit*) OR (('health'/exp OR 'health') AND (state NEXT/1 utilit*)) OR ((health NEXT/1 state*) AND (state* NEXT/1 preference*)) OR 'quality adjusted life year'/exp OR 'quality adjusted life year' OR 'quality adjusted life' OR ('quality adjusted' NEXT/1 survival*) OR qaly* OR qald* OR qale* OR qtime* OR 'disability adjusted life' OR daly* OR 'health survey'/exp OR 'health survey' OR health*year*equivalent OR (health NEAR/2 utility*) OR 'wellbeing'/exp OR 'wellbeing' OR (quality NEAR/2 well*being) OR (willingness NEAR/2 pay) OR (standard NEAR/2 gamble) OR disutili* OR (time NEAR/2 trade*off) OR ('discrete choice' NEXT/1 experiment*) | 780547 |
| 5 | #3 AND #4 | 320 |
| 6 | #5 AND [animals]/lim | 6 |
| 7 | #5 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim) | 35 |
| 8 | #6 OR #7 | 41 |
| 9 | #5 NOT #8 | 279 |
| 10 | #9 AND [english]/lim | 221 |
| 11 | #10 AND [29-4-2020]/sd NOT [21-9-2021]/sd | 31 |

**Table 122: Summary of the search hits retrieved from MEDLINE® (searched via Pubmed.com, search timeframe: 29th April 2020 to 21st September 2021)**

| # | Query | Results |
|---|---|---|
| 1 | Cytomegalovirus infection [MeSH Terms] | 26912 |
| 2 | Cytomegalovirus [MeSH Terms] | 21919 |
| 3 | #1 OR #2 | 36798 |
| 4 | Organ transplantation [MeSH Terms] | 222781 |
| 5 | Hematopoietic stem cell transplantation [MeSH Terms] | 50776 |
| 6 | Solid organ transplant [MeSH Terms] | 9618 |
| 7 | (#4 OR #5 OR #6) | 273262 |
| 8 | #3 AND #7 | 6838 |
| 9 | (utilit* AND (measure* OR outcome* OR state* OR "health" OR score* OR weight* OR "analysis")) OR "health utility index" OR "hui" OR utilit* AND (score* OR value* OR evaluation*) OR "health" AND utilit* OR ("health" AND utilit*) OR ("health" AND "state" AND utilit*) OR ("health" AND state* AND preference*) OR "quality adjusted life year" OR "quality adjusted life" OR "quality adjusted" AND survival* OR qaly* OR qald* OR qale* OR qtime* OR "disability adjusted life" OR daly* OR "health survey" OR "health" AND utility* OR "wellbeing" OR "quality" OR "willingness" AND "pay" OR "standard" AND "gamble" OR disutili* OR "discrete choice" AND experiment* | 2294 |
| 10 | #8 AND #9 | 0 |



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**Table 123: Summary of the search hits retrieved from Cochrane (searched via Cochrane library, search timeframe: 29th April 2020 to 21st September 2021)**

| # | Query | Results |
|---|---|---|
| 1 | MeSH descriptor: [Cytomegalovirus] explode all trees | 317 |
| 2 | MeSH descriptor: [Cytomegalovirus Infections] explode all trees | 705 |
| 3 | "CMV" and cytomegalovirus:ti,ab,kw | 1392 |
| 4 | cytomegalovirus:ti | 980 |
| 5 | #1 OR #2 OR #3 OR #4 | 1770 |
| 6 | MeSH descriptor: [Organ Transplantation] explode all trees | 5763 |
| 7 | MeSH descriptor: [Hematopoietic Stem Cell Transplantation] explode all trees | 1477 |
| 8 | organ next transplant* or hematopoietic next stem next cell next transplant*:ti,ab,kw | 5874 |
| 9 | #6 OR #7 OR #8 | 11414 |
| 10 | #5 AND #9 | 596 |
| 11 | utilit* near/2 (measure* or outcome* or state* or "health" or score* or weight* or "analysis") | 3659 |
| 12 | health utility index or "hui" | 3695 |
| 13 | utilit* next/1 (score* or value* or evaluation*) | 962 |
| 14 | health next/2 utilit* | 1153 |
| 15 | MeSH descriptor: [Health] explode all trees | 9431 |
| 16 | health and ("state" next/1 utilit*) | 224 |
| 17 | hui or ("health" next/1 state* and state* next/1 preference*) | 2002 |
| 18 | MeSH descriptor: [Quality-Adjusted Life Years] explode all trees | 1339 |
| 19 | quality adjusted life year or "quality adjusted life" | 11918 |
| 20 | ("quality adjusted" next/1 survival*) or qaly* or qald* or qale* or qtime* or "disability adjusted life" or daly* | 5878 |
| 21 | MeSH descriptor: [Health Surveys] explode all trees | 30561 |
| 22 | health survey or hye* or health*year*equivalent or "health" near/2 utility* | 22732 |
| 23 | wellbeing or "quality" near/2 well*being or "qwb" | 18797 |
| 24 | willingness near/2 "pay" or "standard" near/2 "gamble" or disutili* | 1694 |
| 25 | time near/2 trade*off or "tto" or "discrete choice" next/1 experiment* | 486 |
| 26 | hrqol or "hqol" | 6343 |
| 27 | MeSH descriptor: [Quality of Life] explode all trees | 25960 |
| 28 | quality of life or "quality-of-life" or "qol" | 136750 |
| 29 | short form 36 or "sf36" or "sf-36" or "sf 36" | 21258 |
| 30 | short form 12 or "sf12" or "sf-12" or "sf 12" | 17485 |
| 31 | short form 6 or "sf6" or "sf-6" or "sf 6" | 17148 |
| 32 | euroqol or euro*qol or "eq5d" or "eq-5d" or "eq 5d" | 10869 |
| 33 | Rosser | 150 |
| 34 | ("visual" next/1 analog*) and (analog* next/1 scale*) | 52366 |
| 35 | #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 | 246149 |
| 36 | #10 AND #35 with Cochrane Library publication date Between Apr 2020 and Sep 2021 | 1 |



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**Table 124: Summary of the search hits retrieved from EconLit (searched via AEAweb.org, search timeframe: 29th April 2020 to 21st September 2021)**

| # | Query | Results |
|---|---|---|
| 1 | (cytomegal* or CMV or HCMV or salivary gland virus* or hhv 5 or (herpesvirus 5 adj human)).ti,ab. | 0 |

***Finale update SLR: 22th September 2021 to 5th July 2022***

**Table 125: Summary of the search hits retrieved from MEDLINE® (searched via Pubmed.com, search timeframe: 22nd September 2021 to 5th July 2022)**

| # | Query | Results |
|---|---|---|
| 1 | Cytomegalovirus infection [MeSH Terms] | 27719 |
| 2 | Cytomegalovirus [MeSH Terms] | 22594 |
| 3 | #1 OR #2 | 37782 |
| 4 | Organ transplantation [MeSH Terms] | 230658 |
| 5 | Hematopoietic stem cell transplantation [MeSH Terms] | 54153 |
| 6 | Solid organ transplant [MeSH Terms] | 10413 |
| 7 | (#4 OR #5 OR #6) | 284500 |
| 8 | #3 AND #7 | 7060 |
| 9 | (utilit* AND (measure* OR outcome* OR state* OR "health" OR score* OR weight* OR "analysis")) OR "health utility index" OR "hui" OR utilit* AND (score* OR value* OR evaluation*) OR "health" AND utilit* OR ("health" AND utilit*) OR ("health" AND "state" AND utilit*) OR ("health" AND state* AND preference*) OR "quality adjusted life year" OR "quality adjusted life" OR "quality adjusted" AND survival* OR qaly* OR qald* OR qale* OR qtime* OR "disability adjusted life" OR daly* OR "health survey" OR "health" AND utility* OR "wellbeing" OR "quality" OR "willingness" AND "pay" OR "standard" AND "gamble" OR disutili* OR "discrete choice" AND experiment* | 2673 |
| 10 | #8 AND #9 | 0 |

**Table 126: Summary of the search hits retrieved from Cochrane (searched via Cochrane library, search timeframe: 22nd September 2021 to 5th July 2022)**

| # | Query | Results |
|---|---|---|
| 1 | MeSH descriptor: [Cytomegalovirus] explode all trees | 332 |
| 2 | MeSH descriptor: [Cytomegalovirus Infections] explode all trees | 821 |
| 3 | "CMV" and cytomegalovirus:ti,ab,kw | 1442 |
| 4 | cytomegalovirus:ti | 1015 |
| 5 | #1 OR #2 OR #3 OR #4 | 1832 |
| 6 | MeSH descriptor: [Organ Transplantation] explode all trees | 5905 |
| 7 | MeSH descriptor: [Hematopoietic Stem Cell Transplantation] explode all trees | 1562 |
| 8 | organ next transplant* or hematopoietic next stem next cell next transplant*:ti,ab,kw | 6192 |
| 9 | #6 OR #7 OR #8 | 11864 |
| 10 | #5 AND #9 | 424 |
| 11 | utilit* near/2 (measure* or outcome* or state* or "health" or score* or weight* or "analysis") | 4002 |
| 12 | health utility index or "hui" | 4045 |
| 13 | utilit* next/1 (score* or value* or evaluation*) | 1089 |
| 14 | health next/2 utilit* | 1272 |

| # | Query | Results |
|---|---|---|
| 15 | MeSH descriptor: [Health] explode all trees | 10276 |
| 16 | health and ("state" next/1 utilit*) | 239 |
| 17 | hui or ("health" next/1 state* and state* next/1 preference*) | 2182 |
| 18 | MeSH descriptor: [Quality-Adjusted Life Years] explode all trees | 1398 |
| 19 | quality adjusted life year or "quality adjusted life" | 13017 |
| 20 | ("quality adjusted" next/1 survival*) or qaly* or qald* or qale* or qtime* or "disability adjusted life" or daly* | 6439 |
| 21 | MeSH descriptor: [Health Surveys] explode all trees | 31656 |
| 22 | health survey or hye* or health*year*equivalent or "health" near/2 utility* | 25425 |
| 23 | wellbeing or "quality" near/2 well*being or "qwb" | 21536 |
| 24 | willingness near/2 "pay" or "standard" near/2 "gamble" or disutili* | 1912 |
| 25 | time near/2 trade*off or "tto" or "discrete choice" next/1 experiment* | 516 |
| 26 | hrqol or "hqol" | 7068 |
| 27 | MeSH descriptor: [Quality of Life] explode all trees | 29233 |
| 28 | quality of life or "quality-of-life" or "qol" | 152325 |
| 29 | short form 36 or "sf36" or "sf-36" or "sf 36" | 23040 |
| 30 | short form 12 or "sf12" or "sf-12" or "sf 12" | 19156 |
| 31 | short form 6 or "sf6" or "sf-6" or "sf 6" | 18631 |
| 32 | euroqol or euro*qol or "eq5d" or "eq-5d" or "eq 5d" | 12355 |
| 33 | Rosser | 159 |
| 34 | ("visual" next/1 analog*) and (analog* next/1 scale*) | 58296 |
| 35 | #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 | 272101 |
| 36 | #10 AND #35 with Cochrane Library publication date Between Sep 2021 and Jul 2022 | 2 |

## H.3 Study selection criteria

The search strategy developed to meet the objective of the SLR was defined using the PICOs framework by the inclusion and exclusion criteria specified in Table 127.

**Table 127: Inclusion and exclusion criteria for the health-related utility review**

| Category | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population (P)** | ▪ CMV infection/disease in SOT or HSCT<br>▪ Adolescents and Adults (≥12 years)<br>▪ Race: No restriction<br>▪ Gender: No restriction | ▪ Patients with other infections or coinfections<br>▪ Studies evaluating children (<12 years) |
| **Interventions (I)** | ▪ No restriction | n/a |
| **Comparator (C)** | ▪ No restriction | n/a |
| **Outcomes (O)** | ▪ Studies reporting utilities or scores for: | ▪ Studies not reporting relevant outcomes of interest |



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| Category | Inclusion criteria | Exclusion criteria |
|---|---|---|
| | ▪ EuroQoL-Five Dimension (five-level or three-level)<br>▪ Short Form-Six Dimension or 36-Item Short Form Survey<br>▪ Health Utilities Index<br>▪ Direct utility elicitation tools: Standard gamble, time trade-off, rating scales<br>▪ Any other health-related utility measurements | |
| **Study design** | ▪ Utility data reporting studies | ▪ Utility data reporting studies |
| **Timeframe** | ▪ Data inception to July 5th, 2022 | n/a |
| **Language** | ▪ Articles in English | ▪ Non-English language |
| **Publication type** | ▪ Peer-reviewed journal articles | ▪ Editorials, newspaper articles, book sections, expert opinion or commentary, trial protocols, and reviews |
| **Others** | n/a | ▪ Studies conducted in-vitro and animals |

Abbreviations: CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplant; n/a, not applicable; SOT, solid organ transplant

Across the four HRQoL SLRs, the database searches yielded 315 citations. Of these, 36 citations were identified as duplicates and were therefore removed. Following title and abstract screening of the remaining 279 citations, 262 citations were excluded, and 17 citations were included for more detailed full-text screening. Following full-text screening, 10 citations were included and 7 excluded. The PRISMA flow diagram of health-related utility studies included in this application is shown in Figure 23 and Table 128 are showing the details of each included study.

Hand-searching of Danish and UK HTA websites identified a total of four HTAs of relevance to the decision problem. Additionally, searches were run from database inception to 5th July 2022 to identify any missing evidence from the previous updates which led to the inclusion of three citations. Therefore, a total of 13 studies and 4 HTAs reporting relevant health-related utility data were included in the SLR.
The PRISMA flow diagram of health-related utility studies included in the current review is shown in Figure 23.



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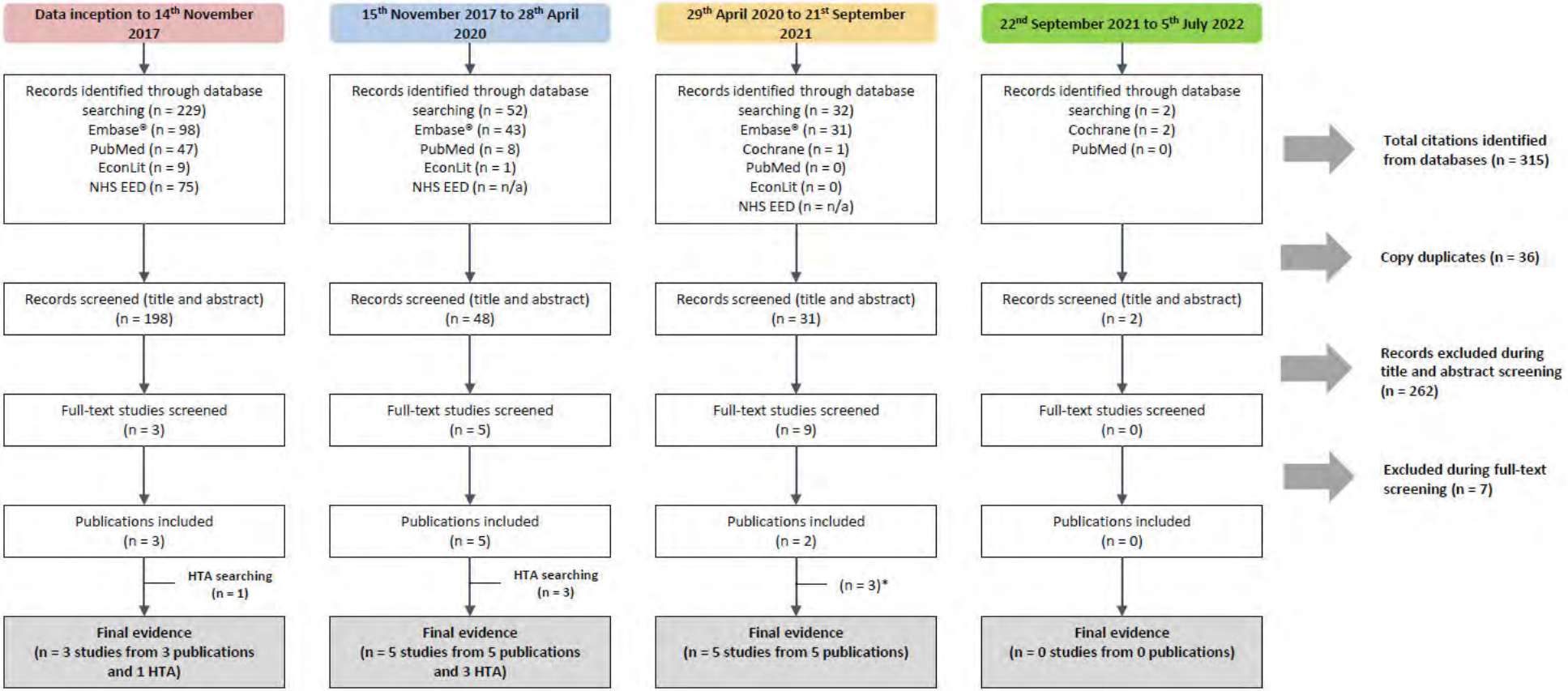
## H.4 Systematic selection of studies

**Figure 23:** PRISMA flow diagram for identification of health-related utility studies




Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; CMV, cytomegalovirus; Embase®, Excerpta Medica Database; MEDLINE, Medical Literature Analysis and Retrieval System Online
*These searches were additionally run from database inception to 29th April 2020 to identify any missing evidence from the previous updates.

**Table 128: Studies reporting health-related utility estimates**

| Study name | Country | Utility study design | Type of utility measure | Valuation technique | Treatment details | Population valuing health state | Disease state description for utility | Mean utility (data spread) | References |
|---|---|---|---|---|---|---|---|---|---|
| **Babigumira 2018** (81) | Spain | CUA/BIM | TTO | CMV utilities taken from original paper for adverse events, infections, and their sequelae | Methylene blue-treated plasma vs. Quarantine plasma (82) | Patients at risk for developing CMV infection (asymptomatic CMV, CMV retinitis, & CMV mononucleosis) or other risks after receiving transfused plasma | • Base utility | • 0.900 (0.720-1.000) | • Custer 2005 (83) |
| | | | | | | | • CMV retinitis | • 0.650 (0.585-0.715) | • Freedberg 1998 (82) |
| | | | | | | | • CMV infectious mononucleosis | • 0.650 (0.585-0.715) | • Freedberg 1998 (82) |
| | | | | | | | • Post-liver transplant | • 0.73 (0.63-0.84) | • Buti 2000 (84) |
| **Puttarajappa 2018** (85) | USA | CUA | TTO | Taken from original paper | Compared screening with CMV-NAAT at different intervals for late-onset CMV infection after completion of 6 months of valganciclovir prophylaxis (86) | Patients at high risk for developing CMV infection after kidney transplant | • Kidney transplant | • 0.73 (0.55-0.87) | • Laupacis 1996 (86) |
| | | | | | | | • Asymptomatic CMV | • 0.73 (0.55-0.87) | • Assumption |
| | | | | | | | • Asymptomatic CMV on treatment | • 0.73 (0.55-0.87) | • Assumption |
| | | | | | | | • Resolved mild CMV | • 0.73 (0.55-0.87) | • Assumption |
| | | | | | | | • Resolved severe CMV | • 0.73 (0.55-0.87) | • Assumption |
| | | | | | | | • Mild CMV | • 0.65 (0.59-0.72) | • Assumption |
| | | | | | | | • Severe outpatient CMV (posthospitalisation) | • 0.55 (0.43-0.69) | • Assumption |
| | | | | | | | • Severe inpatient CMV | • 0.45 (0.30-0.57) | • Assumption |
| | | | | | | | • Dead | • 0 (NR) | • NR |
| | | | | | | | • Dialysis | • 0.53 (NR) | • Laupacis 1996 (86) |
| **Restelli 2019** (87) | Italy | CUA | Treatment utility: EQ-5D | Treatment utility: derived from Phase III trial (88,89) Post-trial utility taken from | Letermovir as prophylaxis vs. no Letermovir | Adult CMV-seropositive (R+) allogeneic HSCT recipients | • Baseline | • LET:0.649 No LET: 0.649 | • Marty 2017, Merck CSR 2017 (88,89) |
| | | | | | | | • Week 14 | • LET:0.756 No LET: 0.674 | • Marty 2017, Merck CSR 2017 (88,89) |
| | | | | | | | • Week 24 | • LET:0.757 No LET: 0.689 | • Marty 2017, Merck |

| Study name | Country | Utility study design | Type of utility measure | Valuation technique | Treatment details | Population valuing health state | Disease state description for utility | Mean utility (data spread) | References |
|---|---|---|---|---|---|---|---|---|---|
| | | | Post-trial utility: TTO | original paper (90) | | | • Week 48<br>• Post-trial (patients with AML) | • LET:0.813 No LET: 0.733<br>• LET:0.760 | CSR 2017 (88,89)<br>• Marty 2017, Merck CSR 2017 (88,89)<br>• Castejón 2018 (90) |
| **Brown 2018** (91) | UK | CUA | Translating EQ-5D responses from the clinical trial into utility values using the UK population based TTO value set | Derived from Phase III RCT (88,89) | Letermovir [480 mg (or 240 mg/d with concomitant ciclosporin-A) for 14 weeks post-transplant (~100 days), starting 0 to 28 days post HSCT] vs. placebo | Adult CMV-seropositive (R+) allogeneic HSCT recipients | • Baseline utility<br>• Δ from baseline at week 14<br>• Δ from baseline at week 24<br>• Δ from baseline at week 48 | • 0.649<br>• LET: 0.107 Placebo: 0.025<br>• LET: 0.108 Placebo: 0.040<br>• LET: 0.164 Placebo: 0.084 | • Marty 2017 (88)<br>• Marty 2017 (88)<br>• Marty 2017 (88)<br>• Marty 2017 (88) |
| **Schelfhout 2018** (92) | USA | CUA | Translating EQ-5D responses from the clinical trial into utility values using the UK population based TTO value set | Derived from Phase III RCT (88,89) | Letermovir [480 mg (or 240 mg/d with concomitant ciclosporin-A) for 14 weeks post-transplant (~100 days), starting 0 to 28 days post HSCT] vs. placebo | Adult CMV-seropositive (R+) allogeneic HSCT recipients | • Baseline utility<br>• Δ from baseline at week 14<br>• Δ from baseline at week 24<br>• Δ from baseline at week 48 | • 0.649<br>• LET: 0.107 Placebo: 0.025<br>• LET: 0.108 Placebo: 0.040<br>• LET: 0.164 Placebo: 0.084 | • Marty 2017 (88)<br>• Marty 2017 (88)<br>• Marty 2017 (88)<br>• Marty 2017 (88) |



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| Study name | Country | Utility study design | Type of utility measure | Valuation technique | Treatment details | Population valuing health state | Disease state description for utility | Mean utility (data spread) | References |
|---|---|---|---|---|---|---|---|---|---|
| **CADTH 2018 Letermovir** (93) | Canada | CUA | EQ-5D | Treatment-specific utilities and post-trial utility: derived from the P001 trial (89)<br><br>Post-transplant utility taken from original paper (94) | Letermovir [480 mg/d PO or IV (240 mg/d with concomitant cyclosporine A) for 100 days, taken with usual care] vs. usual care [weekly CMV viral load monitoring with the initiation of antiviral PET (e.g., ganciclovir & valganciclovir) when CMV viral load exceeded 150 copies/mL to 300 copies/mL &/or treatment of CMV disease] | Adult CMV-seropositive (R+) allogeneic HSCT recipients | • Δ from baseline at week 24<br><br>• CDR reanalysis: Post-trial utility (48 weeks value)<br><br>• Manufacture model: Post-transplant after 1st year (patients with untreated MM undergoing ASCT) | • LET: 0.107 (0.108-0.164)<br>• Usual care: 0.025 (0.040-0.084)<br><br>• 0.768 (limits for one-way analysis 0.703-0.834)<br><br>• 0.76 | • Merck CSR 2017 (89)<br><br>• Merck CSR 2017 (89)<br><br>• Agthoven 2004 (94) |
| **NICE 2019 TA591** (43) | UK | CUA | EQ-5D | Treatment-specific utilities: derived from the P001 trial (89) | Letermovir [480 mg (or 240 mg/d with concomitant ciclosporin-A) for 14 weeks post-transplant (~100 days), starting 0 to 28 days post HSCT] vs. placebo | Adult CMV-seropositive (R+) allogeneic HSCT recipients | • Baseline<br>• Δ from baseline at week 14, 24, 48<br>• Post-trial (patients with AML underwent HSCT)<br>• General population (UK) values<br>Age 60-≤65 years<br>Age 65-≤70 years<br>Age 70-≤75 years<br>Age 75-≤80 years<br>Age 80-≤85 years<br>Age >85 years<br>• GvHD disutility | • 0.649<br>• Redacted<br>• 0.82<br>• Value (95% CI)<br>0.8072 (0.793-0.821)<br>0.8041 (0.79-0.817)<br>0.779 (0.766-0.791)<br>0.7533 (0.739-0.767)<br>0.6985 (0.677-0.719)<br>0.65497 (0.624-0.675)<br>• 0.09 | • Marty 2017 (88)<br>• Marty 2017 (88)<br>• Leunis 2014 (95)<br>• Ara & Brazier 2011 (70) |

| Study name | Country | Utility study design | Type of utility measure | Valuation technique | Treatment details | Population valuing health state | Disease state description for utility | Mean utility (data spread) | References |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | • Relapse after SCT | • 0.0114 | • Pidala 2011, Ara & Brazier 2011 (69,70)<br>• Assumption |
| **Blumberg 2010** (96) | USA | CUA/CEA | TTO | Derived from quality-of-life study (86) and an economic analysis (97) covering the span from pretransplant up to 24 months of posttransplant period | 200-day valganciclovir vs.<br>100-day valganciclovir | CMV D+/R- (high risk) KT recipients | • Prophylaxis<br>• No CMV<br>• CMV<br>• Post-CMV<br>• Acute rejection (CMV-/CMV+)<br>• Graft failure<br>• Dialysis | • Year 1: 0.73<br>Year 2: NR<br>• Year 1: 0.745<br>Year 2: 0.7<br>• Year 1: 0.5<br>Year 2: 0.694<br>• Year 1: 0.745<br>Year 2: 0.7<br>• Year 1: 0.5<br>Year 2: 0.683<br>• Year 1: 0.62<br>Year 2: 0.556<br>• Year 1: 0.53<br>Year 2: 0.55 | • Laupacis 1996 (86)<br>• Laupacis 1996 (86)<br>• Laupacis 1996 (86)<br>• Laupacis 1996 (86)<br>• Laupacis 1996 (86)<br>• Laupacis 1996 (86)<br>• Laupacis 1996, Howard 2009 (86,97) |
| **Luan 2009** (98) | USA | CUA | TTO | Taken from original paper (86,99) | 6 months prophylaxis valganciclovir (450mg) vs. 3 months prophylaxis valganciclovir (450mg) | CMV D+/R- KT &/or pancreas transplant patients | • Functioning kidney transplant<br>• Dialysis<br>• Death | • 0.73<br>• 0.53 (0.5-0.57)<br>• 0 | • Laupacis 1996 (86)<br>• Laupacis 1996, Narayan 2007 (86,99) |
| **Luan 2011** (100) | USA | CUA/CEA | TTO | Taken from original paper (86,99) | Universal prophylaxis with 900mg valganciclovir vs. PET of CMV (viraemia screening) | CMV R+ KT patients | • Functioning kidney transplant<br>• Maintenance dialysis<br>• Death | • 0.73<br>• 0.57<br>• 0 | • Laupacis 1996 (86)<br>• Laupacis 1996, Narayan 2007 (86,99) |



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| Study name | Country | Utility study design | Type of utility measure | Valuation technique | Treatment details | Population valuing health state | Disease state description for utility | Mean utility (data spread) | References |
|---|---|---|---|---|---|---|---|---|---|
| **Alsumali 2021** (101) | USA | CUA | EQ-5D | Obtained from clinical trial (88) | Letermovir versus placebo (no prophylaxis) | Adult CMV-seropositive allo-HCT recipients | • At week 24 in one year of analysis<br>• Utility weight based on long term follow up analysis of AML survivors post allo-HCT | • LET: 0.76<br>No LET: 0.69<br>• 0.82 | • Marty 2017 (88)<br>• Leunis 2014 (95) |
| **Chan 2020** (102) | Hong Kong | CUA | EQ-5D | Treatment specific utility: derived from Letermovir Phase III study (88)<br>Post-trial utility: obtained from a UK societal-based study (90) | Letermovir versus placebo (no prophylaxis) | Adult CMV-seropositive allo-HCT recipients | • Baseline utility<br>• Week 14<br>• Week 24<br>• Post-trial (patients with AML) | • LET:0.649<br>No LET: 0.649<br>• LET:0.756<br>No LET: 0.674<br>• LET:0.757<br>No LET: 0.689<br>• LET:0.760<br>No LET: 0.760 | • Marty 2017, Merck CSR 2017 (88,89)<br>• Marty 2017, Merck CSR 2017 (88,89)<br>• Marty 2017, Merck CSR 2017 (88,89)<br>• Castejón 2018 (90) |
| **Muduma 2016** (103) | UK | CUA | EQ-5D | Taken from a 2002 UK-specific study (104) | Prolonged release tacrolimus relative to immediate release tacrolimus and ciclosporin | De novo adult liver transplant recipients | • First year of base case analysis: 6-month post-transplant utility<br>• For subsequent years: 24-month post-transplant utility | • 0.69<br>• 0.76 [95%CI: 0.73-0.79)] | • Ratcliffe 2002 (104)<br>• Ratcliffe 2002 (104) |
| **Tilden 2004** (105) | Australia | CUA | TTO | Taken from original paper (86) | Valganciclovir prophylaxis vs. placebo (no prophylaxis) | CMV seropositive renal transplant recipients | • Patients with Functioning graft<br>• Patients with Failed graft and receiving dialysis | • 0.70<br>• 0.57 | • Laupacis 1996 (86)<br>• Laupacis 1996 (86) |
| **Das 2000** (106) | NR | CUA | NR | Based on the expert opinion of a group of physicians | IV GCV, Oral GCV, CMV Ig, | Orthotopic Liver transplant recipients | • Healthy<br>• Acute rejection<br>• Chronic rejection | • 1.0 (0.9-1.0)<br>• 0.9 (0.85-1.0)<br>• 0.5 (0.3-0.7) | • Estimate<br>• Estimate<br>• Estimate |

| Study name | Country | Utility study design | Type of utility measure | Valuation technique | Treatment details | Population valuing health state | Disease state description for utility | Mean utility (data spread) | References |
|---|---|---|---|---|---|---|---|---|---|
| | | | | experienced in the post transplantation care of orthotopic liver transplant recipient | ACV 800mg oral for 6 months and 3 months | | • CMV infection<br>• CMV disease<br>• Severe opportunistic infection in patients with CMV disease | • 1.0 (0.9-1.0)<br>• 0.75 (0.5-0.9)<br>• 0.5 (0.3-0.7) | • Estimate<br>• Estimate<br>• Estimate |
| **CADTH 2018 Tolvaptan** (107) | Canada | CUA | EQ-5D | Derived from original paper (108) | Tolvaptan twice daily in split-dose regimens of 60 mg, 90 mg, or 120 mg vs.<br>Standard of care (monitoring and palliative care/symptom management) | Autosomal dominant polycystic kidney disease | • Base utility<br>• End-stage renal disease on dialysis | • 0.57<br>• 0.65 | • McFarlane 2003 (108)<br>• McFarlane 2003 (108) |
| **NICE 2015 TA348** (109) | UK | CUA | EQ-5D | SLR was conducted to identify health-state utility values (7 studies were identified) | Everolimus in combination with reduced-dose tacrolimus compared with standard-dose tacrolimus | Preventing organ rejection in liver transplantation | • Asymptomatic state<br>• Hepatic-rejection<br>• Graft loss (severe chronic rejection)<br>• CKD stage 4 (with dialysis)<br>• CKD stage 5 (with dialysis) | • 0.58<br>• 0.58<br>• 0.53<br>• 0.49<br>• 0.28 | • From SLR (included 7 studies) |

Abbreviations: ACV: Acyclovir; AML: Acute myeloid leukemia; ASCT: Allogenic stem cell transplant; BIM: Budget impact analtsis; CADTH: Canadian Agency for Drugs and Technologies in Health; CDR: CADTH Common Drug Review; CEA: Cost-effectiveness analysis; CMV: Cytomegalovirus; CMV-NAAT: Cytomegalovirus nucleic acid amplification test; CSR: Clinical Study Report; CUA: Cost-utility analysis; EQ-5D: Euro Quality of Life- 5 Dimension; GCV: Ganciclovir; GP: General population; GvHD: Graft vs. host disease; HSCT: Hematopoietic stem cell transplant; HR-QoL: Health-related quality of life; IV: Intravenous; KT: Kidney transplant; MM: Multiple myeloma; PET: Pre-emptive therapy; PO: Orally administrated; LET: Letermovir; RCT: Randomized controlled trial; SCT: Stem cell transplant; SLR: Systematic literature review; TTO: Time trade-off; UK: United Kingdom; USA: United States of America



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## H.5 Description of identified studies

Prior to the latest search (latest search; 22 September 2021 to 5 July 2022), in total, 13 studies and four HTAs were included in the HRQoL SLR. All of the included studies were types of cost-utility analyses reported health-related utility values. The health-related utility values were derived from previously published literature, internal documents, or the authors made assumptions regarding the values. Full details of the included studies are presented in Table 128 .

Of the included studies, two were conducted in the UK (91,103), six were conducted in the USA (85,92,96,98,100,101), one each was conducted in Spain (81), Italy (87), Australia (105), Hong Kong (102), and the country was not reported for one study (106). Two HTAs each were retrieved from CADTH (93,107) and NICE (43,109).

Among the four HTAs that reported utility values of interest, two of these HTAs assessed letermovir for preventing CMV infection/disease (43,93). The third was a HTA for CADTH in 2018 that assessed tolvaptan for autosomal dominant polycystic kidney disease (107) and the fourth HTA was a submission to NICE in 2015 that evaluated everolimus for preventing organ rejection in liver transplantation (109).

Five studies and two HTAs (43,87,91–93,101,102) included patients who underwent allogeneic HSCT. One study included patients who were at risk of CMV after plasma transfusion (81), and the remaining studies (n=7) included SOT recipient (85,96,98,100,103,105,106).

Among the SOT studies, the majority (n=4) included patients who underwent kidney transplants (85,96,100,105), two studies included patients with liver transplants (103,106) while one study included patients that either received a kidney transplant or a pancreas transplant (98).

### *H.5.1 Transplant and post-transplant utility values*

Four cost-utility analysis (CUA) publications included utility values for renal transplant recipients (85,98,100,105), two CUA publications included utility values for liver transplant recipients (81,103), while three CUA publications and two HTAs reports included utility values for allogenic HSCT recipients (43,87,93,101,102).

Kidney transplant utility values (on patients with any condition) in the CUA studies were derived from a Canadian study by Laupacis et al. Utility values from 168 patients were derived using the time-trade-off (TTO) instrument before and up to 2-years post renal transplant (86). Three studies reported that the patients with functioning kidney transplant had a utility value of 0.73 (85,98,100). Tilden et al. reported that patients with functioning graft had a utility value of 0.70 (105).

Babigumira et al. reported the health state utilities that were obtained from the published literature, supported by assumptions where estimates were unavailable. The post-liver transplant value was 0.73 (range 0.63-0.84)[28] and this was derived from a study including patients with chronic hepatitis C virus (81). Muduma et al. reported the utilities for two health states that were derived from a UK-specific study in which an EQ-5D tariff value was elicited from 542 liver transplant recipients (103). For the first year of the base case analysis, the model used the 6-month post-transplant mean EQ-5D tariff value of 0.69. For subsequent years, the 24-month post-transplant value of 0.76 was used (103).

A CUA was submitted to CADTH comparing letermovir as prophylaxis of CMV infection, taken alongside usual care, in adult CMV-seropositive HSCT recipients compared with usual care alone (93). Treatment-specific utility values in the submission were taken from a CUA comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma (MM) receiving autologous HSCT model that was submitted to CADTH

(93), the post-allogenic HSCT value after the first year was 0.76 (94). The post-trial utility value in the CADTH CRD re-analysis was 0.768 (limits for one-way analysis 0.703-0.834) (93) and this was the 48-week value from the P001 study (88).

***H.5.2 Dialysis utilities***

Five studies and one HTA report reported the utility value for dialysis that they identified in published literature (85,96,98,100,105,107). The utility values used by five studies (85,96,98,100,105) were taken from Laupacis et al., Narayan et al. and Howard et al. (86,97,99). The utility values for dialysis ranged from 0.53 (85,98) to 0.57 (100,105). The HTA for CADTH in 2018 looked at tolvaptan for autosomal dominant polycystic kidney disease (107), and reported a utility value for end-stage renal disease on dialysis of 0.65 (base case 0.57). This value was taken from a QoL and cost-utility study on haemodialysis (108).

***H.5.3 Organ rejection utility values***

In the model submitted to NICE assessing letermovir for preventing cytomegalovirus disease after a stem cell transplant (43), a disutility for GvHD was included. This company submission reported a disutility of 0.09, providing Pidela et al and Brazier and Ara references (69,70). Pidala was an US observational study that collected the 36-Item Short Form Survey (SF-36) in 254 HSCT recipients with chronic GvHD (69). The methodology on how the company derived the disutility was not described (43). The model in the NICE submission also included a disutility for relapse after SCT of 0.0114 and this was calculated based on the difference between the utility reported in Leunis et al. (95) and general population mortality source from Ara et al. (70)

The CUA publication by Blumberg et al. included other utility values listed in the paper by Laupacis et al. (86) The utility values for acute kidney rejection in year 1 was 0.5 and year 2 was 0.683, and the utility values for graft failure in year 1 was 0.62 and in year 2 was 0.556. Das et al. (106), a CEA publication presented utility values associated with the different acute and chronic rejection of liver transplant that were based on the expert opinion of a group of physicians experienced in the post-transplantation care of liver transplant recipients. The utility value for acute and chronic rejection was 0.9 (range 0.85-1.0) and 0.5 (range 0.3-0.7), respectively (106).

A submission to NICE in 2015 that looked at everolimus for preventing organ rejection in liver transplantation (109) presented the health-related utility values after transplantation for asymptomatic state (0.58), hepatic-rejection (0.58), graft loss (severe chronic rejection, 0.53), chronic kidney disease stage 4 (with dialysis, 0.49), and chronic kidney disease stage 5 (with dialysis, 0.28). The values were found through an SLR and network meta-analysis that the manufacturer conducted in liver transplantation. The company found seven studies, on which five were studies measuring EQ-5D in a UK population. The HTA submission reported on two of these seven studies. Utility scores for the health states in the hepatic rejection model and the renal sub-model were based on Ratcliffe et al. (104) and Neri et al. (110) respectively, both UK studies using EQ-5D.

## Quality assessment and generalizability of estimates

Economic model publications were assessed for quality using the BMJ Checklist (Drummond 1996) (111). The BMJ Economic Checklist is comprised of 35 questions that aids reviewers in qualitatively evaluating an economic analysis. These questions address the study quality across three domains: study design, data collection, and analysis and interpretation of results (112).

## Unpublished data

The unpublished data that has been used as part of utility analysis in this application is attached as supplementary documentation.

# Appendix I Mapping of HRQoL data

In Study 303 the data was collected using the EQ-5D-5L instrument.

The impact of treatment and response on health state utility values (HSUV) was more formally assessed using a linear mixed effects models fitted to observed data. The details of the mixed modelling are provided below.

The descriptive summaries and mixed modelling analysis are based on EQ-5D-5L crosswalk utilities.

Furthermore, to investigate if there is a trend in EQ-5D responses, TUDD analysis was performed by directly using the EQ-5D-5L responses. The TUDD analysis was performed to assess the treatment effect impact on EQ-5D-5L responses for each individual domain and overall health. The details of these analyses are provided below.

In summary, the following analysis related to QoL were presented:

Descriptive summaries of EQ-5D-5L crosswalk utilities, by treatment

Mixed modelling of EQ-5D-5L utility scores, including treatment and response and main effects TUDD analyses of EQ-5D-5L responses, by treatment

All analyses are also conducted by individual IAT type in Appendix O EQ5D5L analysis additional outputs).

**Exploratory analysis**

The results of the exploratory analyses of HSUV by health state and response is presented in Table 129, while the HSUV by transplant type is presented in Table 130.

**Table 129: EQ-5D-5L Danish crosswalk HSUVs (utilities) by health state (response vs no-response) at different study time points by treatment arm**

| | IAT (N=117) | | | Maribavir 400 mg BID (N=235) | | | Overall (N=352) | | |
|---|---|---|---|---|---|---|---|---|---|
| | m/n | Mean | SE | m/n | Mean | SE | m/n | Mean | SE |
| Response (week 0-20) | [redacted] | | | | | | | | |
| No-response (week 0-20) | | | | | | | | | |
| Response (at week 8) | | | | | | | | | |
| No-response (at week 8) | | | | | | | | | |

Abbreviations: BID: Twice daily; EQ-5D-5L: EuroQoL Group 5-Dimension 5-Level; HSUV: Health state utility value; IAT: Investigator-assigned anti-CMV treatment; m/n: Number of records/ number of unique patients in that category; SE: Standard error; Denmark

**Table 130: EQ5D Danish crosswalk HSUVs (utilities) by health state (response vs no-response) at different study time points by transplant type**

| | | IAT | | | Maribavir | | | Overall | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | m/n | Mean | SE | m/n | Mean | SE | m/n | Mean | SE |
| Response | SOT | [redacted] | | | | | | | | |

| | | |
|---|---|---|
| **(wk 0-20)** | HSCT | [redacted] |
| **No response (wk 0-20)** | SOT | |
| | HSCT | |
| **Response (at wk 8)** | SOT | |
| | HSCT | |
| **No response (at wk 8)** | SOT | |
| | HSCT | |

Abbreviations: EQ-5D-5L: EuroQoL Group 5-Dimension 5-Level; HSUV: Health state utility value; HSCT: Hematopoietic stem cell transplant; m/n: Number of records/ number of unique patients in that category; Se: Standard error; SOT: Solid organ transplant; Denmark

The utility values are also generated by treatment and transplant type at week 8 and between week 8 to week 20 for response vs no-response health status and the results are provided in Appendix O EQ5D5L analysis additional outputs).

**Observation from exploratory analysis**

Utility values are observed at primary analysis timepoint, i.e., at week 8, at the latest timepoint, i.e., week 20, and also for the entire duration of the study i.e., between week 0-20. Utility summaries for Denmark show that responders have higher utilities compared to non-responders. This trend is mostly consistent across two treatment arms, for overall data and the same pattern is observed for both transplant types. Maribavir arm showed higher utilities compared to IAT arm in descriptive summaries for both responder and non-responder status. SOT patients showed higher utilities compared to HSCT patients in descriptive summaries for both responder and non-responder status.

**Mixed modelling**

The impact of treatment and response status on HSUV was formally assessed using a linear mixed effects model fitted to observed data. Random effects were included to reflect that each patient provides multiple values. The outcome $Y_i$ in the model was the crosswalk EQ-5D HSUV*;* following the notation of Verbeke & Molenberghs (Verbeke 2000 (113)):

$$\boldsymbol{Y_i} = X_i\boldsymbol{\beta} + Z_i\boldsymbol{b_i} + \boldsymbol{\varepsilon_i}$$

Where $X_i$ and $Z_i$ are the ($n_i$ x $p$) and ($n_i$ x $q$) matrices of known covariates, $\boldsymbol{\beta}$ is the p-dimensional vector of fixed effects, $\boldsymbol{b_i}$ is the $q$-dimension vector containing the random effects, and $\boldsymbol{\varepsilon_i}$ is an $n_i$-dimensional vector of residual components. In this framework, $\boldsymbol{b_i}$ follows a N(**0**, $D$) distribution with $D$ denoting a ($q$ x $q$) covariance matrix, and $\boldsymbol{\varepsilon_i}$ follows a N(**0**, $\sigma^2 I_i$) distribution with $I_i$ denoting a ($n_i$ x $n_i$) identity matrix. The only random effect included was a random intercept per subject, and so $\boldsymbol{b_i}$ followed a univariate normal distribution.

The following factors were included as fixed effects in the model:

- Treatment arm (IAT/maribavir)
- Response status at week 8 (response/no-response)
- The following nested models were fit, and relevant statistical outputs obtained:
- Only treatment arm as main effect

- Only response status as main effect
- Both treatment arm and response status main effects but no interaction (treatment arm + response)
- Both treatment arm and response status main effect and their interaction (Treatment arm x Response)
- In addition to the main effects, the baseline transplant type, baseline age and CMV disease status at baseline were considered as additional covariates in the model. Results were produced for models with and without additional covariates.
- The following statistics were output from the analysis:
- Goodness-of-fit statistics:
    - Akaike information criterion (AIC)
    - Bayesian information criterion (BIC)
- Type 3 tests of fixed effects
    - Degrees of freedom (numerator, denominator)
    - F value
    - p-value
- Likelihood ratio tests for the nested models with
    - Treatment effect
    - Progression effect
- Least square estimates
    - Estimate
    - Standard error
    - 95% CI of estimates

The results of Goodness of fit, Likelihood test and Type 3 test are presented in the following tables.

**Table 131: Mixed effects models: Goodness-of-fit statistics by model (smaller is better) without covariate for EQ-5D-5L UK crosswalk HSUVs (utilities)**

| Model | AIC | BIC |
|---|---|---|
| Treatment Arm | [redacted] | |
| **Response** | | |
| Treatment Arm + Response | | |
| Treatment Arm X Response | | |

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; EQ-5D-5L: EuroQoL Group 5-Dimension 5-Level; HSUV: Health state utility value; Denmark



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### Table 132: Likelihood ratio tests for nested models with treatment effect comparison -without covariates for EQ-5D-5L UK crosswalk HSUVs (utilities)

| Model Name | Model N | AIC | BIC | log Likelihood | Test | Likelihood Ratio | p-value |
|---|---|---|---|---|---|---|---|
| Treatment | [redacted] | | | | | | |
| Treatment+Response | | | | | | | |
| TreatmentxResponse | | | | | | | |

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; EQ-5D-5L: EuroQol Group 5-Dimension 5-Level; HSUV: Health state utility value; Denmark

### Table 133: Likelihood ratio tests for nested models with response effect comparison -without covariates for EQ-5D-5L UK crosswalk HSUVs (utilities)

| Model Name | Model N | AIC | BIC | log Likelihood | Test | Likelihood Ratio | p-value |
|---|---|---|---|---|---|---|---|
| Response | [redacted] | | | | | | |
| Treatment+Response | | | | | | | |
| TreatmentxResponse | | | | | | | |

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; EQ-5D-5L: EuroQol Group 5-Dimension 5-Level; HSUV: Health state utility value; Denmark

### Table 134: Type 3 tests of fixed effects by model-without covariates for EQ-5D-5L UK crosswalk HSUVs (utilities)

| Term | DF | F-value | p-value |
|---|---|---|---|
| **Treatment Arm** | [redacted] | | |
| **Treatment** | | | |
| **Response** | | | |
| **Response** | | | |
| **Treatment+Response** | | | |
| **Treatment** | | | |
| **Response** | | | |
| **TreatmentXResponse** | | | |
| **Treatment** | | | |
| **Response** | | | |
| **Treatment:Response interaction** | | | |

Abbreviations: DF: Degrees of freedom; EuroQol Group 5-Dimension 5-Level; HSUV: Health state utility value; Denmark



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**Table 135: Mixed effects models: Goodness-of-fit statistics by model (smaller is better) with covariates for EQ-5D-5L UK crosswalk HSUVs (utilities)**

| Model | AIC | BIC |
|---|---|---|
| Intercept only | [redacted] | |
| Age | | |
| Transplant Type | | |
| Age + Transplant Type | | |
| CMV disease status at baseline | | |
| Age + CMV disease status at baseline | | |
| Transplant Type + CMV disease status at baseline | | |
| Age + Transplant Type + CMV disease status at baseline | | |
| Treatment | | |
| Age + Treatment | | |
| Transplant Type + Treatment | | |
| Age + Transplant Type + Treatment | | |
| CMV disease status at baseline + Treatment | | |
| Age + CMV disease status at baseline + Treatment | | |
| Transplant Type + CMV disease status at baseline + Treatment | | |
| Age + Transplant Type + CMV disease status at baseline + Treatment | | |
| Response | | |
| Age + Response | | |
| **Transplant Type + Response** | | |
| Age + Transplant Type + Response | | |
| CMV disease status at baseline + Response | | |
| Age + CMV disease status at baseline + Response | | |
| Transplant Type + CMV disease status at baseline + Response | | |
| Age + Transplant Type + CMV disease status at baseline + Response | | |
| Treatment + Response | | |
| Age + Treatment + Response | | |
| Transplant Type + Treatment + Response | | |
| Age + Transplant Type + Treatment + Response | | |
| CMV disease status at baseline + Treatment + Response | | |
| Age + CMV disease status at baseline + Treatment + Response | | |
| Transplant Type + CMV disease status at baseline + Treatment + Response | | |
| Age + Transplant Type + CMV disease status at baseline + Treatment + Response | | |
| Treatment x Response | | |
| Age + Treatment x Response | | |
| Transplant Type + Treatment x Response | | |
| Age + Transplant Type + Treatment x Resp_wk8 | | |
| CMV disease status at baseline + Treatment x Response | | |
| Age + CMV disease status at baseline + Treatment x Response | | |
| Transplant Type + CMV disease status at baseline + Treatment x Response | | |
| Age + Transplant Type + CMV disease status at baseline + Treatment x Response | | |



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Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CMV: Cytomegalovirus; EQ-5D-5L: EuroQol Group 5-Dimension 5-Level; HSUV: Health state utility value; Denmark

**Table 136: Nested comparisons of models including all covariates for EQ-5D-5L UK crosswalk HSUVs (utilities)**

| Model | Number | Comparison | log-likelihood | df | LRT | p-value |
|---|---|---|---|---|---|---|
| Age + Transplant Type + CMV disease status at baseline + Treatment * Response | | | | | | |
| Age + Transplant Type + Treatment * Response | | | | | | |
| Age + CMV disease status at baseline + Treatment * Response | | | | | | |
| Transplant Type + CMV disease status at baseline +Treatment * Response | | | | | | |
| Age + Transplant Type + CMV disease status at baseline + Treatment + Response | | | | | | |
| Age + Transplant Type + CMV disease status at baseline + Treatment | | | | | | |
| Age + Transplant Type + CMV disease status at baseline + Response | | | | | | |

Abbreviations: CMV: Cytomegalovirus; DF: Degrees of freedom; EQ-5D-5L: EuroQol Group 5-Dimension 5-Level; HSUV: Health state utility value; LRT: Likelihood ratio test; UK: Denmark

**Table 137: Type 3 test of fixed effect models including all covariates for EQ5D UK crosswalk HSUVs (utilities)**

| Term | DF | F-value | p-value |
|---|---|---|---|
| **Treatment Arm** | | | |
| **Age** | | | |
| **Transplant Type** | | | |
| **CMV disease status at baseline** | | | |
| **Treatment** | | | |
| **Response** | | | |
| **Age** | | | |
| **Transplant Type** | | | |
| **CMV disease status at baseline** | | | |
| **Response** | | | |
| **Treatment+Response** | | | |
| **Age** | | | |
| **Transplant Type** | | | |
| **CMV disease status at baseline** | | | |
| **Treatment** | | | |
| **Response** | | | |
| **TreatmentXResponse** | | | |
| **Age** | | | |
| **Transplant Type** | | | |
| **CMV disease status at baseline** | | | |
| **Treatment** | | | |
| **Response** | | | |
| **Treatment:Response interaction** | | | |

Abbreviations: CMV: cytomegalovirus; DF; Degrees of Freedom; EQ-5D-5L: EuroQol Group 5-Dimension 5-Level; HSUV: Health state utility value; Denmark



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The remaining outputs of mixed modelling i.e., least square estimates of treatment and response effects with and without covariates are provided in Appendix O.

### Observation from mixed modelling of EQ-5D-5L Danish crosswalk HSUVs

The goodness of fit statistics, likelihood ratio test and type 3 tests for both types of modelling i.e., with and without covariates showed that response effect is significant but not the treatment effect (see Table 131, Table 132, Table 133). Transplant type as covariate added to response effect came out to be significant (Table 134). Hence the mixed modelling analysis did not establish a significant effect of treatment on utilities (Table 135). Response effect and transplant type were significant on utilities from this analysis.

### Time until definitive deterioration

The EQ-5D-5L domain specific data was further investigated by performing the TUDD analysis in each of the five domains - mobility, self-care, usual activity, pain/discomfort, anxiety/depression and for overall health. The reason was to observe if there is any trend of slow deterioration or improvement over time in QoL responses favoring one treatment over another. A sensitivity analysis was also performed by censoring patients at the last visit prior to rescue therapy use. Both the main and sensitivity analyses of TUDD failed to generate any significant hazard ratio, restricted mean difference favoring any particular treatment. The results are provided below for 'pain/discomfort' domain and remaining results of other domain and overall health including sensitivity analysis are provided in Table 138, Table 139, Table 140, Table 141 and Figures in Appendix O EQ5D5L analysis additional outputs.

**Table 138: Survival modelling estimates: TUDD in pain**

| | N | events | RMST | SE | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|
| IAT | [redacted] | | | | | |
| Maribavir | | | | | | |

Abbreviations: CI: Confidence interval; IAT: investigator-assigned anti-CMV treatment; RMST: Restricted mean survival time, SE: Standard error; TUDD: Time until definitive deterioration

**Table 139: Hazard ratio: TUDD in pain**

| HR | 95% CI for HR | p- value |
|---|---|---|
| 1.1 | [redacted] | |

Abbreviations: HR: Hazard ratio; TUDD: Time until definitive deterioration

**Table 140: Restricted Mean survival time difference: TUDD in pain**

| RMST difference (Maribavir -IAT) | Lower 95% CI | Upper 95% CI | p-value |
|---|---|---|---|
| -4.061 | [redacted] | | |

Abbreviations: CI: Confidence interval; IAT: investigator-assigned anti-CMV treatment; RMST: Restricted mean survival time, TUDD: Time until definitive deterioration
RMST is based on maximum follow up time 191 days

**Table 141: Assumptions-testing -Grambsch-Therneau test-TUDD in pain**

| Treatment | Chi-square | p-value |
|---|---|---|
| Maribavir | [redacted] | |

Abbreviations: TUDD: Time until definitive deterioration

[redacted]



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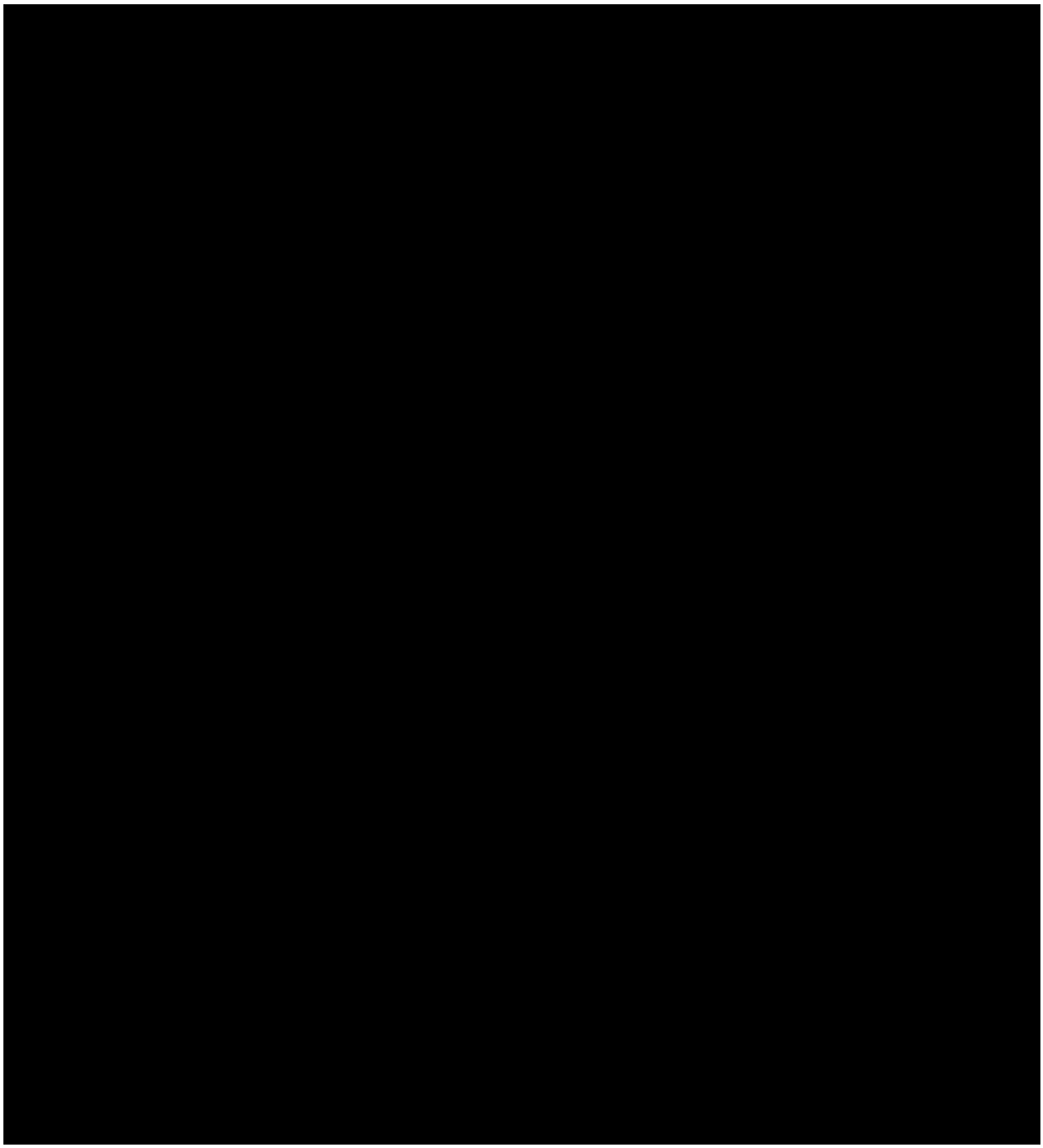

**Observations from EQ-5D-5L pain domain analysis (TUDD):**

The hazard ratios and restricted mean survival times of all five individual domains were not significant

It cannot be concluded that one treatment has a delayed deterioration of QoL scores compared to the other

**Overall recommendations from EQ-5D-5L analysis:**

The recommendation from statistical analysis of QoL was to use EQ-5D-5L utilities for response and no-response health status for the overall/pooled data and by transplant type as inputs to the CEM.

In particular, outputs from the mixed modelling indicated that transplant type and response status (i.e., csCMV or n-csCMV) had a significant effect on utilities and that treatment arm did not have a significant impact.



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For this reason, in the base case analysis, transplant and health state specific utility values at week 8 were selected for inclusion in the CEM.

A specific time point was preferred over a summary statistic from a broader time horizon (i.e., week 0 to 20) in order to align with the primary endpoint and therefore, the utility values of these summary statistics do not appropriately capture the impacts of health state on quality-of-life outcomes.

**Vignette study utilities**

| Health state descriptions | Mean (SD) N = 1020 | Median (N=1020) | Mean - after exclude speeders* (N = 942) | Mean - after excluding same value** (N = 879) | Mean - after excluding any inconsistencies*** (N=612) | Mean - after excluding speeders + same value + Nsc-CMV < CS-sCMV + CS-aCMV (N=738) **** |
|---|---|---|---|---|---|---|
| Clinically significant - Symptomatic | | | | | | |
| Clinically significant - Symptomatic + Graft-versus-host disease | | | | | | |
| Clinically significant - Symptomatic + Graft loss KIDNEY Transplant | | | | | | |
| Clinically significant - Symptomatic + Graft loss LUNG Transplant | | | | | | |
| Clinically significant - Asymptomatic | | | | | | |
| Clinically significant - Asymptomatic + Graft-versus-host disease | | | | | | |
| Clinically significant - Asymptomatic + Graft loss KIDNEY Transplant | | | | | | |
| Clinically significant - Asymptomatic + Graft loss LUNG Transplant | | | | | | |
| Non-clinically significant | | | | | | |
| Non-clinically significant + Graft-versus-host disease | | | | | | |
| Non-clinically significant + Graft loss KIDNEY Transplant | | | | | | |
| Non-clinically significant + Graft loss LUNG Transplant | | | | | | |



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# Appendix J Deterministic base case

**Table 142: Base case setting**

| Setting | Base case value/assumption | Justification |
|---|---|---|
| **CEM settings** | | |
| Analysis mode | Deterministic | |
| Time horizon | Lifetime | A 47-year time horizon was chosen to represent a lifetime model. The starting age of the cohort entering the model is 53 years old, leading to all patients being dead at the end of the model once they reach 100-years of age. The Age of the population align with the baseline patient profile in Study 303 and is assumed representative for the Danish population. See section 5. |
| Willingness-to-Pay (WTP) threshold | Arbitrary. The threshold can easily be modified on the model control sheet of the model. | N/A |
| Perspective | Danish Payer | In line with the methods from the Danish Medicines Council |
| Cost of maribavir (USD) | [redacted] | List price Provided by Takeda |
| Cohort size | 1,000 | N/A |
| Currency | DKK | Model takes a Danish perspective |
| Discount rate (costs and benefits) | In line with the methods of the Danish Medicines Council | See section 8 |
| Number of PSA simulations | 2,500 | The number of simulations was chosen to ensure cost and QALYs in the model achieve convergence |
| Cycle length | 4-week from year 0 to 3<br>Annual cycles from year 3 to lifetime | Study-303 CSR indicates that patients on treatment with maribavir achieve faster clearance compared with IAT, a 4-week cycle length was chosen to allow flexibility in the model to capture the benefit of this faster clearance. However, it should be noted in the base case the first transition events occur at week 8 to ensure the model aligns with the primary endpoint of the Study 303 trial.<br><br>To optimize model speed, it was decided that users would not require to track CMV status beyond year 3 in a sensitivity analysis and therefore annual cycles have been used from year 3 onwards |
| **Population** | | |
| Age | 53 years | |



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| Setting | Base case value/assumption | Justification |
|---|---|---|
| Weight (kg) | 74.80 | The population characteristics align with the baseline patient profile in Study 303 and is assumed equal to the Danish population. See section 5. |
| Sex (male, %) | 61 | |
| Average time since transplant (days) - SOT | 258 | Aligned with Study 303 |
| Average time since transplant (days) - HSCT | 73 | |
| % of SOT patients | 73% | The population characteristics align with what is presented in section 5 about the Danish population |
| % of HSCT patients | 27% | |
| **Treatment pathway** | | |
| Treatment arm | Maribavir then retreatment with IAT | Maribavir is the intervention investigated in Study 303; and in the base case retreatment will be with IAT though the model retains functionality to consider retreatment with maribavir which is included as a scenario |
| Comparator arm | IAT then retreatment with IAT | The comparator in Study 303 contains a mix of the four commonly used anti-CMV agents: valganciclovir, ganciclovir, foscarnet, and cidofovir); it is plausible that retreatment will be with IAT |
| **IAT treatment distribution (initial treatment and retreatment)** | | |
| Ganciclovir | 25.40% | The distribution of treatments used in Study 303, adjusted for patients on multiple therapies (see section 8) |
| Valganciclovir | 25.90% | |
| Foscarnet | 43.50% | |
| Cidofovir | 5.20% | |
| **Model structure** | | |
| Stage 1 Markov | 0-78 weeks | This time period was deemed appropriate by external experts (clinicians and health economists) participating in the advisory board (Takeda UK Ltd 2021), and supported by finding from OTUS |
| Stage 2 Markov (alive/dead model) | 78 weeks onwards | |
| **Cost and utility** | | |
| Total time on treatment (weeks)– Maribavir | 7.50 | Aligned with mean time on treatment (ToT) for maribavir in Study 303 |
| Total time on treatment (weeks) – IAT | 5.14 | Aligned with mean ToT for IAT in Study 303 |
| Quality of life measure | EQ-5D | In line with the Danish Medicines Council, EQ-5D was used as the measure of QoL. The sources used for the utility values were Study 303 and Vignette |
| Clearance effectiveness | Treatment specific clearance rates are used for initial treatment.<br>For retreatment, the clearance rates are the same as the initial treatment | In the base case it was agreed with Takeda that effectiveness of IAT in a retreatment setting will be the same as initial treatment. |



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| Setting | Base case value/assumption | Justification |
|---|---|---|
| Recurrence effectiveness | Time dependent recurrences<br>First recurrence (time in n-csCMV health state 0 to 12 weeks) – risk sourced from Study 303<br>First recurrence (time in n-csCMV health state greater than 12 weeks) – risk sourced from OTUS<br>Subsequent recurrences – risk taken from OTUS | Both Study 303 and OTUS provide evidence of decreasing rates of recurrence over time. Source of the 1st recurrence risk depends the initial treatment taken, on duration of time in the n-csCMV health state and recurrence number (i.e., first or subsequent recurrence) |

**Table 143: Base case input**

| Setting | Base case input selection/assumption | Justification | Source |
|---|---|---|---|
| **Treatment efficacy** | | | |
| Clearance and clinically significant recurrence | Clearance at week 8: Study 303 primary endpoint<br><br>Clearance > week 8: Study 303 IAT<br><br>1st Recurrence weeks 12-20: Study 303 & OTUS<br>Subsequent recurrences: OTUS | It was agreed with clinicians that clearance and recurrence rates would be similar in both SOT and HSCT patients. The ITT population preserves the randomisation for this important input parameter.<br>Benefit of maribavir over IAT was observed regardless of transplant type or IAT drug.<br><br>Clinically significant recurrence includes the requirement of treatment which was validated with clinicians at the Danish advisory board who explained that sometimes watching and waiting for a natural immune response is preferred over immediate treatment.<br><br>Study 303 and OTUS provide evidence of decreasing rates of recurrence and therefore time dependent recurrence rates are included in the model | Study 303 CSR report (23)<br><br>OTUS studies (Supplementary documentatoion)<br><br>Danish advisory board (Takeda Pharma A/S 2022) |
| **Adverse events** | | | |
| AE incidence rates – maribavir and IAT | Clinically important adverse events (maribavir or IAT) as determined by clinicians and treatment emergent AE incidence >=10% in either the maribavir or IAT arm | Incidence rates align with those seen in Study 303 and include a number of other events which clinicians deemed clinically relevant | Study 303 IPD report (42) |
| AE costs – maribavir and IAT | Costs for each AE is based on the Danish DRG 2022 system | Model takes a Danish payer perspective and thus uses the Danish DRG 2022 system | DRG 2022 (58) |

| Setting | Base case input selection/assumption | Justification | Source |
|---|---|---|---|
| AE disutility – maribavir and IAT | AE disutility was sourced from the literature, with studies assumed to have presented the disutility of chronic conditions over one year unless otherwise specified<br><br>Utility decrement was adjusted for duration of each adverse event type | EQ-5D utility decrements sourced from Danish tariffs to align with guidelines from the Danish Medicine Council.<br><br>When utility decrement was unavailable for an adverse event type, a proxy disease area was used. | *Sullivan, Slejko et al. (2011)* (51), *Nafees, Lloyd et al. (2017)*(53), *Tolley, Goad et al. (2013)*(56), *Bullement, Nathan et al. (2019)*(54), *Beusterien, Davies et al. (2010)*(55), *(Nafees, Stafford et al. 2008)*(71), *Ossa, Briggs et al. (2007)*(52) |
| **Costs** | | | |
| Cyclical 4-week acquisition costs – maribavir | [redacted] | The Danish list price is provided by Takeda and is based on the US list price of $50,000 for an 8-week treatment course provided by Takeda. | Provided by Takeda |
| Cyclical 4-week acquisition costs – all IAT drugs | Based on list prices sourced from medicinpriser.dk<br><br>Cost of foscarnet is estimated based on AMKP price provided by the Danish Medicine Council. | Model takes a Danish payer perspective and thus uses medicinpriser.dk, DRG 2022, and labportal.rh.dk | Method guidelines from the Danish Medicines Council (44) |
| Administration unit costs | DRG 2022 | | DRG 2022 (58) |
| Monitoring unit costs | Labportal.rh.dk | | Labportal.rh.dk (59) |
| Monitoring frequency – ganciclovir, valganciclovir, foscarnet | Medicines.org | Model takes a Danish payer perspective and thus uses costs derived from medicinpriser.dk | Medicines.org (2020)(114) Medicinpriser.dk (57) |
| Monitoring frequency – cidofovir | Gilead sciences | Unavailable in medcicines.org and therefore the manufacturers recommendations have been used | Gilead Sciences Inc. (2010) (72) |
| Monitoring frequency - maribavir | Medicines.org – same as valganciclovir | Valganciclovir is the only treatment in the IAT group that is an oral drug, and as maribavir is also administered orally it is assumed to have the same monitoring requirements | Assumption |
| Health resource utilisation (HRU) - SOT (hospitalisations only) | By health state and transplant type | Aligns with Study 303 | Study 303 IPD report (42) |
| Health resource utilisation (HRU) – HSCT (hospitalisations only) | By health state and transplant type | Aligns with Study 303 | Study 303 IPD report (42) |
| Health resource utilisation unit costs (HRU) | DRG 2022 | Model takes a Danish payer perspective and thus uses DRG 2022 | DRG 2022 (58) |
| **Disease complications** | | | |



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| Setting | Base case input selection/assumption | Justification | Source |
|---|---|---|---|
| Graft loss – baseline transplant distribution | ITT with "Other" transplant calculated as 1-sum (named transplants). Entire SOT population is used – not treatment specific | Aligns with Study 303 | Study 303 IPD report (42) |
| 4-week probability of graft loss | Hakimi et al. 2017 –L-CMV-6M cohort (infection occurring 6 or more months post-transplant), health state specific | While Study 303 did not observe any graft loss, clinicians indicated during the advisory board that it is an important consideration, therefore values from the literature were used. In the absence of data comparing a cohort with active CMV vs cleared CMV, a comparison of patients who have had CMV versus those patients who have never had CMV is used to estimate risk of graft loss by health state | Hakimi, Aballea et al. (2017) (13) |
| Retransplant costs | DRG 2022 Costs. Retransplant costs are assumed to be the same as initial transplant costs | Cost for retransplant are not available on the DRG 2022 system | DRG 2022 (58) |
| Retransplant disutility | Vignette study | There was no graft loss in Study 303 and therefore values are sourced from the vignette study data<br>To capture the lifetime impact of a graft loss event, the utility decrement is applied for a lifetime after a graft loss event has occurred | Vignette Study (Supplementary documentation) |
| Retransplant mortality | Literature. The HR for "other" transplants is a weighted average of the named transplant HRs, using the baseline transplant distributions as the weight | Assumes increase in mortality in the base case for patients who have retransplant | Miller, Clarke et al. (2019) (62), Panchal, Muskovich et al. (2015)(63), (Kawut, Lederer et al. 2008)(64), Kim, Larson et al. (2010) (65) |
| Proportion of patients on lifetime dialysis | Turned off in base case | There is a lack of literature evidence to inform the correct proportion to use when including lifetime dialysis | N/A |
| Annual cost of dialysis | DRG 2022 | Model takes a Danish payer perspective and thus uses DRG 2022 | DRG 2022 (58) |
| Years of dialysis | Based on data request from Takeda Pharma A/S to Scandiatransplant.org | Aligns with the Danish population used in the base case and their average time on dialysis | Scandiatransplant.org |
| Hazard ratio - dialysis mortality | Literature (turned off in base case) | Assumed there is no patient on permanent dialysis in the base | Rayner, Pisoni et al. (2004) (66) |



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| Setting | Base case input selection/assumption | Justification | Source |
|---|---|---|---|
| | | case. In a scenario analysis when a proportion of patients are on permanent dialysis, literature hazard rates for mortality are used to estimate mortality in patients who have had dialysis. | |
| Dialysis disutility | Literature | Literature value is used to inform a NICE guideline on the cost-effectiveness of haemodialysis treatment | Liem, Bosch et al. (2008) (68) (used in NICE NG107) |
| 4-week probability of GvHD event | Literature (turned off in base case) | Turned off in base case as there is limited evidence for the causal relationship that CMV causes GvHD.<br><br>However, values included for GvHD are sourced from the literature and are included in a scenario analysis | Hahn, McCarthy et al. (2008) (48), Cantoni, Hirsch et al. (2010)(49) |
| GvHD costs | NICE TA591 (turned off in base case) | | (NICE 2019)(43) |
| GvHD disutility | Literature (turned off in base case) | | (NICE 2019) (43),Pidala, Kurland et al. (2011)(69), Ara and Brazier (2008)(115) |
| 4-week probability of leukaemia relapse | Haematological Malignancy Research Network (HMRN) (turned off in base case) | Turned off in base case to ensure the model retains focus on CMV | HMRN(50) |
| Leukaemia relapse cost | NICE TA451 (turned off in base case) | | (NICE 2017) (116) |
| Leukaemia disutility | Literature (turned off in base case) | | Leunis et. al. 2014 (95), Ara et al. 2011 (70) |
| **Utility** | | | |
| EQ-5D utility value – maribavir and IAT (week 0-78) | Vignette and Study 303 | Vignette and Study 303 (transplant and health state specific) were used as the IPD analysis indicated that transplant type and response status have a significant impact on QoL, while the treatment arm did not. | Study 303 IPD report (42) |
| Background utility 78 week onwards (at week 20 utility values) | Study 303. The difference between the Danish general population utility and week 20 SOT and HSCT utility values were used | Assumed most representative for Danish population | Study 303 IPD report (42), Jensen et al. (2021) (67) |
| **Mortality** | | | |
| Mortality (weeks 0-8) | Transplant specific<br><br>Study 303 pooled maribavir and IAT mortality by transplant type | Danish advisory board participants agreed that Study 303 did not indicate role of treatment on mortality.<br><br>Danish advisory board participants also advised the underlying disease is more important. | Study 303 IPD report (42)<br><br>Danish advisory board (Takeda Pharma A/S 2022) |



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| Setting | Base case input selection/assumption | Justification | Source |
|---|---|---|---|
| Mortality (weeks 8 to 78) | Study 303, Health state specific.: csCMV (SOT), csCMV(HSCT), n-csCMV(SOT), n-csCMV (HSCT) | Health state specific mortality was incorporated to better reflect outcomes associated with CMV status | |
| General population mortality – HSCT (week 78 onwards) | HMRN for year 1 to 5 Survival curve extrapolations of Martin et al. 2010 for year 5 onwards | To account for the unavailability of HMRN data after year 5, survival data from Martin et al. (2010) is extrapolated to inform HSCT background mortality estimates. For SOT patients an alternative method was incorporated which leverages a comprehensive data source from the NHS. Linear extrapolation was assumed between years | (NICE 2019) (43), Martin et. al 2010 (61) |
| General population mortality – SOT (week 78 onwards) | NHS Organ Donation and Transplantation Annual Activity Report: Survival Rates Following Transplantation 2020/21 | | Danmarks statistic (47), NHS Blood and Transplant (2021) (46) |



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# Appendix K Deterministic sensitivity analyses

**Table 144: Summary of DSA parameters**

| Parameter | Base case value | Variation direction | Variation type | Variation value | Method of variation |
|---|---|---|---|---|---|
| **Transition probability** | | | | | |
| Clearance maribavir (SOT and HSCT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Recurrence maribavir (SOT and HSCT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Clearance IAT (SOT and HSCT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Recurrence IAT (SOT and HSCT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Clearance maribavir (SOT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Clearance maribavir (HSCT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Recurrence maribavir (SOT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Recurrence maribavir (HSCT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Clearance IAT (SOT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Clearance IAT (HSCT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Recurrence IAT (SOT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Recurrence IAT (HSCT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| **Model Settings** | | | | | |
| Time Horizon | 47 | Lower<br>Upper | Absolute | 30<br>50 | Assumption |



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| Parameter | Base case value | Variation direction | Variation type | Variation value | Method of variation |
|---|---|---|---|---|---|
| Discount rate (costs) | 3.5% | Lower<br>Upper | Absolute | 0.00%<br>8.00% | Assumption |
| Discount (benefits) | 3.5% | Lower<br>Upper | Absolute | 0.00%<br>8.00% | Assumption |
| **Population** | | | | | |
| Age | 53 | Lower<br>Upper | Absolute | 52<br>54 | 95% CI |
| Proportion male | 60.5% | Lower<br>Upper | Absolute | 0.554<br>0.656 | 95% CI |
| Weight (kg) | 75 | Lower<br>Upper | Absolute | 72.89<br>76.71 | 95% CI |
| Median time (days) since transplant – SOT | 258 | Lower<br>High | Percent | 80%<br>120% | 20% in both directions |
| Median time (days) since transplant – HSCT | 73 | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Proportion SOT | 73% | Lower<br>Upper | Percent | 53%<br>93% | 20% in both directions |
| **Structure** | | | | | |
| Stage 2 Markov begins (week) | 78 | Lower<br>Upper | Absolute | 24<br>104 | Assumption |
| **Mortality** | | | | | |
| Mortality from week 0 to 8 (SOT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Mortality from week 8 to 78 (SOT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Mortality from week 0 to 8 (HSCT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Mortality from week 8 to 78 (HSCT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| **Costs** | | | | | |
| Number of IV days ( ganciclovir) | 28 | Lower<br>Upper | Absolute | 23<br>33 | 95% CI |
| | 4 | Lower | Absolute | 3 | |



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| Parameter | Base case value | Variation direction | Variation type | Variation value | Method of variation |
|---|---|---|---|---|---|
| Number of IV days (cidofovir) | | Upper | | 5 | 95% CI |
| Number of IV days (foscarnet) | 28 | Lower | Absolute | 23 | 95% CI |
| | | Upper | | 33 | |
| Drug acquisition costs (maribavir) | [redacted] | Lower | Percent | 80% | 20% in both directions |
| | | Upper | | 120% | |
| Drug acquisition costs (all IAT drugs) | N/A (grouped variation) | Lower | Percent | 80% | 20% in both directions |
| | | Upper | | 120% | |
| IV cost per day | 2513 | Lower | Absolute | 1.626 kr. | 95% CI |
| | | Upper | | 3.590 kr. | |
| Healthcare resource use (SOT) | N/A (grouped variation) | Lower | Percent | 80% | 20% in both directions |
| | | Upper | | 120% | |
| Healthcare resource use (HSCT) | N/A (grouped variation) | Lower | Percent | 80% | 20% in both directions |
| | | Upper | | 120% | |
| Healthcare resource use (SOT and HSCT) | N/A (grouped variation) | Lower | Percent | 80% | 20% in both directions |
| | | Upper | | 120% | |
| Healthcare resource use unit cost | N/A (grouped variation) | Lower | Percent | 80% | 20% in both directions |
| | | Upper | | 120% | |
| Time on treatment (Maribavir) (weeks) | [redacted] | Lower | Absolute | [redacted] | 95% CI |
| | | Upper | | | |
| Time on treatment (IAT) (weeks) | | Lower | Absolute | | 95% CI |
| | | Upper | | | |
| IAT discontinuation | | Lower | Absolute | | 95% CI |
| | | Upper | | | |
| **Adverse events** | | | | | |
| Cost per event | N/A (grouped variation) | Lower | Percent | 80% | 20% in both directions |
| | | Upper | | 120% | |
| Utility decrement per event | N/A (grouped variation) | Lower | Percent | 80% | 20% in both directions |
| | | Upper | | 120% | |
| Duration per event | N/A (grouped variation) | Lower | Percent | 80% | 20% in both directions |
| | | Upper | | 120% | |



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| Parameter | Base case value | Variation direction | Variation type | Variation value | Method of variation |
|---|---|---|---|---|---|
| Incidence (maribavir) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Incidence (IAT) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| **Disease complications** | | | | | |
| Graft loss risk (csCMV) | [redacted] | Lower<br>Upper | Absolute | [redacted] | 95% CI |
| Graft loss risk (n-csCMV) | | Lower<br>Upper | Absolute | | 95% CI |
| Graft loss costs | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Graft loss utility decrement | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| **Utility** | | | | | |
| All utilities | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Maribavir (all utility) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| IAT (all utility) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Maribavir (SOT utility only) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| IAT (SOT utility only) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| Maribavir (HSCT utility only) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| IAT (HSCT utility only) | N/A (grouped variation) | Lower<br>Upper | Percent | 80%<br>120% | 20% in both directions |
| | [redacted] | Lower | Absolute | [redacted] | 95% CI |



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| Parameter | Base case value | Variation direction | Variation type | Variation value | Method of variation |
|---|---|---|---|---|---|
| Background utility (at week 20 - SOT) | | Upper | | [redacted] | |
| Background utility (at week 20 - HSCT) | [redacted] | Lower<br>Upper | Absolute | [redacted] | 95% CI |

The +/- 20% in the table is chosen as a standardized value to show sensitivity in the deterministic sensitivity analysis.



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## Table 145: One-way sensitivity analyses results

| Parameter Group | Parameter Name | Variation Type | Variation Direction | Variation Value | Intervention | | | Comparator | | | Incremental | | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Costs | Life Years | QALYs | Costs | Life Years | QALYs | Costs | QALYs | |
| Base Case | - | - | - | - | [redacted] | | | | | | | | |
| Transition Probability | Maribavir clearance | Percent | Lower | 0,80 | | | | | | | | | |
| Transition Probability | Maribavir clearance | Percent | Upper | 1,20 | | | | | | | | | |
| Transition Probability | First recurrence | Percent | Lower | 0,80 | | | | | | | | | |
| Transition Probability | First recurrence | Percent | Upper | 1,20 | | | | | | | | | |
| Transition Probability | IAT Clearance | Percent | Lower | 0,80 | | | | | | | | | |
| Transition Probability | IAT Clearance | Percent | Upper | 1,20 | | | | | | | | | |
| Transition Probability | Second recurrence | Percent | Lower | 0,80 | | | | | | | | | |
| Transition Probability | Second recurrence | Percent | Upper | 1,20 | | | | | | | | | |
| Model Settings | Time Horizon | Absolute | Lower | 30,00 | | | | | | | | | |
| Model Settings | Time Horizon | Absolute | Upper | 50,00 | | | | | | | | | |
| Model Settings | Discount Cost | Absolute | Lower | 0,00 | | | | | | | | | |
| Model Settings | Discount Cost | Absolute | Upper | 0,08 | | | | | | | | | |
| Model Settings | Discount Benefits | Absolute | Lower | 0,00 | | | | | | | | | |
| Model Settings | Discount Benefits | Absolute | Upper | 0,08 | | | | | | | | | |
| Population | Age | Absolute | Lower | 51,62 | | | | | | | | | |
| Population | Age | Absolute | Upper | 54,38 | | | | | | | | | |
| Population | Proportion Male | Absolute | Lower | 0,55 | | | | | | | | | |
| Population | Proportion Male | Absolute | Upper | 0,66 | | | | | | | | | |
| Population | Weight (kg) | Absolute | Lower | 72,89 | | | | | | | | | |
| Population | Weight (kg) | Absolute | Upper | 76,71 | | | | | | | | | |
| Population | Time since transplant | Percent | Lower | 0,80 | | | | | | | | | |
| Population | Time since transplant | Percent | Upper | 1,20 | | | | | | | | | |
| Population | Time since transplant | Percent | Lower | 0,80 | | | | | | | | | |

| | | | | | [redacted] |
|---|---|---|---|---|---|
| Population | Time since transplant | Percent | Upper | 1,20 | |
| Population | Proportion SOT | Percent | Lower | 0,80 | |
| Population | Proportion SOT | Percent | Upper | 1,20 | |
| Structure | Phase 2 Markov week | Absolute | Lower | 52,00 | |
| Structure | Phase 2 Markov week | Absolute | Upper | 104,00 | |
| Mortality | Mortality from week 0 to 8 (SOT) | Percent | Lower | 0,80 | |
| Mortality | Mortality from week 0 to 8 (SOT) | Percent | Upper | 1,20 | |
| Mortality | Mortality from week 8 to 78 (SOT) | Percent | Lower | 0,80 | |
| Mortality | Mortality from week 8 to 78 (SOT) | Percent | Upper | 1,20 | |
| Mortality | Mortality from week 0 to 8 (HSCT) | Percent | Lower | 0,80 | |
| Mortality | Mortality from week 0 to 8 (HSCT) | Percent | Upper | 1,20 | |
| Mortality | Mortality from week 8 to 78 (HSCT) | Percent | Lower | 0,80 | |
| Mortality | Mortality from week 8 to 78 (HSCT) | Percent | Upper | 1,20 | |
| Costs | Number of IV days (induction, ganciclovir) | Absolute | Lower | 22,51 | |
| Costs | Number of IV days (induction, ganciclovir) | Absolute | Upper | 33,49 | |
| Costs | Number of IV days (induction, cidofovir) | Absolute | Lower | 3,22 | |
| Costs | Number of IV days (induction, cidofovir) | Absolute | Upper | 4,78 | |



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| | | | | | |
|---|---|---|---|---|---|
| Costs | Number of IV days (induction, foscarnet) | Absolute | Lower | 22,51 | [redacted] |
| Costs | Number of IV days (induction, foscarnet) | Absolute | Upper | 33,49 | |
| Costs | Drug acquisition costs (induction, maribavir) | Percent | Lower | 0,80 | |
| Costs | Drug acquisition costs (induction, maribavir) | Percent | Upper | 1,20 | |
| Costs | Drug acquisition costs (induction, all IAT drugs) | Percent | Lower | 0,80 | |
| Costs | Drug acquisition costs (induction, all IAT drugs) | Percent | Upper | 1,20 | |
| Costs | IV cost per day | Absolute | Lower | 1626,28 | |
| Costs | IV cost per day | Absolute | Upper | 3589,58 | |
| Costs | Healthcare resource use (SOT) | Percent | Lower | 0,80 | |
| Costs | Healthcare resource use (SOT) | Percent | Upper | 1,20 | |
| Costs | Healthcare resource use (HSCT) | Percent | Lower | 0,80 | |
| Costs | Healthcare resource use (HSCT) | Percent | Upper | 1,20 | |
| Costs | Healthcare resource use (SOT and HSCT) | Percent | Lower | 0,80 | |
| Costs | Healthcare resource use (SOT and HSCT) | Percent | Upper | 1,20 | |
| Costs | Healthcare resource use unit cost | Percent | Lower | 0,80 | |



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| | | | | |
|---|---|---|---|---|
| Costs | Healthcare resource use unit cost | Percent | Upper | 1,20 |
| Costs | Time on treatment (Maribavir) | Absolute | Lower | 7,29 |
| Costs | Time on treatment (Maribavir) | Absolute | Upper | 7,72 |
| Costs | Time on treatment (IAT) | Absolute | Lower | 4,69 |
| Costs | Time on treatment (IAT) | Absolute | Upper | 5,63 |
| Costs | IAT Discontinuation | Percent | Lower | 0,80 |
| Costs | IAT Discontinuation | Percent | Upper | 1,20 |
| Costs | Patient time cost | Percent | Lower | 0,80 |
| Costs | Patient time cost | Percent | Upper | 1,20 |
| Costs | Transportation cost | Percent | Lower | 0,80 |
| Costs | Transportation cost | Percent | Upper | 1,20 |
| Costs | Hours of IV infusions per cycle | Percent | Lower | 0,80 |
| Costs | Hours of IV infusions per cycle | Percent | Upper | 1,20 |
| Costs | Number of IV trips to hospital | Percent | Lower | 0,80 |
| Costs | Number of IV trips to hospital | Percent | Upper | 1,20 |
| Costs | Proportion of patients already hospitalised | Percent | Lower | 0,80 |
| Costs | Proportion of patients already hospitalised | Percent | Upper | 1,20 |
| Adverse events | Cost per event | Percent | Lower | 0,80 |
| Adverse events | Cost per event | Percent | Upper | 1,20 |



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| | | | | | |
|---|---|---|---|---|---|
| Adverse events | Utility decrement per event | Percent | Lower | 0,80 | [redacted] |
| Adverse events | Utility decrement per event | Percent | Upper | 1,20 | |
| Adverse events | Duration per event | Percent | Lower | 0,80 | |
| Adverse events | Duration per event | Percent | Upper | 1,20 | |
| Adverse events | Incidence (maribavir) | Percent | Lower | 0,80 | |
| Adverse events | Incidence (maribavir) | Percent | Upper | 1,20 | |
| Adverse events | Incidence (IAT) | Percent | Lower | 0,80 | |
| Adverse events | Incidence (IAT) | Percent | Upper | 1,20 | |
| Disease complication | Graft loss risk (csCMV) | Absolute | Lower | 0,00 | |
| Disease complication | Graft loss risk (csCMV) | Absolute | Upper | 0,01 | |
| Disease complication | Graft loss risk (n-csCMV) | Absolute | Lower | 0,00 | |
| Disease complication | Graft loss risk (n-csCMV) | Absolute | Upper | 0,00 | |
| Disease complication | Graft loss costs | Percent | Lower | 0,80 | |
| Disease complication | Graft loss costs | Percent | Upper | 1,20 | |
| Disease complication | Graft loss utility decrement | Percent | Lower | 0,80 | |
| Disease complication | Graft loss utility decrement | Percent | Upper | 1,20 | |
| Utility | Maribavir (all utility) | Percent | Lower | 0,80 | |
| Utility | Maribavir (all utility) | Percent | Upper | 1,20 | |
| Utility | IAT (all utility) | Percent | Lower | 0,80 | |
| Utility | IAT (all utility) | Percent | Upper | 1,20 | |
| Utility | Maribavir (SOT utility only) | Percent | Lower | 0,80 | |
| Utility | Maribavir (SOT utility only) | Percent | Upper | 1,20 | |



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| | | | | |
|---|---|---|---|---|
| Utility | IAT (SOT utility only) | Percent | Lower | 0,80 |
| Utility | IAT (SOT utility only) | Percent | Upper | 1,20 |
| Utility | Maribavir (HSCT utility only) | Percent | Lower | 0,80 |
| Utility | Maribavir (HSCT utility only) | Percent | Upper | 1,20 |

[redacted]



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# Appendix L Probabilistic sensitivity analyses

Distributions were applied to the parameters in the model depending on their characteristics, with probabilities assigned a beta distribution (due to values being bounded between 0 and 1), costs assigned a gamma distribution, and other parameters assigned a normal or log-normal distribution as appropriate (shown in Table 146. The mean disutility values were multiplied by -1 to ensure that they were positive and a beta distribution could be used.

**Table 146: Probabilistic sensitivity analysis**

| Parameter group | Parameter name | Distribution | Values located |
|---|---|---|---|
| **Population characteristics** | **Age** [+] | Normal | Table 36 |
| | Weight (kg) | | |
| | Sex (Male, %) | | |
| | Time since transplant | Log-normal | |
| **Other parameter groups** | Rate of discontinuation | Beta | Table 73 |
| | Time on treatment | Log-normal | |
| **Treatment efficacy** | CMV clearance | Beta | Table 41 |
| | CMV clinically significant recurrence | | Table 29 and Table 30 |
| **Mortality** | Maribavir | Beta | Section 8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice |
| | IAT | | |
| | csCMV | | |
| | n-csCMV | | |
| **IAT distribution** | Ganciclovir | Dirichlet | Table 72 |
| | Valganciclovir | | |
| | Foscarnet | | |
| | Cidofovir | | |
| **Number of IV days** | Ganciclovir | Normal | Table 74 |
| | Foscarnet | | |
| | Cidofovir | | |
| **Costs** | Administration costs | Gamma | Se section 8.5 Resource use and costs |
| | Monitoring costs | | Table 78 |
| **Monitoring frequency** | Maribavir | Normal | Table 77 |
| | Ganciclovir | Normal | |
| | Valganciclovir | Normal | |
| | Foscarnet | Normal | |
| | Cidofovir | Normal | |
| **Health resource utilisation** | HRU utilisation | Log-Normal | Table 79 |
| | Costs | Gamma | Table 80 |
| **Graft loss** | Baseline transplant type | Dirichlet | Table 60 |
| | Risk of graft loss | Beta | Table 59 |
| | Transplant costs | Gamma | Table 81 |
| | Transplant disutility | Beta | Table 70 |
| | Transplant mortality - relative risk | Log-normal | Table 59 |



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| Parameter group | Parameter name | Distribution | Values located |
|---|---|---|---|
| | Proportion of patients on lifetime dialysis | Beta | Table 61 |
| | Annual cost of dialysis | Gamma | Table 81 |
| | Years of dialysis | Log-normal | Table 61 |
| | Hazard ratio - dialysis mortality | Log-normal | |
| | Dialysis disutility | Beta | Table 70 |
| GvHD † | Risk | Beta | See section 8. Health economic analysis |
| | Cost | Gamma | See section 8. Health economic analysis |
| | Disutility | Beta | See section 8.4 |
| Utilities | Maribavir EQ-5D | Beta | Table 69 |
| | IAT EQ-5D | Beta | |
| | Background utility (week 78 onwards) | Beta | See section 8.4.2 Health state utility values used in the health economic model |
| Adverse events | Costs | Gamma | Table 82 |
| | Disutility | Beta | Table 71 |
| | Duration | Normal | |
| | Incidence – all drugs | Beta | Table 63 |
| General population mortality | SOT | Beta | See section 8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice |
| | HSCT | Beta | See section 8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice |

**Table 147: PSA cost-effectiveness result per patient (SOT)**

| Outcome | Maribavir | IAT | Incremental |
|---|---|---|---|
| Costs | [redacted] | | |
| QALYs total | | | |
| ICER (DKK/QALY) | | | |



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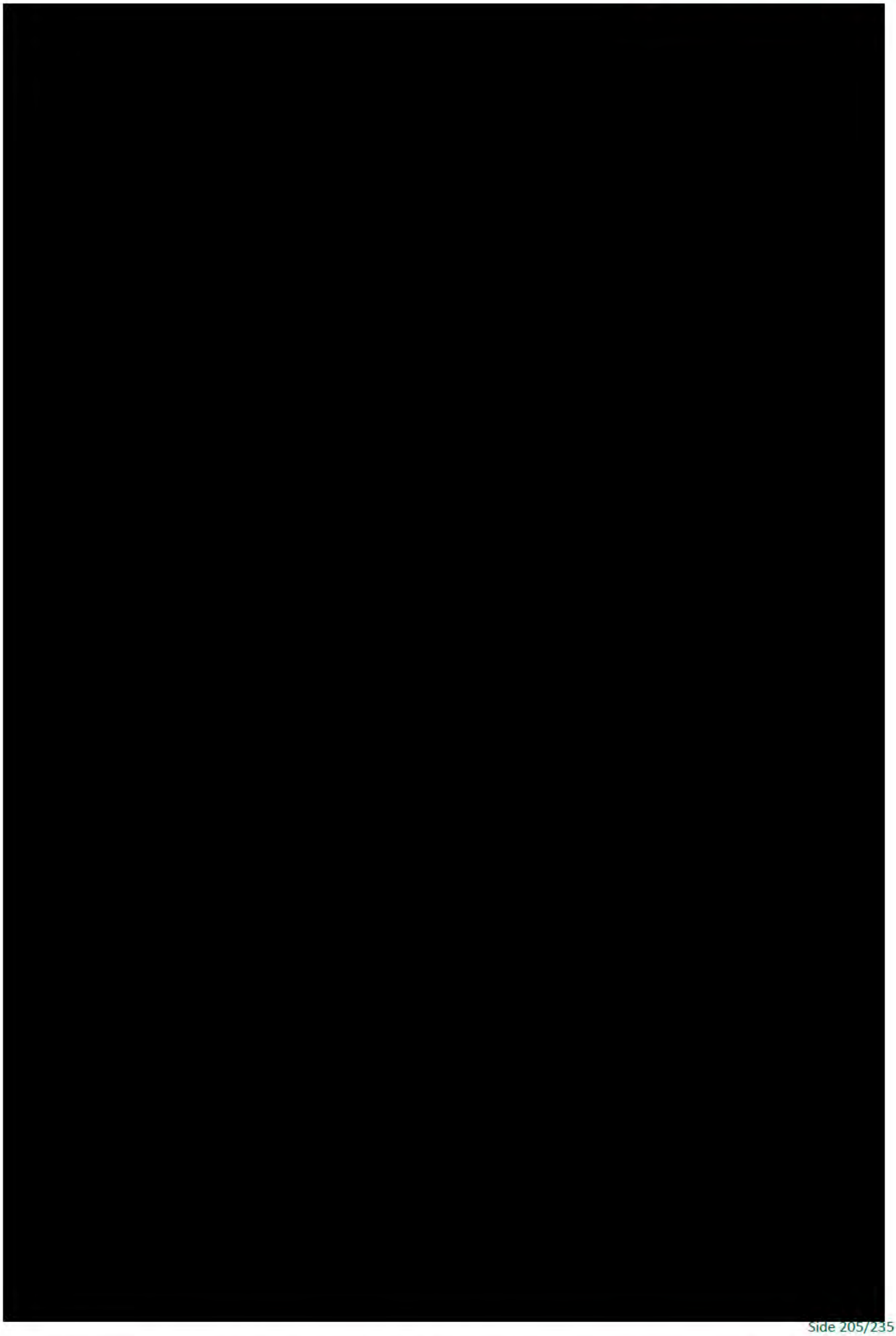



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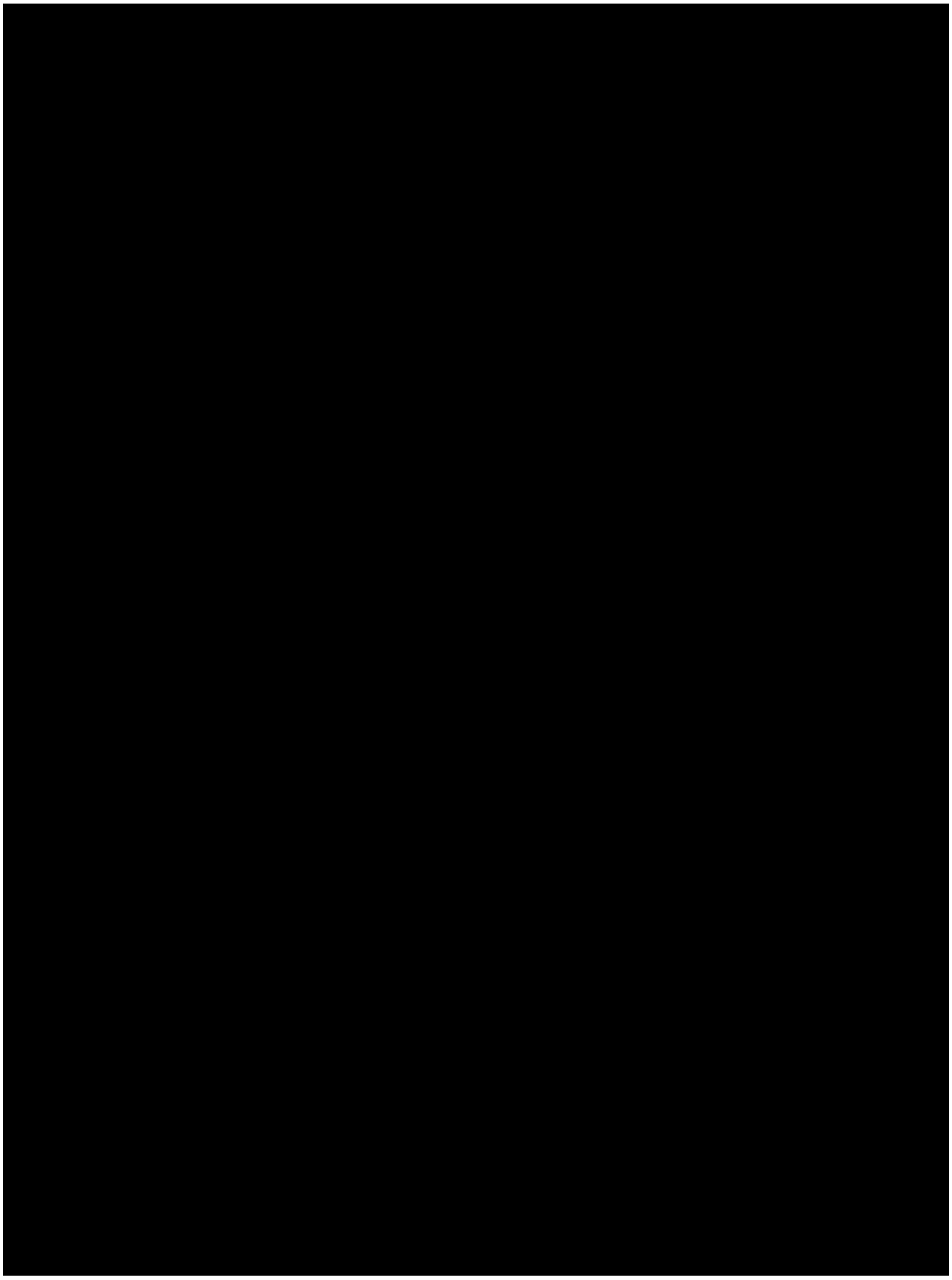



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# Appendix M Validation of model

**Internal validity**

Clinical and health economic experts continually guided the model development from the conceptual stage until the finalisation of the core model. To verify the results of the cost-effectiveness model, internal and external quality control procedures have been undertaken to ensure that the mathematical calculations were performed correctly and were consistent with the model's specifications. The verification exercise has been completed by senior analysts employed by Parexel who were not involved with model development. This process included:

- Review of formula/calculations in the model, to ensure that they are functioning as expected
- Review of data inputs included in the model
- Sense check of model results and key outcomes
- Extreme value testing to ensure that changes to the model inputs and settings impact the results as expected

**External validity**

The model results were validated with the Study 303 trial results. At week 8, the clearance numbers generated by the model [redacted] are aligned with the primary endpoint of Study 303. For clinically significant recurrence, in the trial, [redacted] of patients had a clinically relevant recurrence in the maribavir arm and [redacted] of patients had a clinically relevant recurrence in the IAT arm. The model results are very closely aligned with the recurrence endpoint where [redacted] of patients had a recurrence in the maribavir arm and [redacted] of patients had a recurrence in the IAT arm. The small difference in the recurrence endpoint is likely to be driven by the implementation of health state mortality from week 8 onwards rather than the direct mortality values observed in Study 303 between 8 and 20.



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# Appendix N Transition matrices

The tables below summarise the transition probabilities applied in the model (using SOT mortality for the Week 0 to 4 period), with both the clearance and recurrence rates outlined in section 8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice. adjusted for the mortality rates also outlined in section 8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice.

**Table 149: Maribavir – Week 0 to 4 transition probabilities (SOT)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|
| csCMV | | | |
| n-csCMV | | | |
| Dead | | | |

**Table 150: Maribavir – Week 0 to 4 transition probabilities (HSCT)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|
| csCMV | | | |
| n-csCMV | | | |
| Dead | | | |

**Table 151: IAT – Week 0 to 4 transition probabilities (SOT)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|
| csCMV | | | |
| n-csCMV | | | |
| Dead | | | |

**Table 152: IAT – Week 0 to 4 transition probabilities (HSCT)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|
| csCMV | | | |
| n-csCMV | | | |
| Dead | | | |

**Table 153: Maribavir – Week 4 to 8 transition probabilities (SOT)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|
| csCMV | | | |
| n-csCMV | | | |
| Dead | | | |

**Table 154: Maribavir – Week 4 to 8 transition probabilities (HSCT)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|
| csCMV | | | |
| n-csCMV | | | |
| Dead | | | |

**Table 155: IAT – Week 4 to 8 transition probabilities (SOT)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|
| csCMV | | | |
| n-csCMV | | | |
| Dead | | | |

**Table 156: IAT – Week 4 to 8 transition probabilities (HSCT)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|

| | |
|---|---|
| csCMV | [redacted] |
| n-csCMV | |
| Dead | |

For the transition probabilities for the 1st recurrence, the clearance probabilities are treatment specific and time dependent. The recurrence probabilities are the same for 4 weeks to 12 weeks since clearance, then they are the same when time since clearance is 16 weeks to 20 weeks and then there is a single transition probability for 24 weeks onwards.

**Table 157: 1st recurrence (Time since clearance: 4 to 12 weeks) transition probabilities (most recent treatment maribavir)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|
| csCMV | [redacted] | | |
| n-csCMV | | | |
| Dead | | | |

**Table 158: 1st recurrence (Time since clearance: 16 to 24 weeks) transition probabilities (most recent treatment maribavir)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|
| csCMV | [redacted] | | |
| n-csCMV (16-20 weeks) | | | |
| n-csCMV (24 weeks onwards) | | | |
| Dead | | | |

**Table 159: 1st recurrence (Time since clearance: 4 to 12 weeks) transition probabilities (most recent treatment IAT)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|
| csCMV | [redacted] | | |
| n-csCMV | | | |
| Dead | | | |

**Table 160: 1st recurrence (Time since clearance: 16 to 24 weeks) transition probabilities (most recent treatment IAT)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|
| csCMV | [redacted] | | |
| n-csCMV (16-20 weeks) | | | |
| n-csCMV (24 weeks onwards) | | | |
| Dead | | | |

For the transition probabilities for 2nd recurrence, the transition probabilities for recurrence (n-csCMV to csCMV) depends on the patient's treatment history (i.e., patients whose most recent treatment was maribavir will have maribavir specific recurrence, and patients whose most recent treatment was IAT will have IAT specific recurrence), with the assumption that re-treatment with IAT has the same effectiveness as the initial treatment. This assumption is tested in Scenario Analysis (See section 8.7 Sensitivity analyses). Therefore, the clearance probabilities for IAT are applied for both maribavir and IAT patients for second recurrence patients. Recurrence probabilities are also time dependent, depending on the time since clearance.

**Table 161: 2nd recurrence (Time since clearance: 4 to 12 weeks) transition probabilities (most recent treatment IAT)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|
| csCMV | [redacted] | | |
| n-csCMV | | | |
| Dead | | | |

**Table 162: 2nd recurrence (Time since clearance: 16 to 24 weeks) transition probabilities (most recent treatment IAT)**

| From/to | csCMV | n-csCMV | Dead |
|---|---|---|---|

| | |
|---|---|
| csCMV<br>n-csCMV (16-20 weeks)<br>n-csCMV (24 weeks onwards)<br>Dead | [redacted] |



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# Appendix O EQ5D5L analysis additional outputs

**Table 163: Mixed effects models: Least square estimates for treatment and response effect without covariate for EQ5D DANISH crosswalk HSUVs (utilities)**

| Treatment | Response | lsmean | SE | Lower CL | Upper CL |
|---|---|---|---|---|---|
| IAT | No | | | | |
| Maribavir | No | | | | |
| IAT | Yes | | | | |
| Maribavir | Yes | | | | |

Abbreviations: CL: Confidence Limit; EQ5D: EuroQoL Group 5-Dimension; HSUV: Health state utility values; IAT: Investigator Assigned Treatment; ls: least square; SE: Standard Error,

**Table 164: Mixed effects models: Least square estimates for treatment and response effect with covariate for EQ5D DANISH crosswalk HSUVs (utilities)**

| Treatment | Response | LS Mean | SE | Lower CL | Upper CL |
|---|---|---|---|---|---|
| IAT | No | | | | |
| Maribavir | No | | | | |
| IAT | Yes | | | | |
| Maribavir | Yes | | | | |

Abbreviations: CL: Confidence Limit; EQ5D: EuroQoL Group 5-Dimension; HSUV: Health state utility values; IAT: Investigator Assigned Treatment; ls: least square; SE: Standard Error,

The time until definitive deterioration (TUDD) in EQ-5D in each individual domain (mobility, self-care, usual activity, pain, anxiety) will be defined as the time interval between randomization and the first worsening in domain level that is maintained throughout all remaining study visits compared to the baseline score.

All definitive deteriorations must be confirmed by worsening since baseline at all subsequent visits. Patients that experience a worsening since baseline at their last EQ-5D-5L visit, which cannot be confirmed by subsequent visits, will be censored for the analysis.

**Table 165: Survival modelling estimates: TUDD in mobility**

| | N | events | RMST | SE | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|
| IAT | | | | | | |
| Maribavir | | | | | | |

Abbreviations: CI: Confidence interval; IAT: Investigator Assigned Treatment; RMST: Restricted Mean survival time; SE: Standard Error; TUDD: time until definitive deterioration

**Table 166: Hazard ratio: TUDD in mobility**

| HR | 95% CI for HR | p- value |
|---|---|---|
| 1.0 | | |

Abbreviations: CI: Confidence interval; HR: hazard ratio; TUDD: time until definitive deterioration

**Table 167: Restricted Mean survival time difference: TUDD in mobility**

| RMST difference (Maribavir -IAT) | Lower 95% CI | Upper 95% CI | p-value |
|---|---|---|---|
| | | | |

Abbreviations: CI: Confidence interval; IAT: Investigator Assigned Treatment; RMST: Restricted Mean survival time; TUDD: time until definitive deterioration

RMST is based on maximum follow up time 191 days

**Table 168: Assumptions-testing -Grambsch-Therneau test- TUDD in mobility**



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| Treatment | Chi-square | p-value |
|---|---|---|
| Maribavir | [redacted] | [redacted] |

Abbreviations: TUDD: time until definitive deterioration

[redacted]



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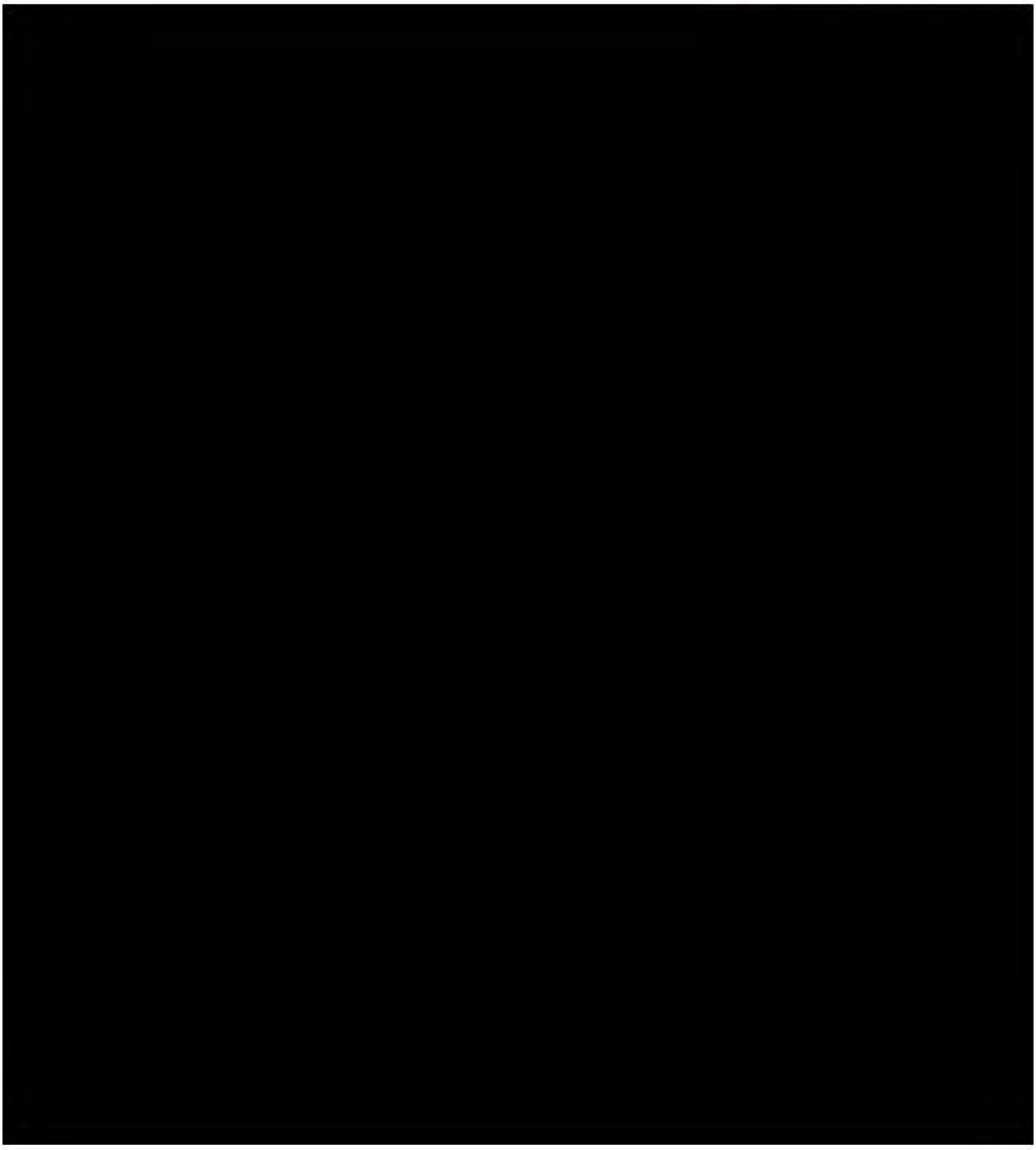



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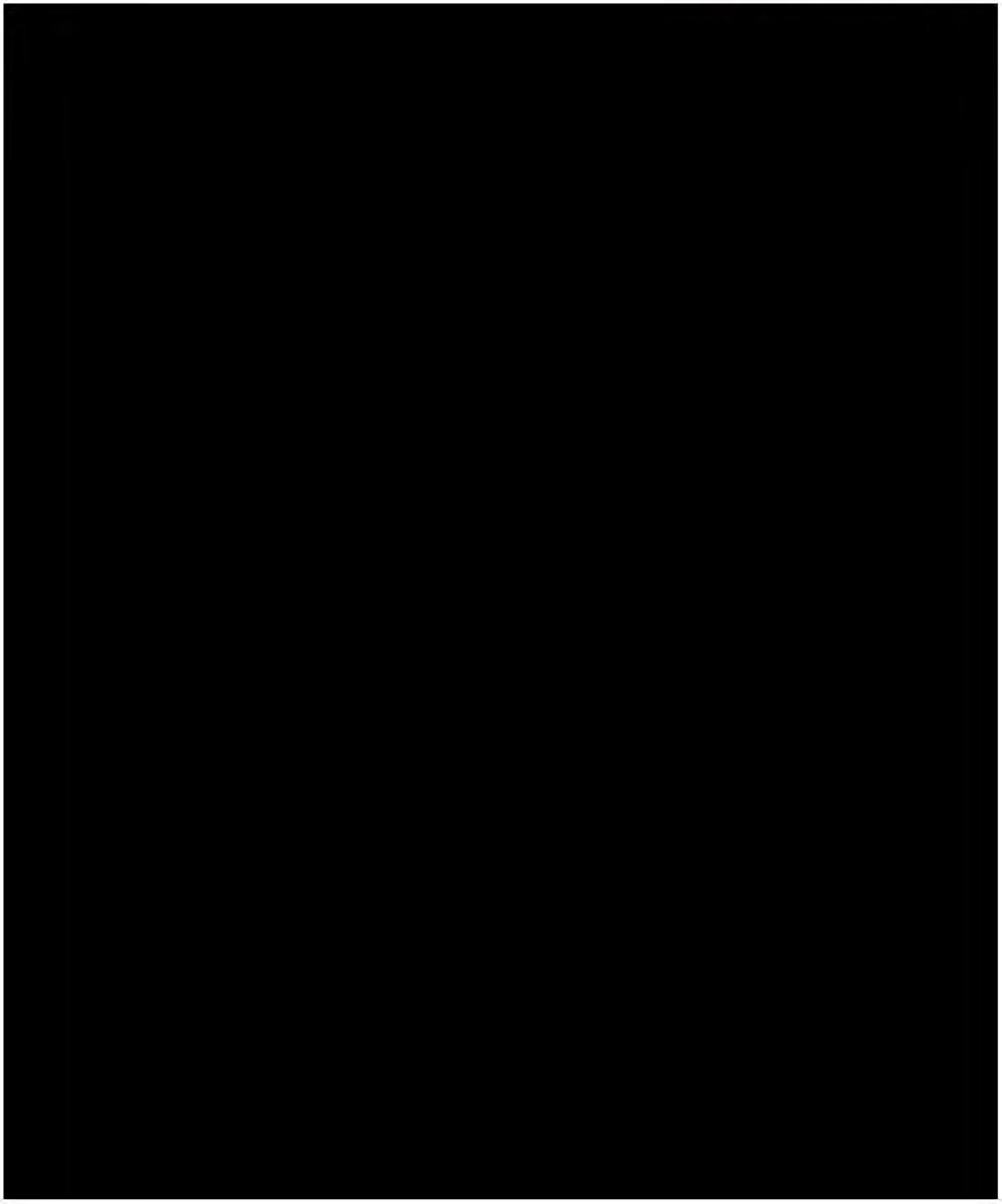



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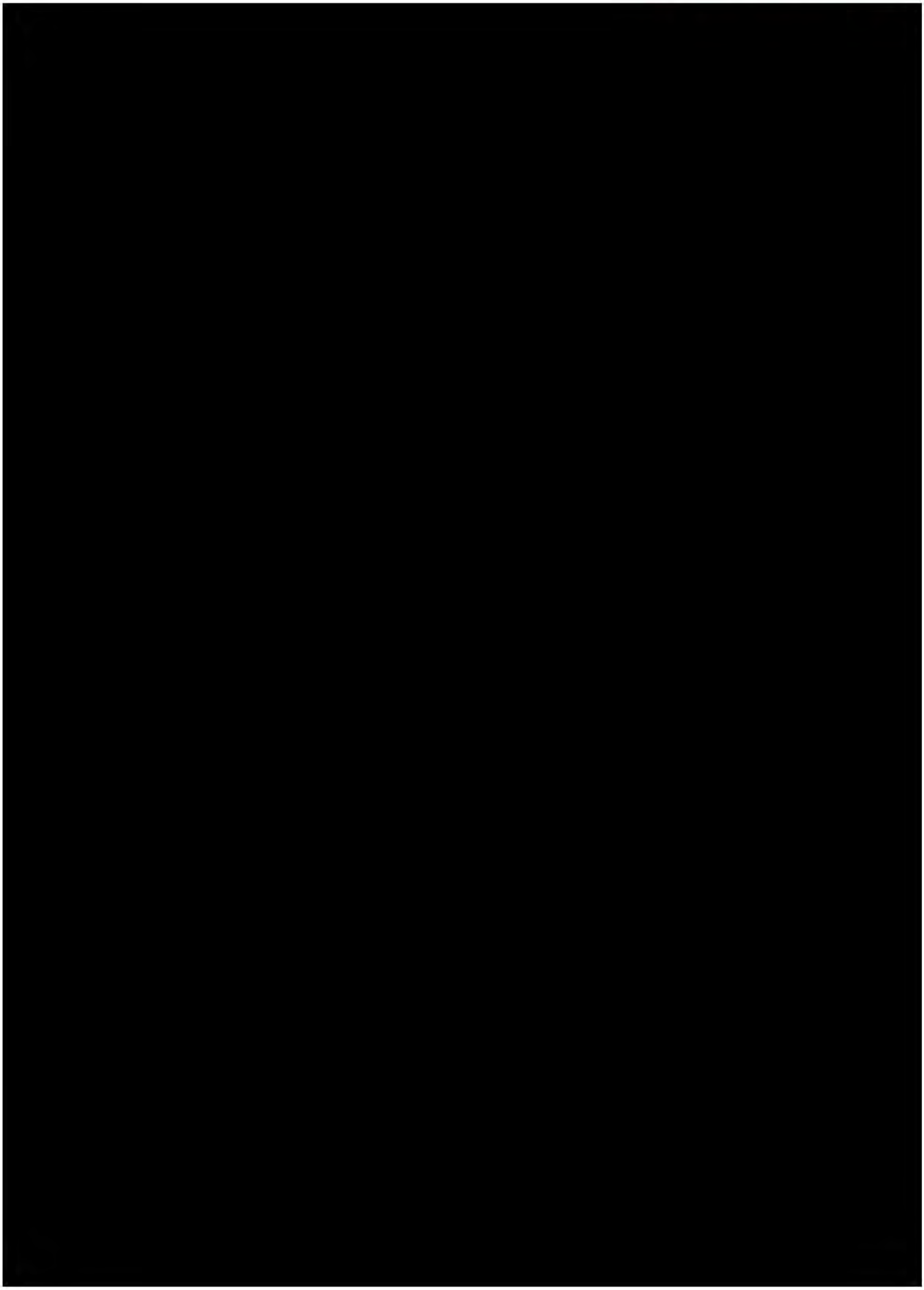



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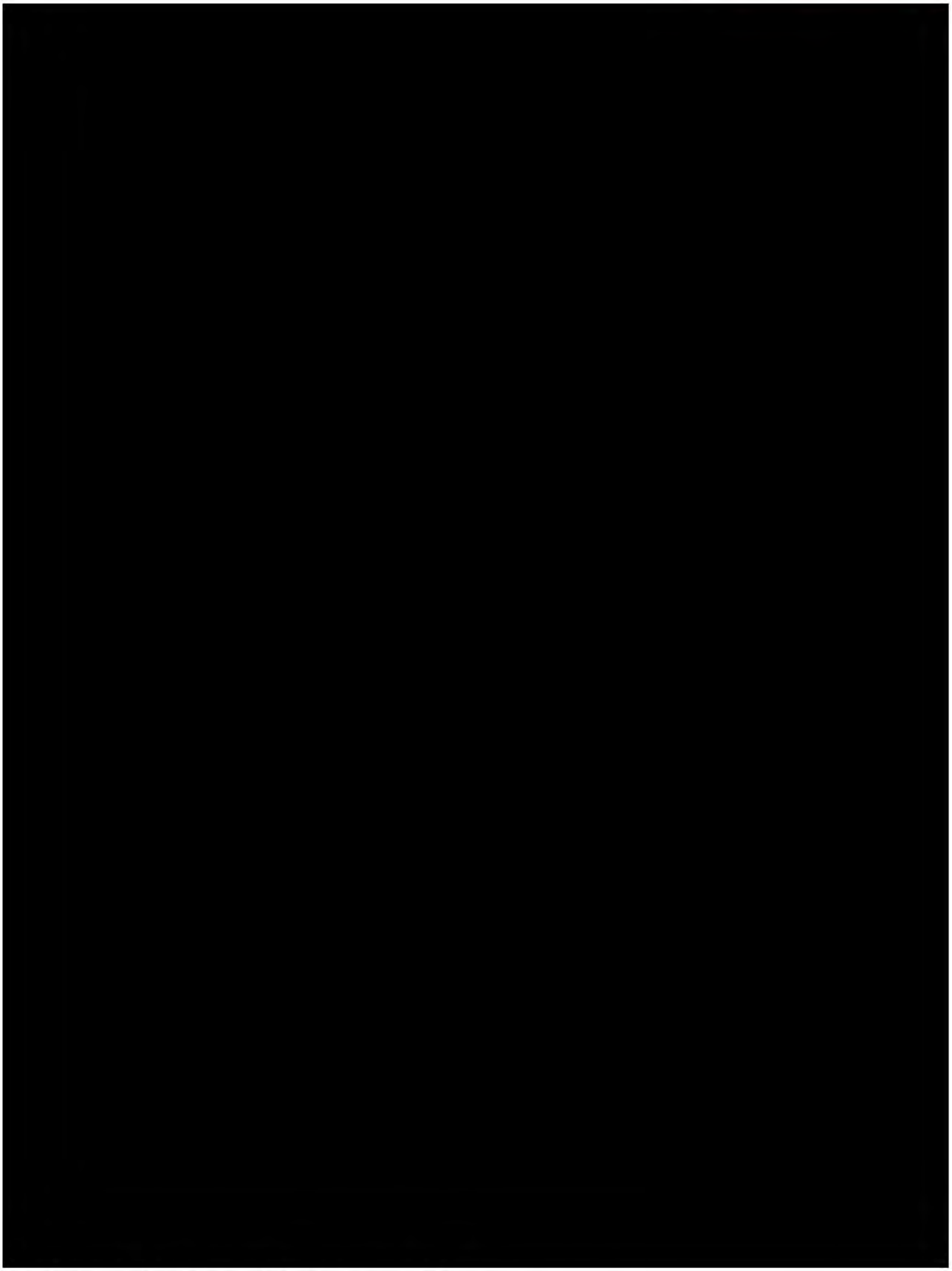

The definition of TUDD in overall health is given as follows-

- There should be a definitive deterioration in at least one domain without an improvement in any domains.
- The definitive deterioration in individual domains is defined as above.



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- Improvement is defined as the first improvement in EQ-5D response compared to baseline which is maintained throughout the remaining visits, however, if improvement of score is observed only at the last EQ-5D visit, then this is not considered as a definitive improvement.
- For patients who experience definitive deterioration in at least one domain without any improvement in other domain, the time of deterioration is the time where the first definitive deterioration occurred.
- If there is improvement observed in at least one EQ-5D domain, then patient is censored for TUDD at the first improvement time point.
- If there is neither improvement nor deterioration at any domain, then the patient is censored at the last EQ5D visit.
- However, for patients who experienced definitive deterioration in more than one domain without any improvement in other domains, the earliest time point of deterioration is considered as time of deterioration.



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[redacted]

**Sensitivity analyses**

Sensitivity analyses were performed to account for the effect of rescue therapy i.e., maribavir rescue therapy on QoL (QoL may temporarily improve with the start of the rescue therapy). In this case, the definition of TUDD will be amended to censor patients at the time of last EQ-5D visit record prior to start of the first rescue therapy effectively removing all QoL records collected after first rescue therapy. The patients who had an event prior to receiving first rescue therapy, will be considered as having an event like the main TUDD analysis.

As the comparison is made from baseline, subjects with no baseline assessment available or subjects with no records available post baseline were removed from the analysis. The analyses were performed on subjects with available EQ-5D-5L data at study specific visits

[redacted]



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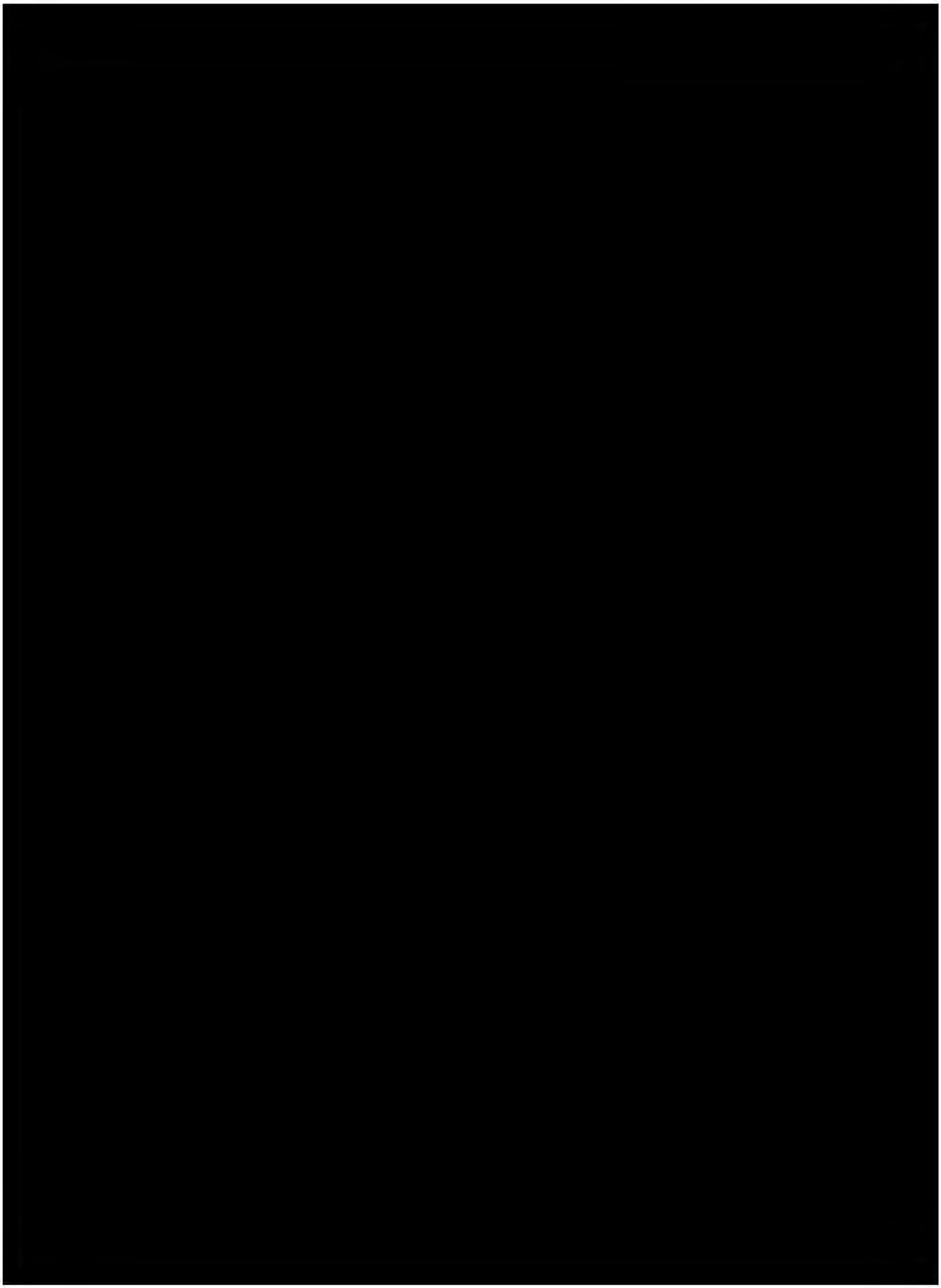



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[redacted]

Table 193: Survival modelling estimates: TUDD in usual activity-sensitivity analysis



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| | N | events | RMST | SE | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|
| IAT | [redacted] | | | | | |
| Maribavir | | | | | | |

Abbreviations: CI: Confidence interval; IAT: Investigator Assigned Treatment; RMST: Restricted Mean survival time; SE: Standard Error; TUDD: time until definitive deterioration

### Table 194: Hazard ratio: TUDD in usual activity -sensitivity analysis

| HR | 95% CI for HR | p- value |
|---|---|---|
| 1.4 | [redacted] | |

Abbreviations: CI: Confidence interval; HR: hazard ratio; TUDD: time until definitive deterioration

### Table 195: Restricted Mean survival time difference: TUDD in usual activity-sensitivity analysis

| RMST difference (Maribavir -IAT) | Lower 95% CI | Upper 95% CI | p-value |
|---|---|---|---|
| [redacted] | | | |

Abbreviations: CI: Confidence interval; IAT: Investigator Assigned Treatment; RMST: Restricted Mean survival time; TUDD: time until definitive deterioration
RMST is based on maximum follow up time 151 days

### Table 196: Assumptions-testing -Grambsch-Therneau test-TUDD in usual activity-sensitivity analysis

| Treatment | Chi-square | p-value |
|---|---|---|
| Maribavir | [redacted] | |

Abbreviations: TUDD: time until definitive deterioration

[redacted]



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[redacted]

### Table 198: Hazard ratio: TUDD in pain- sensitivity analysis

| HR | 95% CI for HR | p- value |
|---|---|---|
| 0.97 | [redacted] | |

Abbreviations: CI: Confidence interval; HR: hazard ratio; TUDD: time until definitive deterioration

### Table 199: Restricted Mean survival time difference: TUDD in pain -sensitivity analysis

| RMST difference (Maribavir -IAT) | Lower 95% CI | Upper 95% CI | p-value |
|---|---|---|---|
| [redacted] | | | |

Abbreviations: CI: Confidence interval; IAT: Investigator Assigned Treatment; RMST: Restricted Mean survival time; TUDD: time until definitive deterioration
RMST is based on maximum follow up time 151 days

### Table 200: Assumptions-testing -Grambsch-Therneau test-TUDD in pain-sensitivity analysis

| Treatment | Chi-square | p-value |
|---|---|---|
| Maribavir | [redacted] | |

Abbreviations: TUDD: time until definitive deterioration

[redacted]



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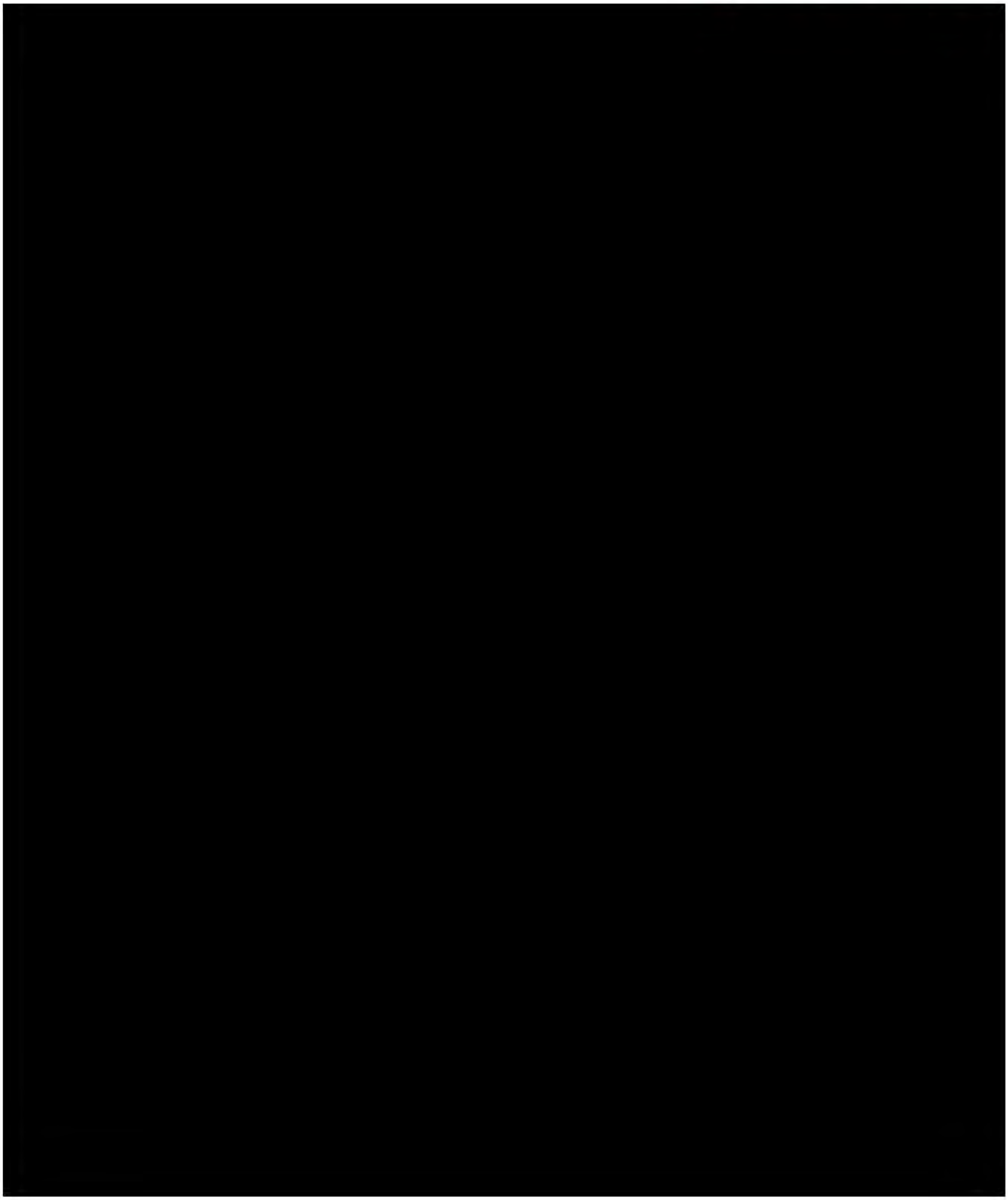



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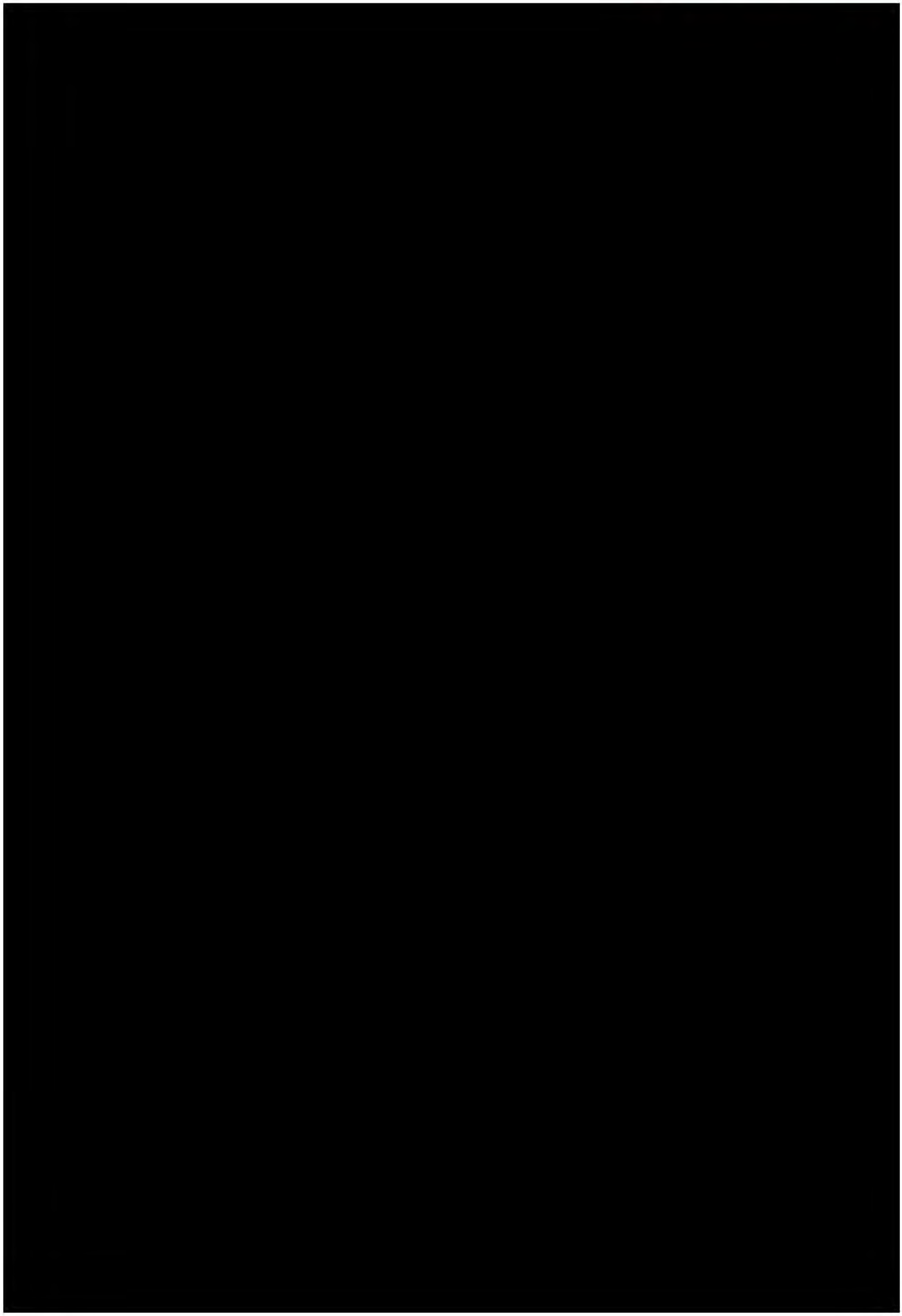



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[redacted]

As the responder's status is not used from week 52 onwards in the Global CEM, an overall HSUV by transplant type and CMV health state was calculated from the definition of CMV/no CMV in the CSR.

**Table 210: EQ5D DANISH crosswalk HSUVs (Utilities) by CMV and no CMV health state for overall duration of study by transplant type**

| | CMV | | | no CMV | | | Overall | | |
|---|---|---|---|---|---|---|---|---|---|
| Transplant Type | N | Mean | SD | N | Mean | SD | N | Mean | SD |
| HSCT | [redacted] | | | | | | | | |



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| | |
|---|---|
| SOT | [redacted] |

Abbreviations: CMV: Cytomegalovirus; EQ5D: EuroQoL Group 5-Dimension: HSCT: Hematopoietic stem cell transplant; SD: standard deviation; HSUV; health state utility value; SOT: solid organ transplant; DANISH:



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# Appendix P Results stratified based on transplant type

**Table 211: SOT patient population**

| Per patient | Maribavir | IAT | Incremental |
|---|---|---|---|
| **Effect** | [redacted] | | |
| Total life years gained | | | |
| Total QALYs | | | |
| **Costs** | | | |
| Total costs | | | |
| Drug costs | | | |
| Administrative costs | | | |
| Monitoring cost | | | |
| Hospital admissions costs | | | |
| Adverse reactions costs | | | |
| Patient time and transport costs | | | |
| Re-treatment costs | | | |
| Graft loss costs | | | |
| **Incremental results** | | | |
| **ICER (per QALY)** | | | |

**Table 212: HSCT patient population**

| Per patient | Maribavir | IAT | Incremental |
|---|---|---|---|
| **Effect** | [redacted] | | |
| Total life years gained | | | |
| Total QALYs | | | |
| **Costs** | | | |
| Total costs | | | |
| Drug costs | | | |
| Administrative costs | | | |
| Monitoring cost | | | |



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| Per patient | Maribavir | IAT | Incremental |
|---|---|---|---|
| Hospital admissions costs | | | |
| Adverse reactions costs | | | |
| Patient time and transport costs | | | |
| Re-treatment costs | | | |
| Graft loss costs | | | |
| **Incremental results** | | | |
| **ICER (per QALY)** | | | |



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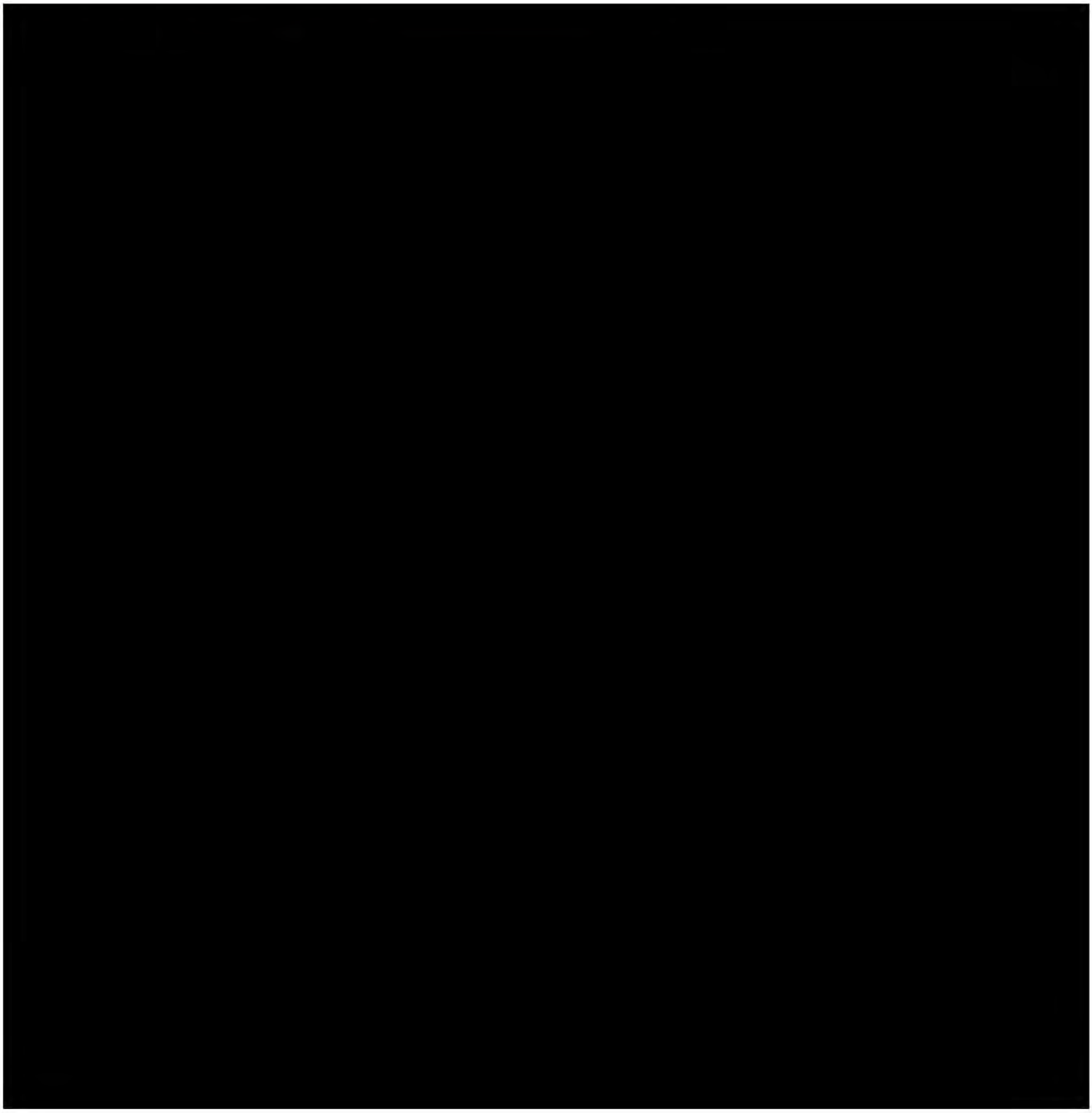
# Appendix Q Additional data on recurrence

**Table 213: Recurrence requiring treatment**

| Treatment | Model | Week 8 | Week 12 | Week 16 |
|---|---|---|---|---|
| IAT | Kaplan-Meier | | | |
| Maribavir | Kaplan-Meier | | | |





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# Appendix R Description of the IPCW method used

**Brief description of IPCW method:**

The IPCW method was selected as the base case scenario, as it does not require a common-treatment effect assumption. The steps included in the model fitting are described as follows:

The IPCW method consists of censoring data for switchers at the point of switch and weighting the remaining observations with the aim of removing any censoring-related selection bias. The key assumption made by the IPCW method is the "no unmeasured confounders" assumption – that is, there are no important independent mortality predictors missing to predict informative censoring models. In practice, this is unlikely to be perfectly true, but the method is likely to work adequately if the "no unmeasured confounders" assumption is approximately true. This method requires the following steps:

Sort data into 'panel' format, with observations for individuals recorded at regular intervals through time until death or censoring. Patients are then artificially censored at the time of switch.

**Calculate and assess stabilized weights**

Remaining observations are weighted based on a model of the probability of being censored. Patients who do not switch and have similar characteristics to patients who did switch receive higher weights.

Run IPCW-based Cox regression and calculate the 95% confidence intervals of the HRs with a robust variance estimation approach by clustering the observations

The following covariates are proposed for modelling:

**Table 215: List of covariates/predictors used in IPCW method**

| Methods | Covariates |
|---|---|
| Baseline covariates | Transplant type, baseline plasma CMV DNA level, Graft status. Age, Acute GvHD, Chronic GvHD |
| Time-varying covariates | No time varying covariates were considered |
| Significant covariates | Transplant type, Graft status. Age, Acute GvHD |

**Steps performed in IPCW method:**

**Calculation of weights**

The stabilized weights were used in the IPCW method and the description of estimation of weights are given below-

**Creating panel data**

- Method adjusts estimates of a treatment effect in the IAT arm in the presence of any type of informative censoring.
- Data were sorted into a panel format, with observations for individuals recorded at regular intervals (i.e., between visits) through time until death or censoring.
- Patients were artificially censored at the time of switch, and remaining observations were weighted based upon covariate values and a model of the probability of being censored.
- This method allows patients who have not been artificially censored to be weighted to reflect their similarities to patients who have been censored in an attempt to remove the selection bias caused by

the censoring: patients who do not switch and have similar characteristics to patients who did switch receive higher weights.

**Selection of final list of covariates**

- Both Null models and Full models were developed for numerator and denominator weights.
- A stepwise selection of final covariates was conducted by removing sequentially covariates which were not statistically significant, or the removal improved goodness-of-fit (AIC).
- Final baseline covariates (if any of the baseline covariate turned out to be significant) for the numerator model were forced in the denominator model for consistency.
- Stepwise selection of covariates improved goodness-of-fit models but had only a very limited impact on the value of stabilized weights.

**Estimation of weights**

- Stabilised weights (SW) are calculated as the probability of having remained uncensored (i.e., not switched) until time *t* given baseline covariates (SW numerator), divided by the probability of having remained uncensored until time *t* given baseline and time-dependent covariates (SW denominator).
- Logistic regression is used to calculate weights with switch variable as dependent variable and regressing over a 'time' variable and relevant baseline and time varying covariates.
- Time is flexibly modelled by including a 5-knot spline.
- Finally, Cox regression model was used to calculate the HR and 95% CI of Maribavir vs adjusted IAT arm based on the weighted data.

**Parameter estimates and associated measures of precision from the logistic regression model**

**Table 216: Stabilized Weights-Numerator model parameter estimates and predicted probabilities**

| Parameter | Null Model | | Full Model | | Restricted Model | |
|---|---|---|---|---|---|---|
| | Estimate (SE) | OR [95%CI] | Estimate (SE) | OR [95%CI] | Estimate (SE) | OR [95%CI] |
| Intercept –Spline 1 | [redacted] | | | | | |
| Spline 2 | | | | | | |
| Spline 3 | | | | | | |
| Spline 4 | | | | | | |
| Spline 5 | | | | | | |
| Transplant type | | | | | | |
| baseline plasma CMV DNA level (High vs low) | | | | | | |
| baseline plasma CMV DNA level (Intermediate vs low) | | | | | | |
| Graft Status | | | | | | |
| Age | | | | | | |
| Acute GvHD | | | | | | |



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[redacted]

**Table 217: Stabilized Weights-Denominator model parameter estimates and predicted probabilities**

| Parameter | Null Model | | Full Model | | Restricted Model | |
|---|---|---|---|---|---|---|
| | Estimate (SE) | OR [95%CI] | Estimate (SE) | OR [95%CI] | Estimate (SE) | OR [95%CI] |
| Intercept –Spline 1 | [redacted] | | | | | |
| Spline 2 | | | | | | |
| Spline 3 | | | | | | |
| Spline 4 | | | | | | |
| Spline 5 | | | | | | |
| Transplant type | | | | | | |
| baseline plasma CMV DNA level (High vs low) | | | | | | |
| baseline plasma CMV DNA level (Intermediate vs low) | | | | | | |
| Graft Status | | | | | | |
| Age | | | | | | |
| Acute GvHD | | | | | | |
| Chronic GvHD | | | | | | |
| AIC | | | | | | |

[redacted]

**Distribution of weights**

The distribution of weights obtained from the null, full, and restricted models are calculated as per the estimation of weights explained above and no weights were truncated.

[redacted]



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[redacted]

**The Final Outcome model**

Based on the weighted data from the restricted model, Cox regression model was used to calculate the hazard ratio and associated 95% CI.

The panel data was aggregated for each patient to compute the robust sandwich variance estimate by summing up the score residuals for each distinct pattern. The Hazard ratio and associated 95% CI for using treatment switching adjustment using the IPCW method is given in the following table.

The results of the IPCW method regardless of alternative anti-CMV treatment use and by censoring for anti-CMV treatment use are provided below.

**Table 219: Time to all-cause mortality regardless of alternative anti-CMV treatment use by treatment arm adjusted for treatment switch by IPCW method in treated patients**

| | Investigator Assigned Treatment (N=116) | Maribavir 400 mg BID (N=234) |
|---|---|---|
| Kaplan-Meier Estimates of Time to Death (days) [95% CI] | [redacted] | |
| 50th (Median) | | |
| | | |
| Hazard Ratio (95% CI) | | |
| Treatment Arm: Maribavir vs IAT | | |
| | | |

NA is Not Available
Percentages are based on the number of subjects in the Randomized Set. Treatment switching analysis is performed for treated patients only

[redacted]



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The figure is based on weighted K-M method for the IPCW adjusted IAT treatment arm. As no switch is considered for the maribavir arm, a weight =1 was given to each observation in the weighted KM analysis.

# Supplementary documentation



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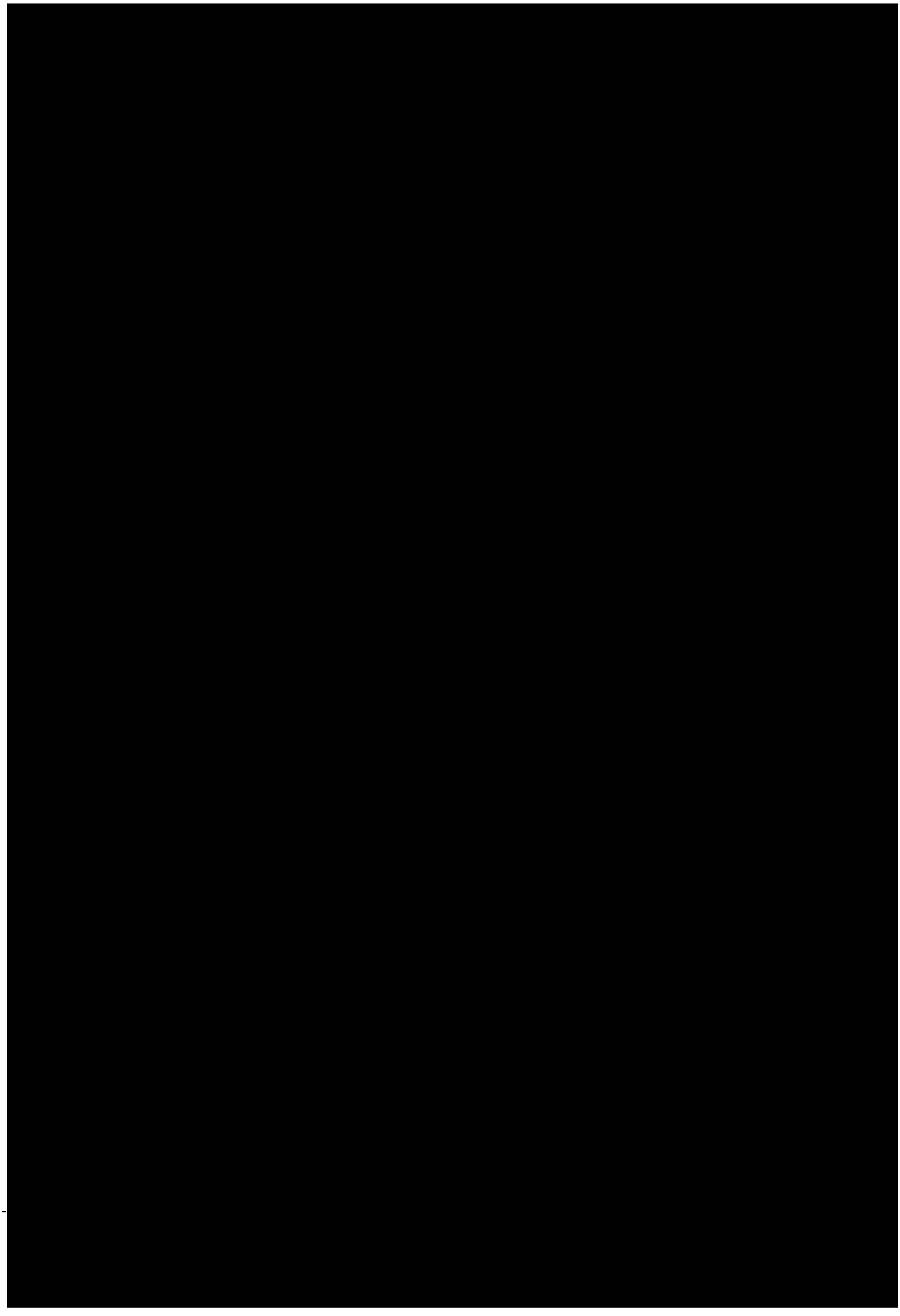
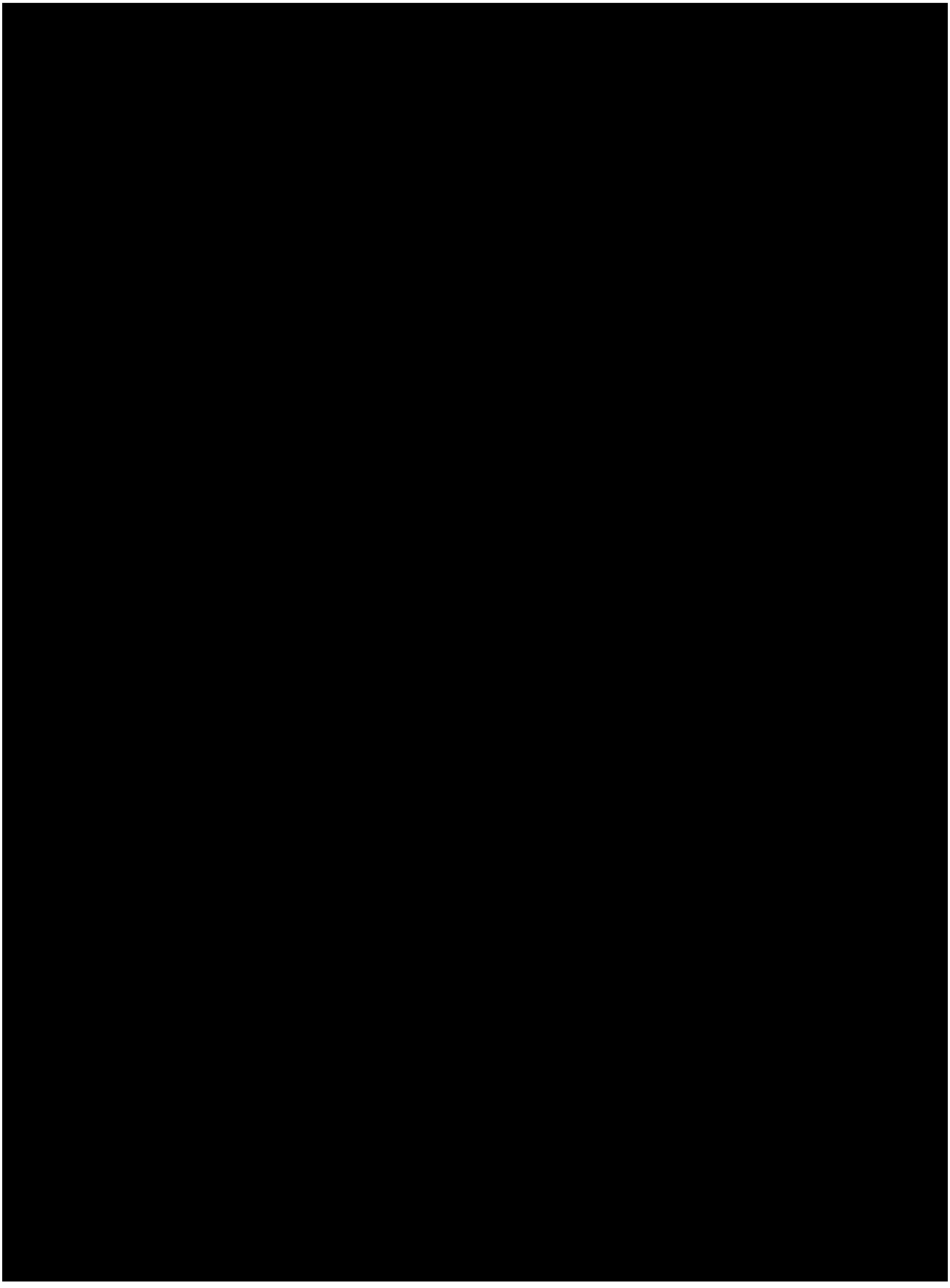
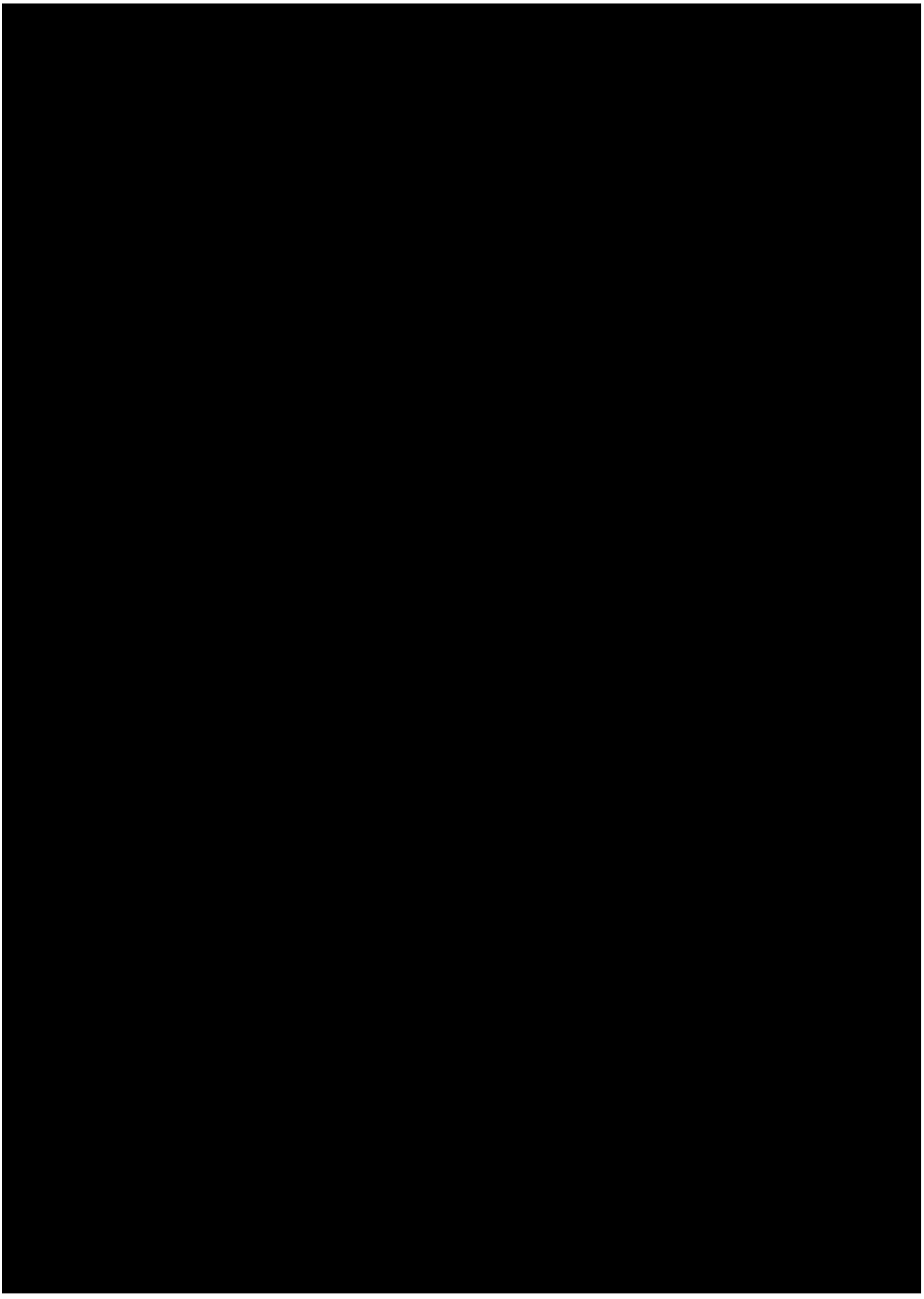
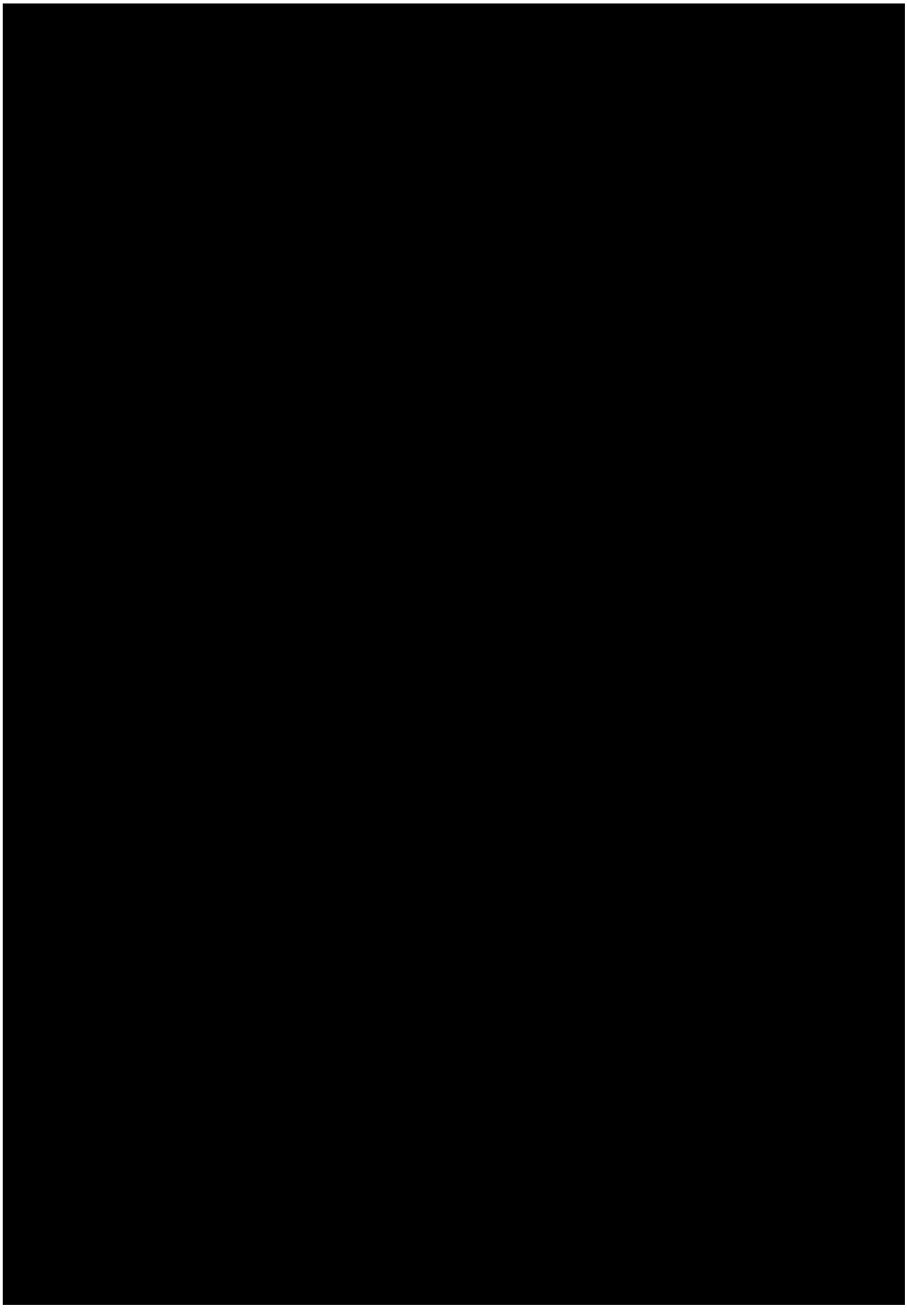
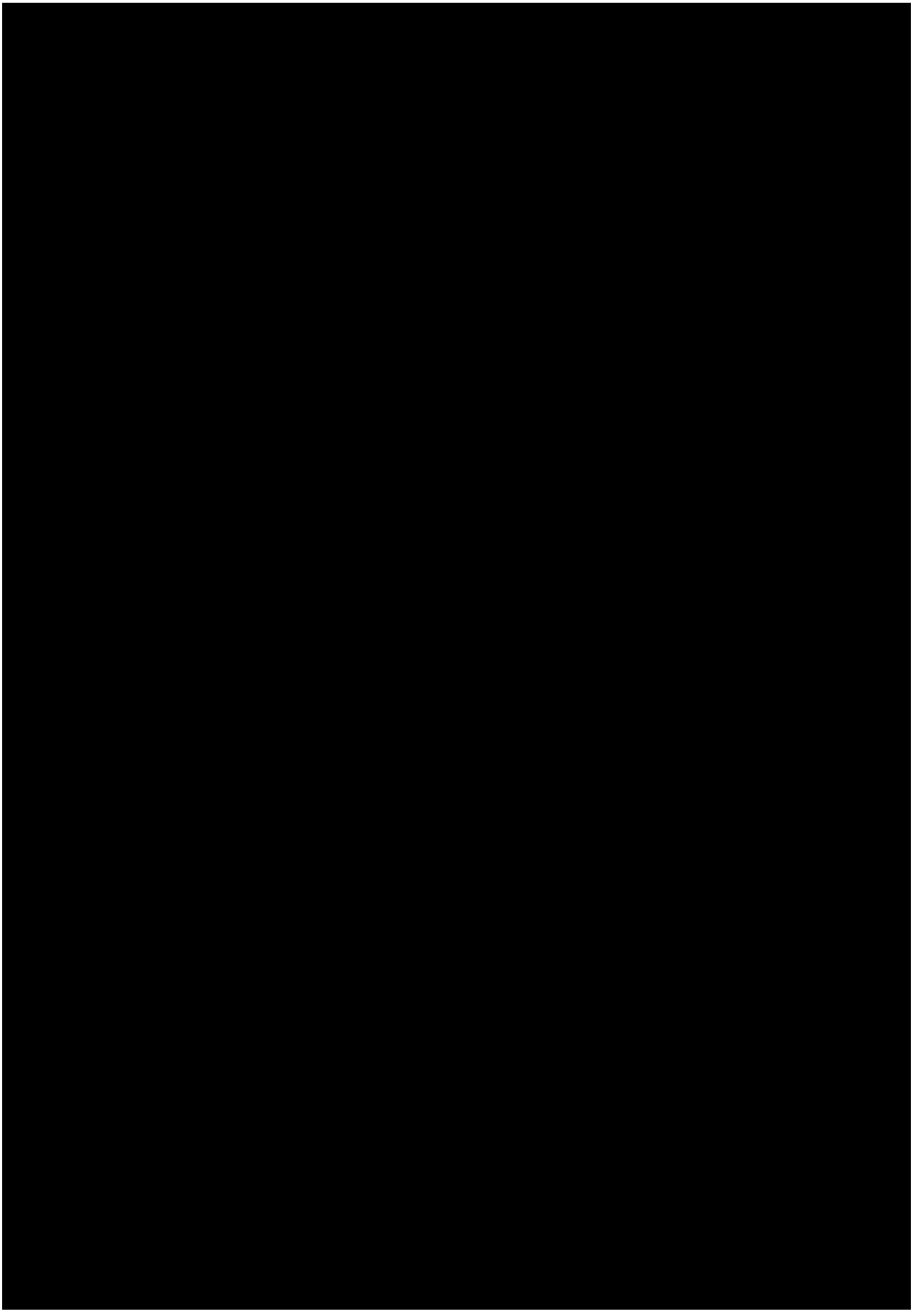
# GENOME study report

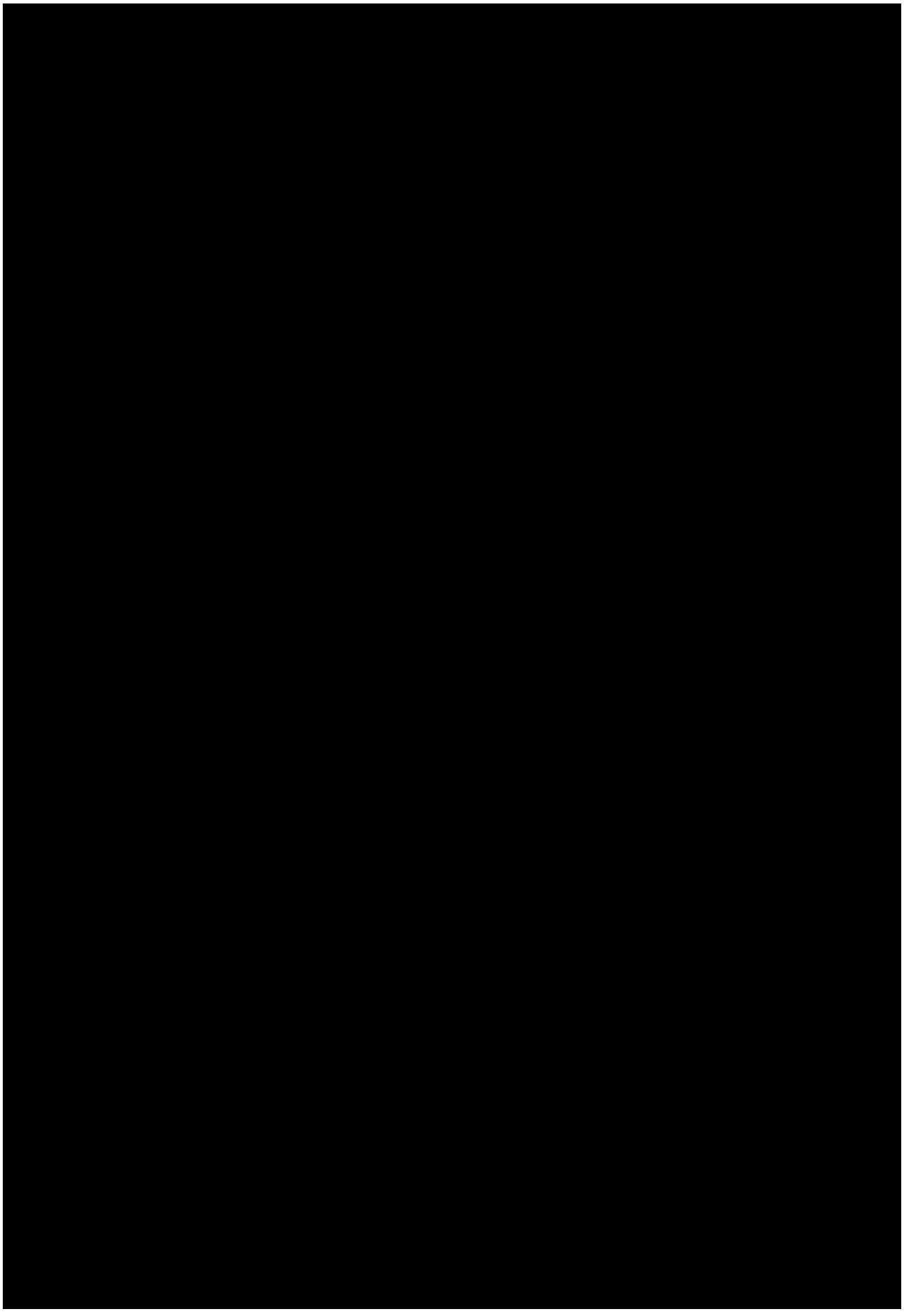


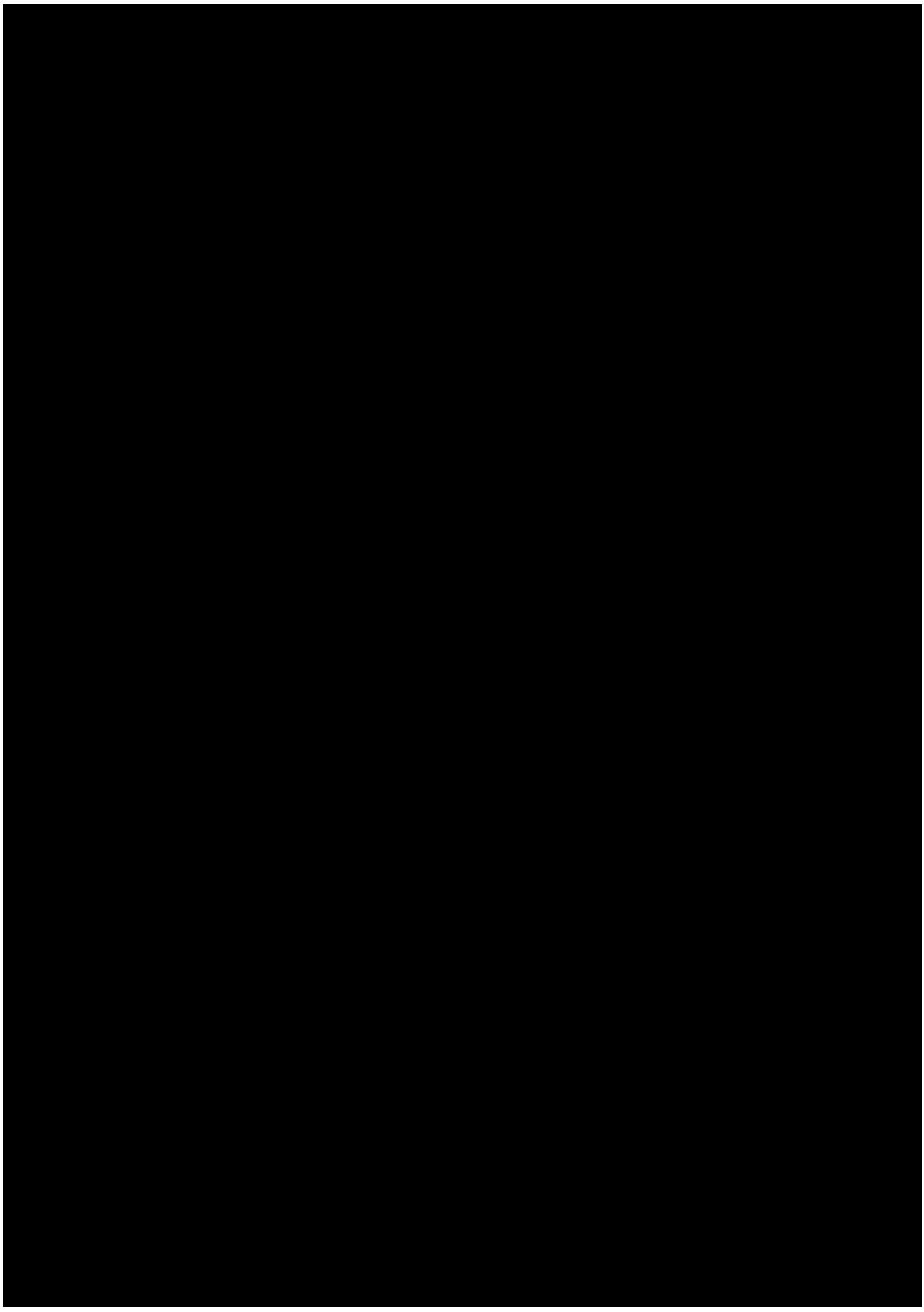


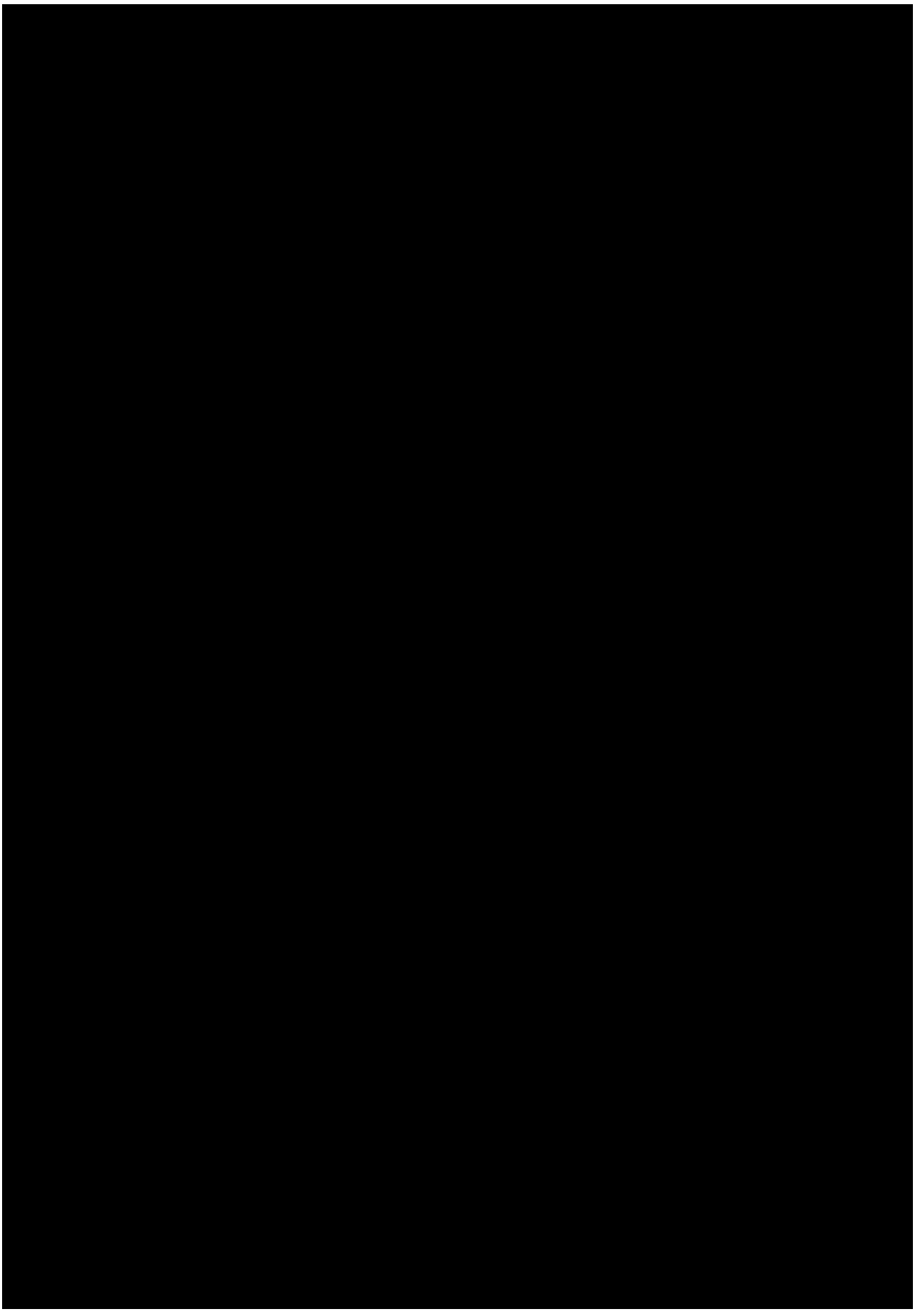




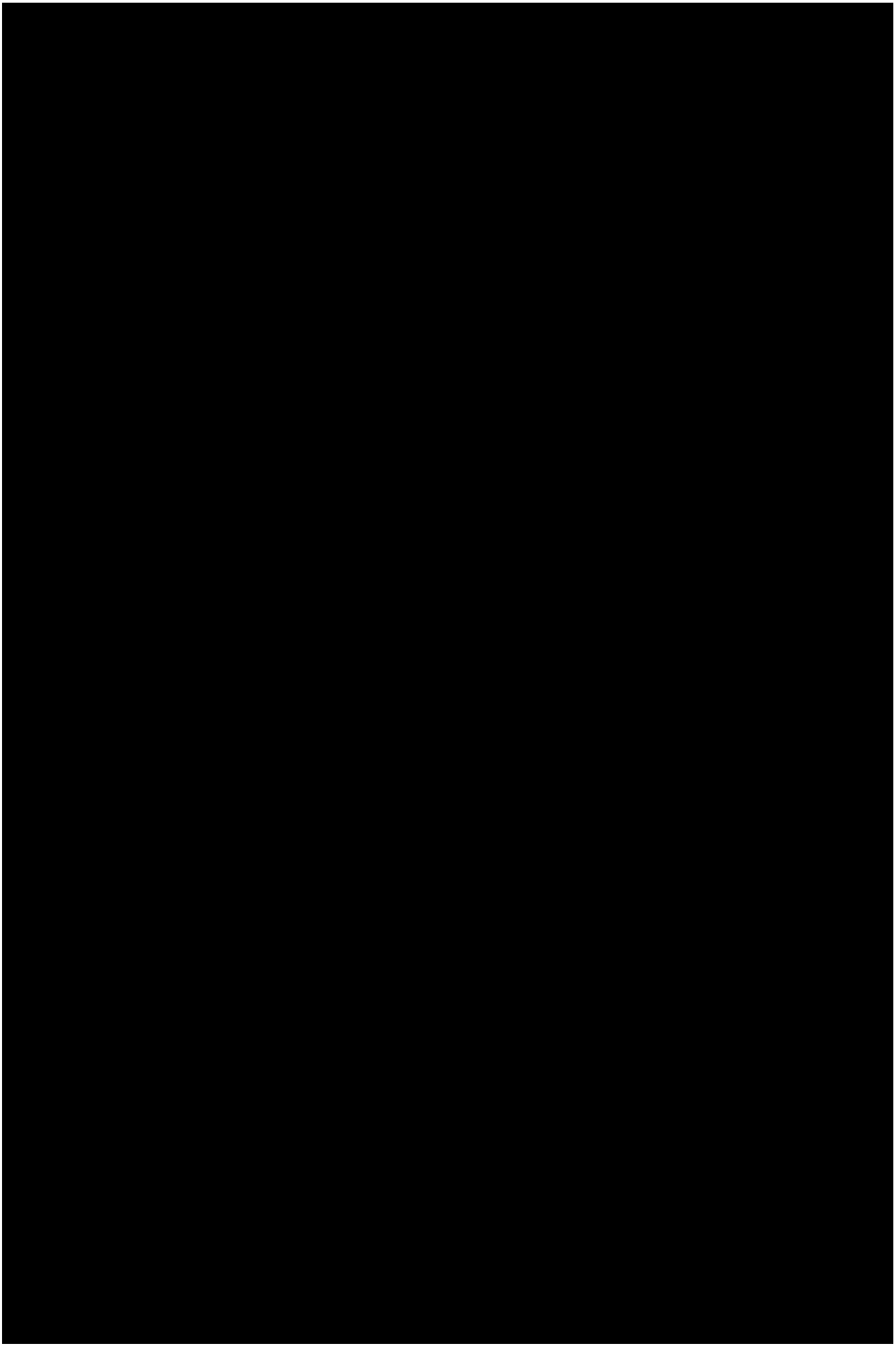


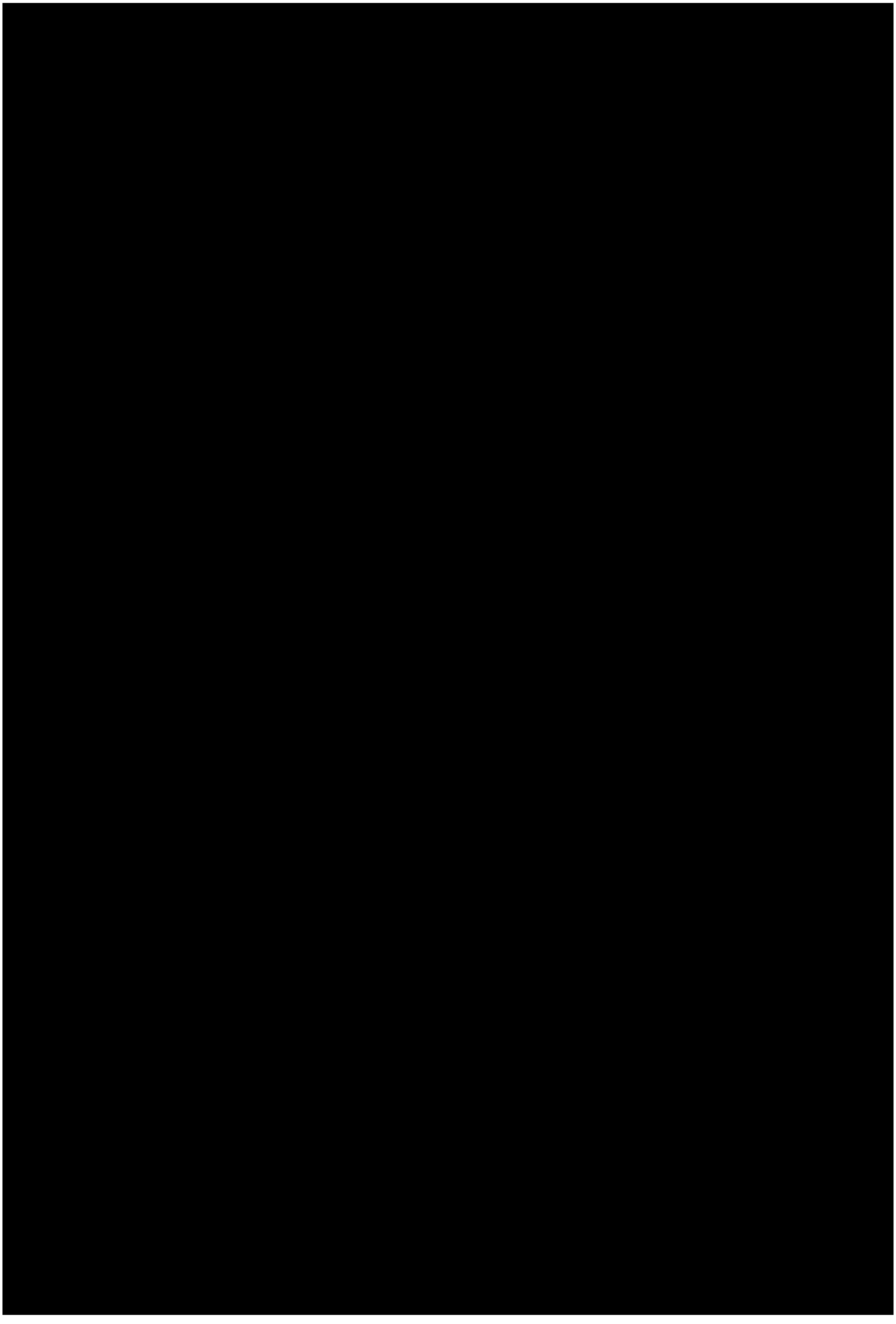


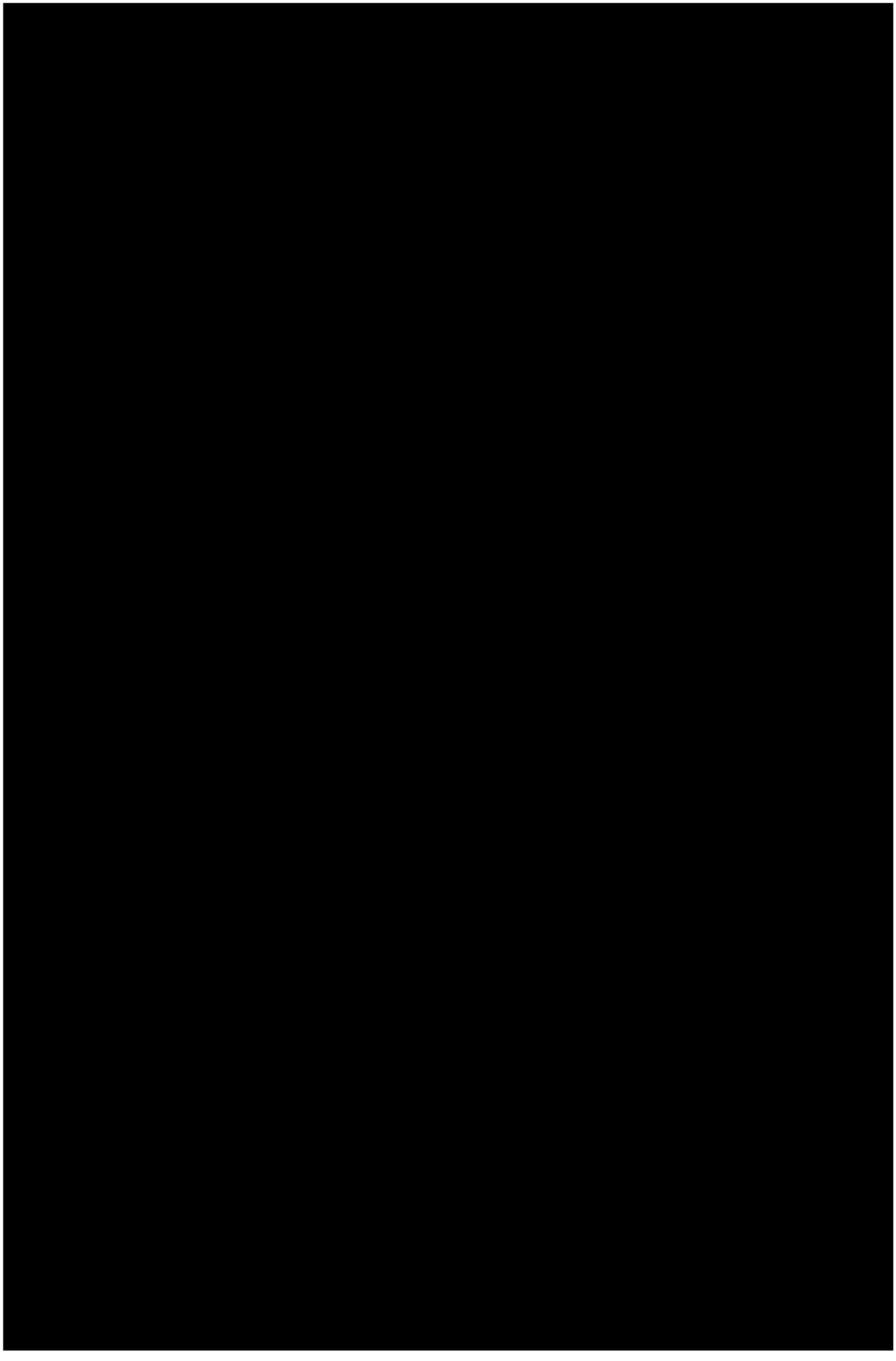


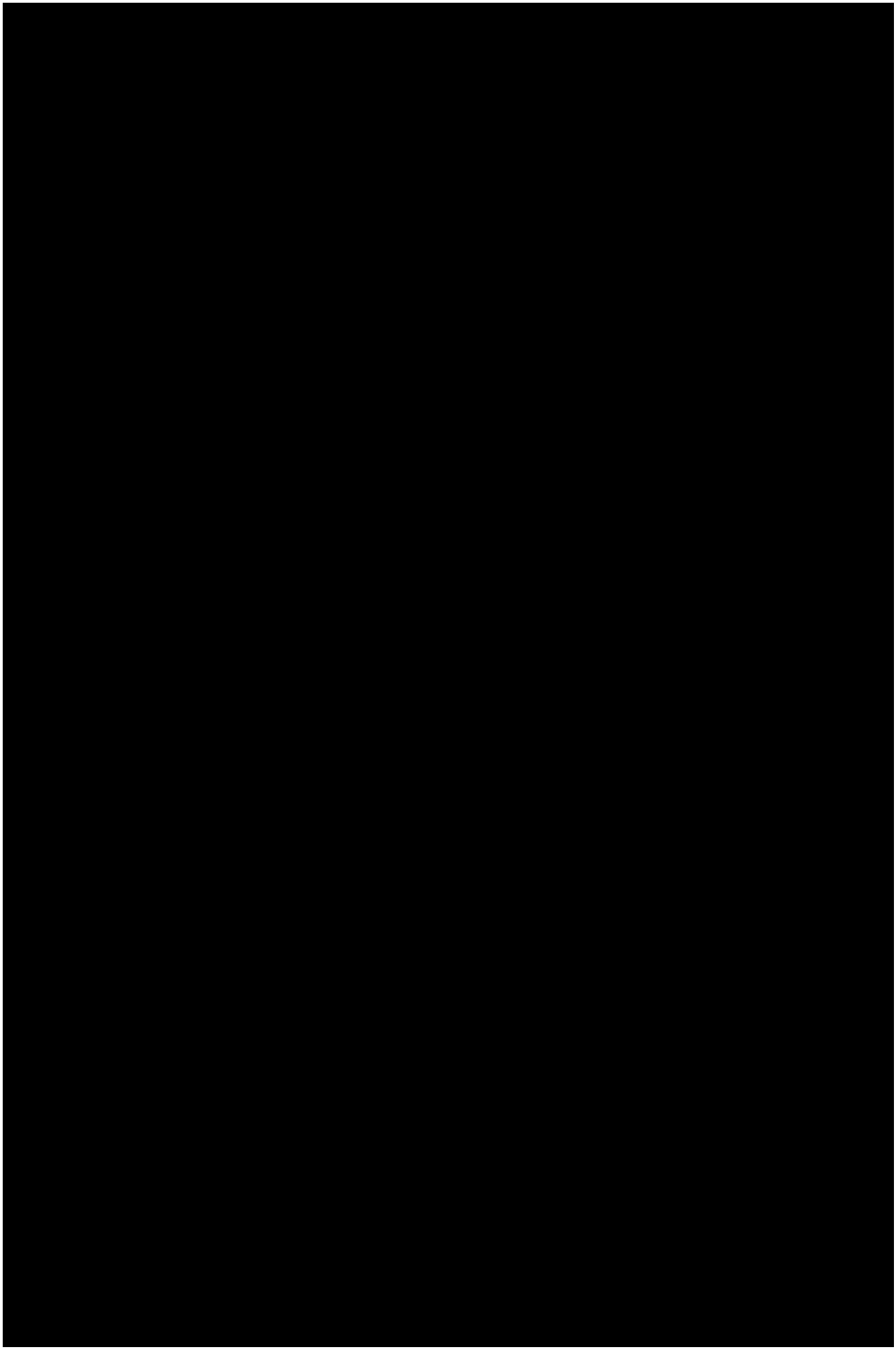


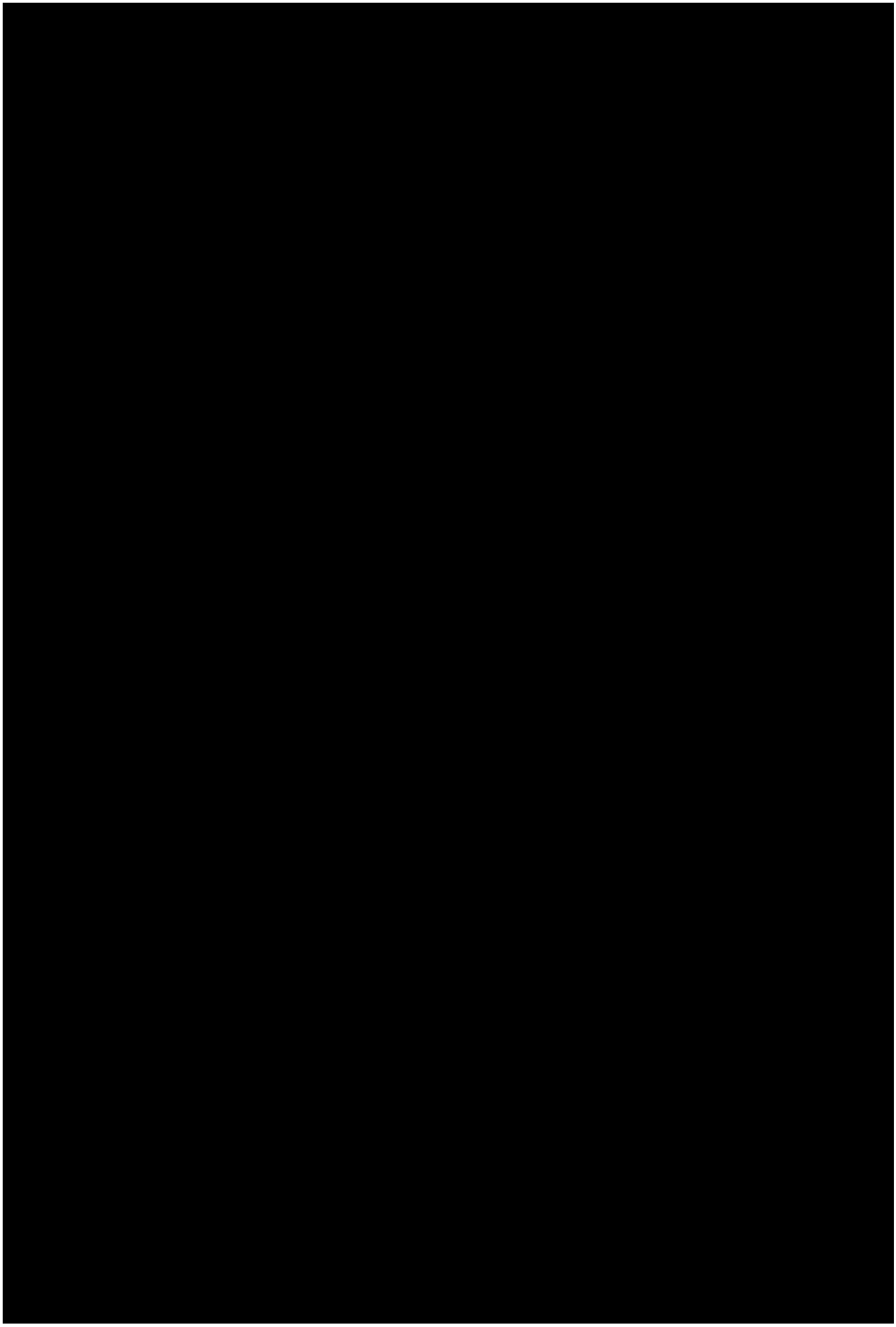
# OTUS study report

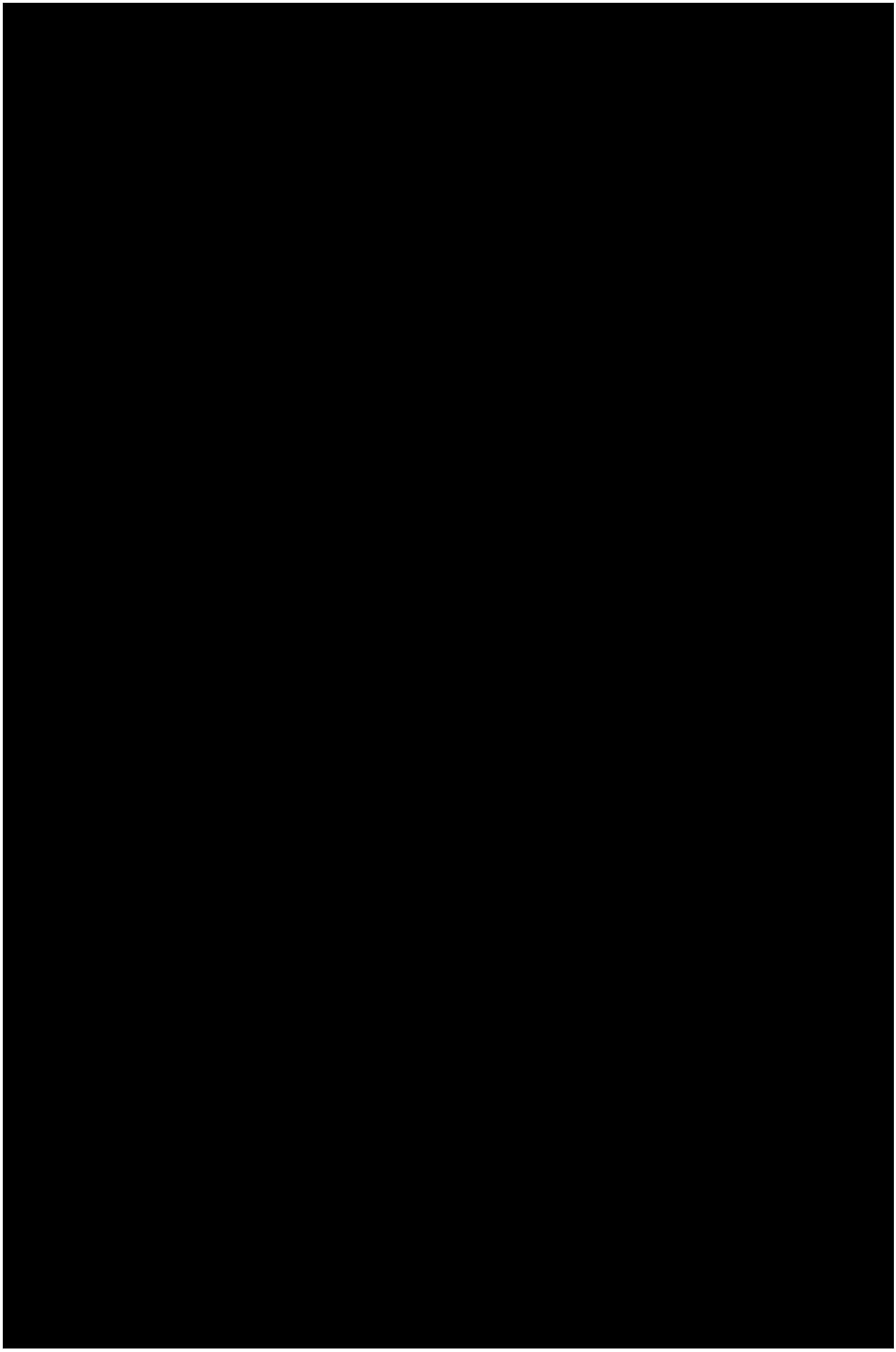


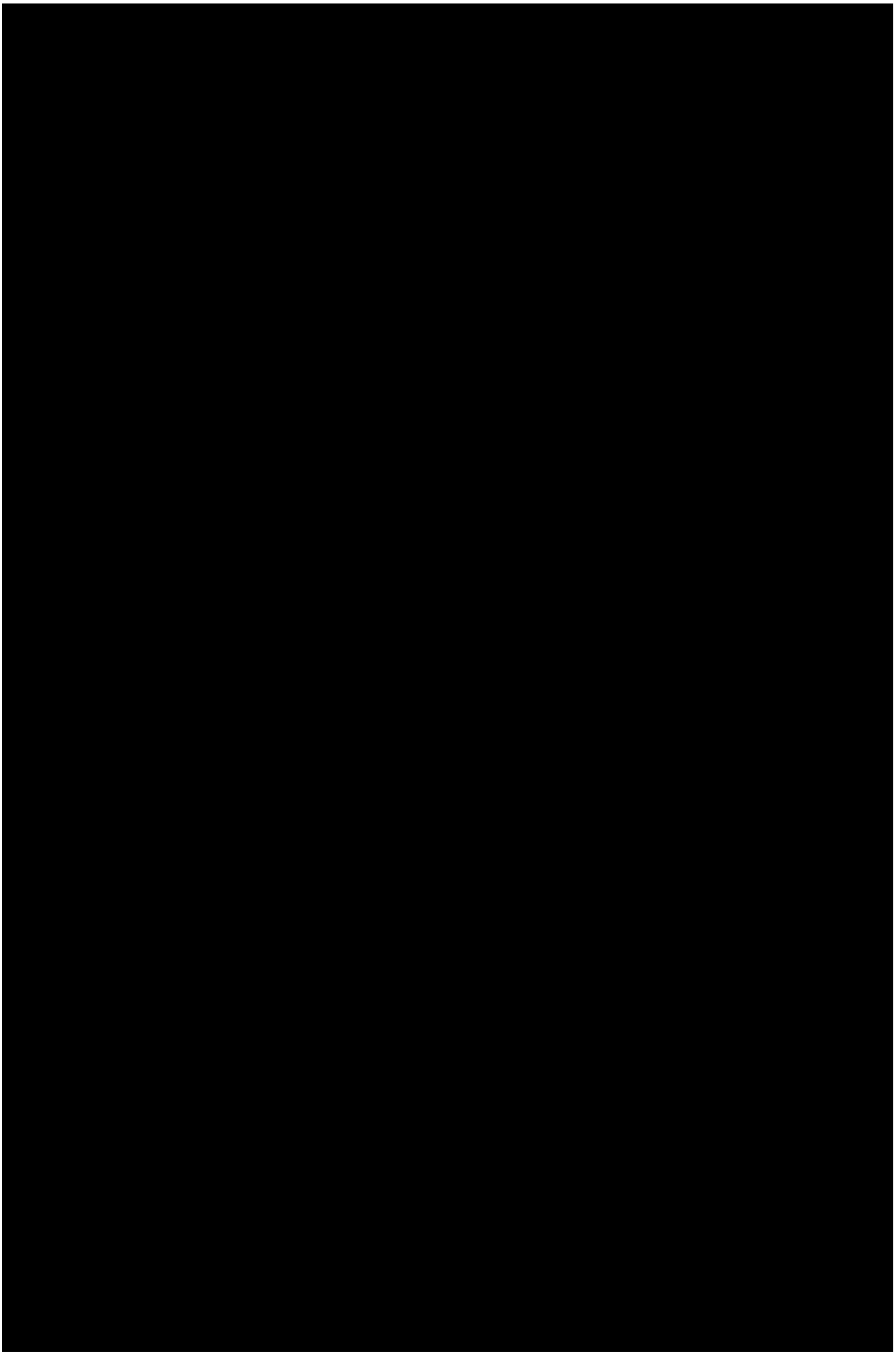


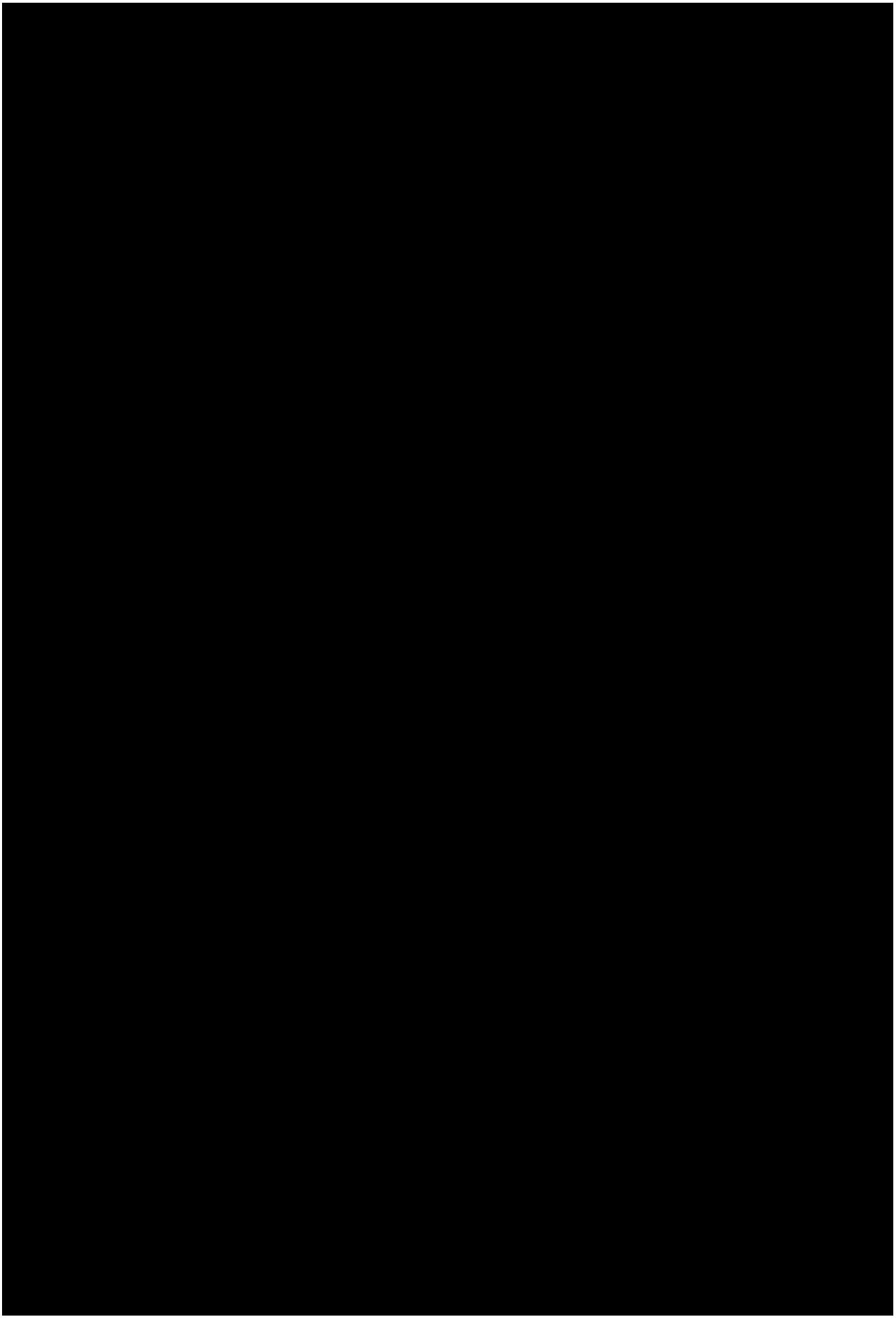


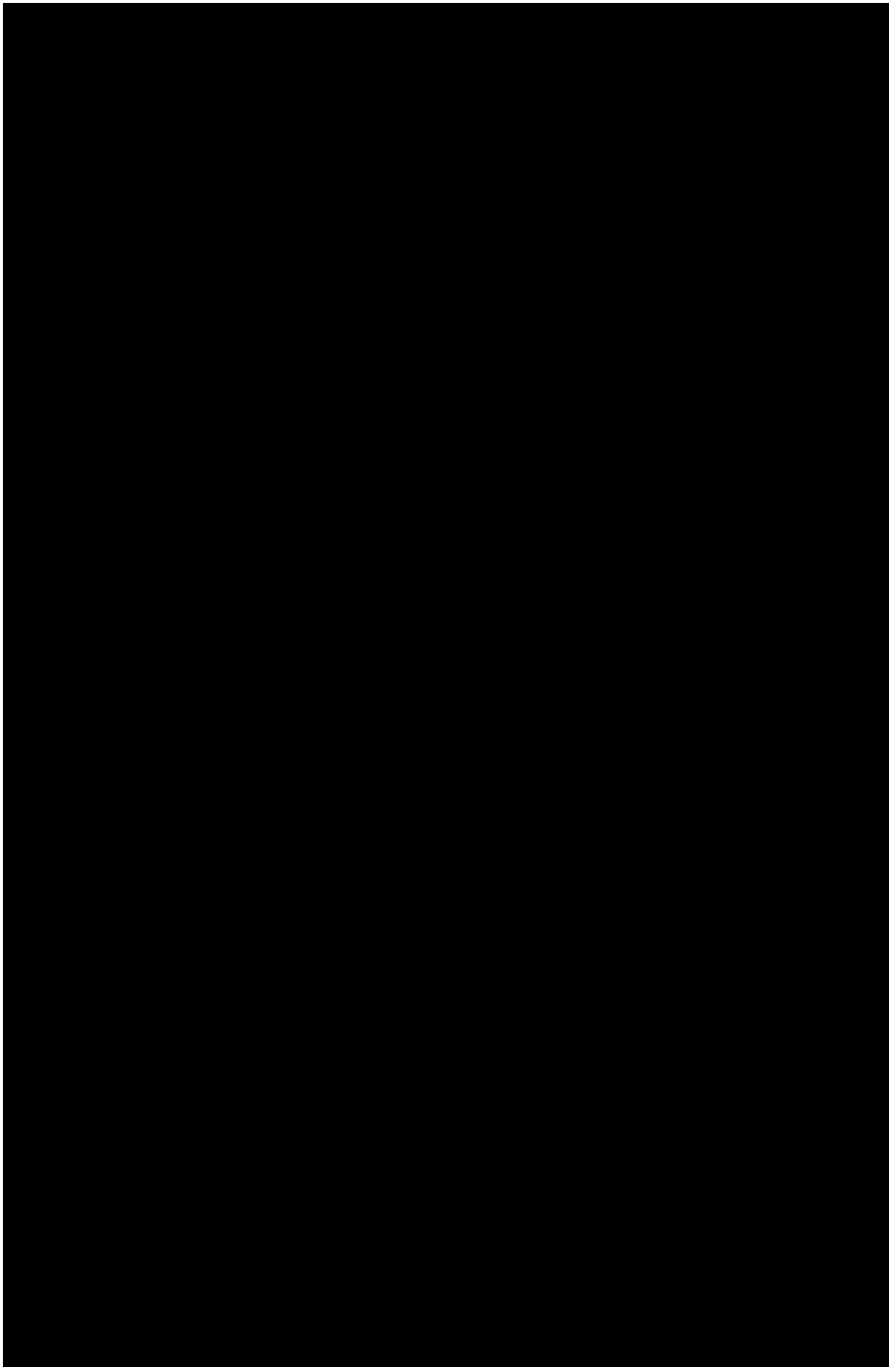


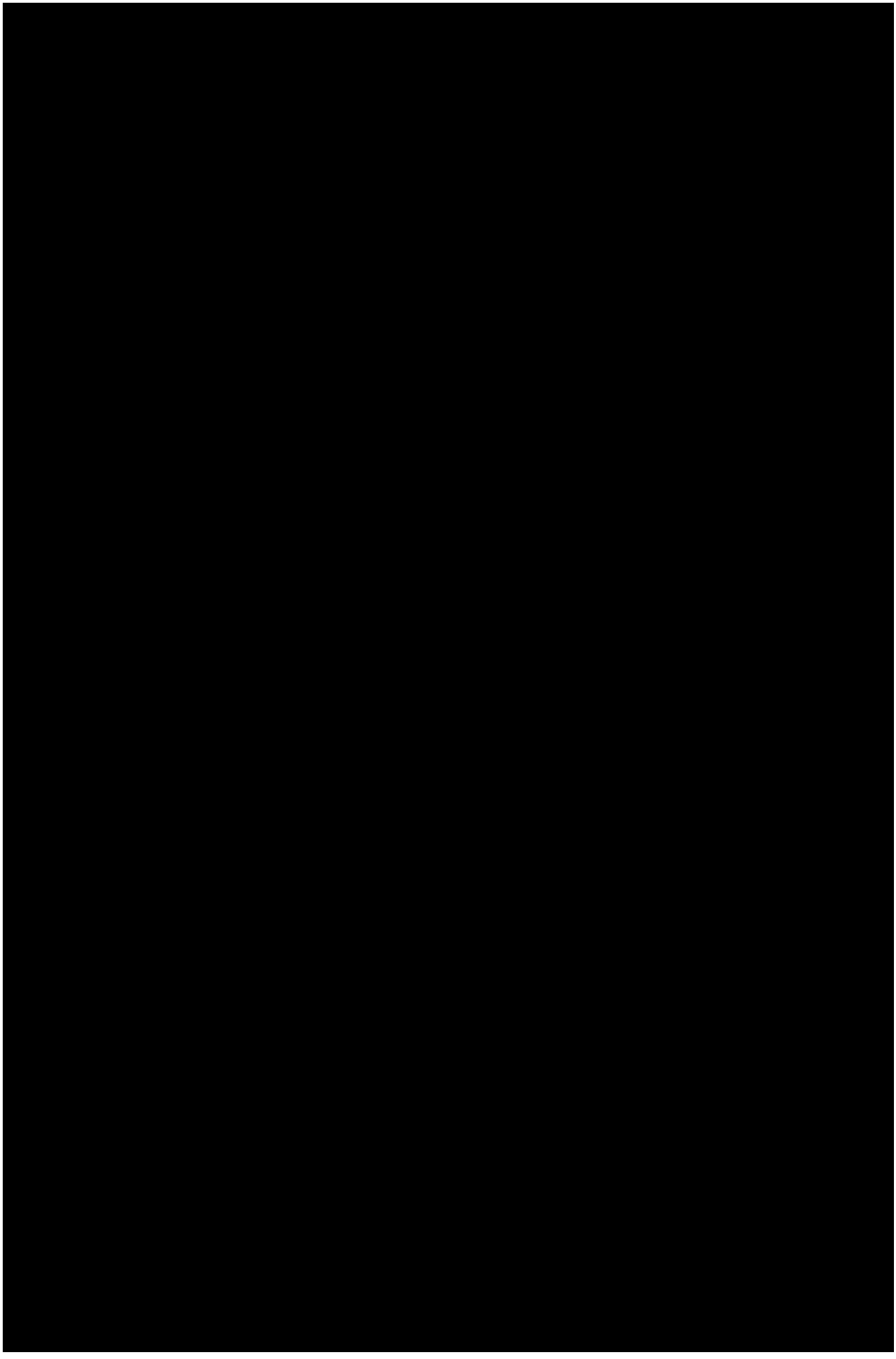




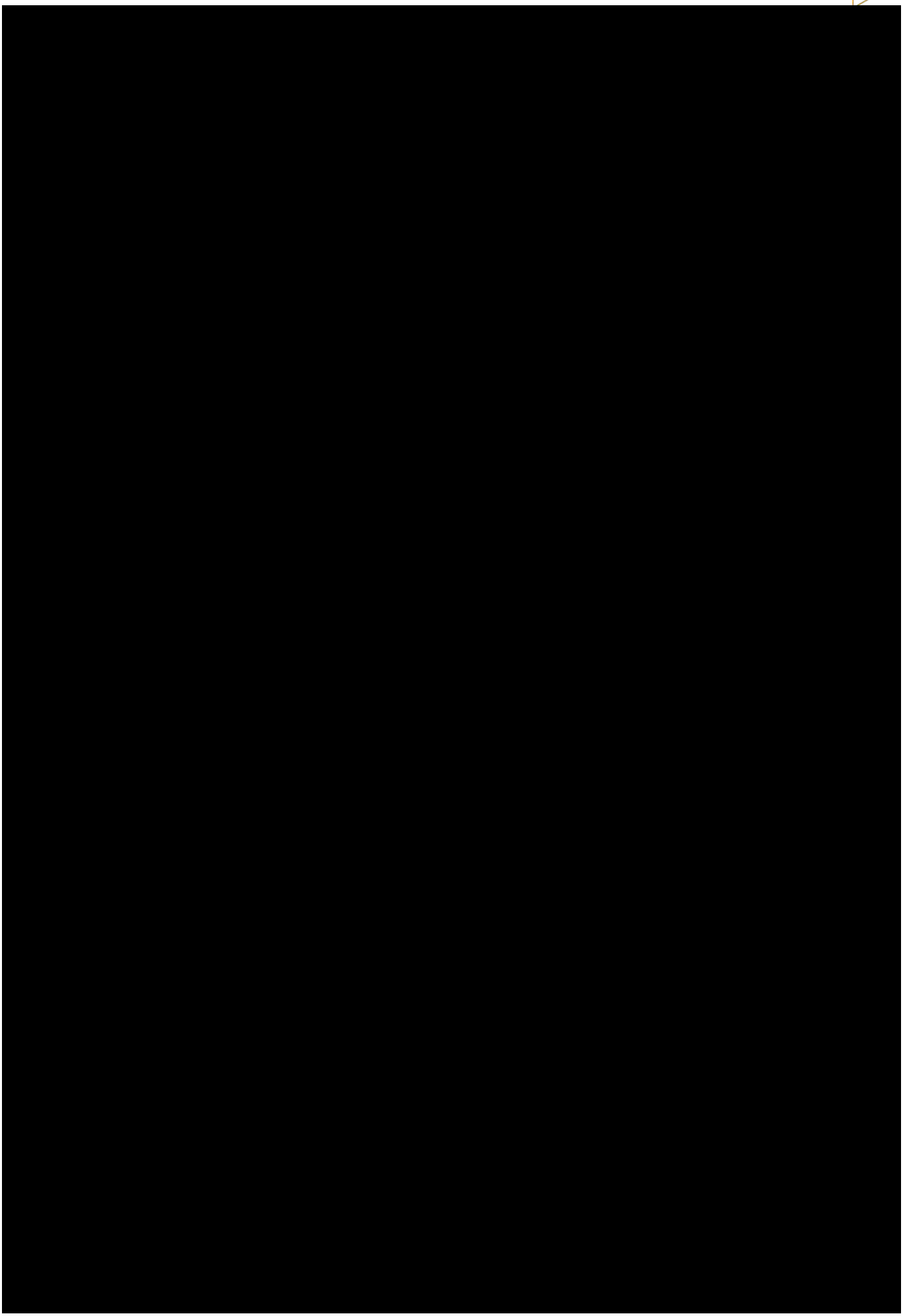


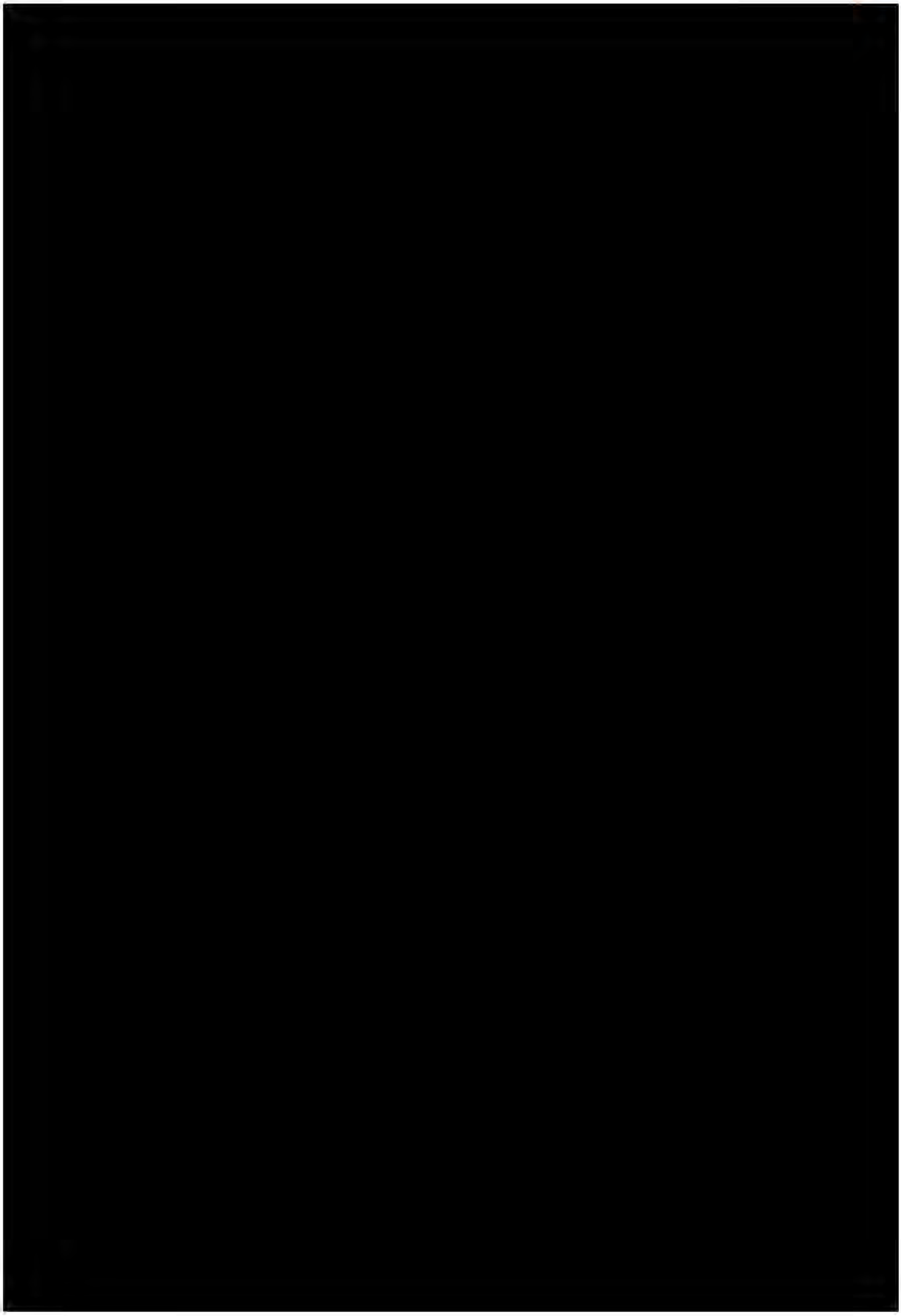




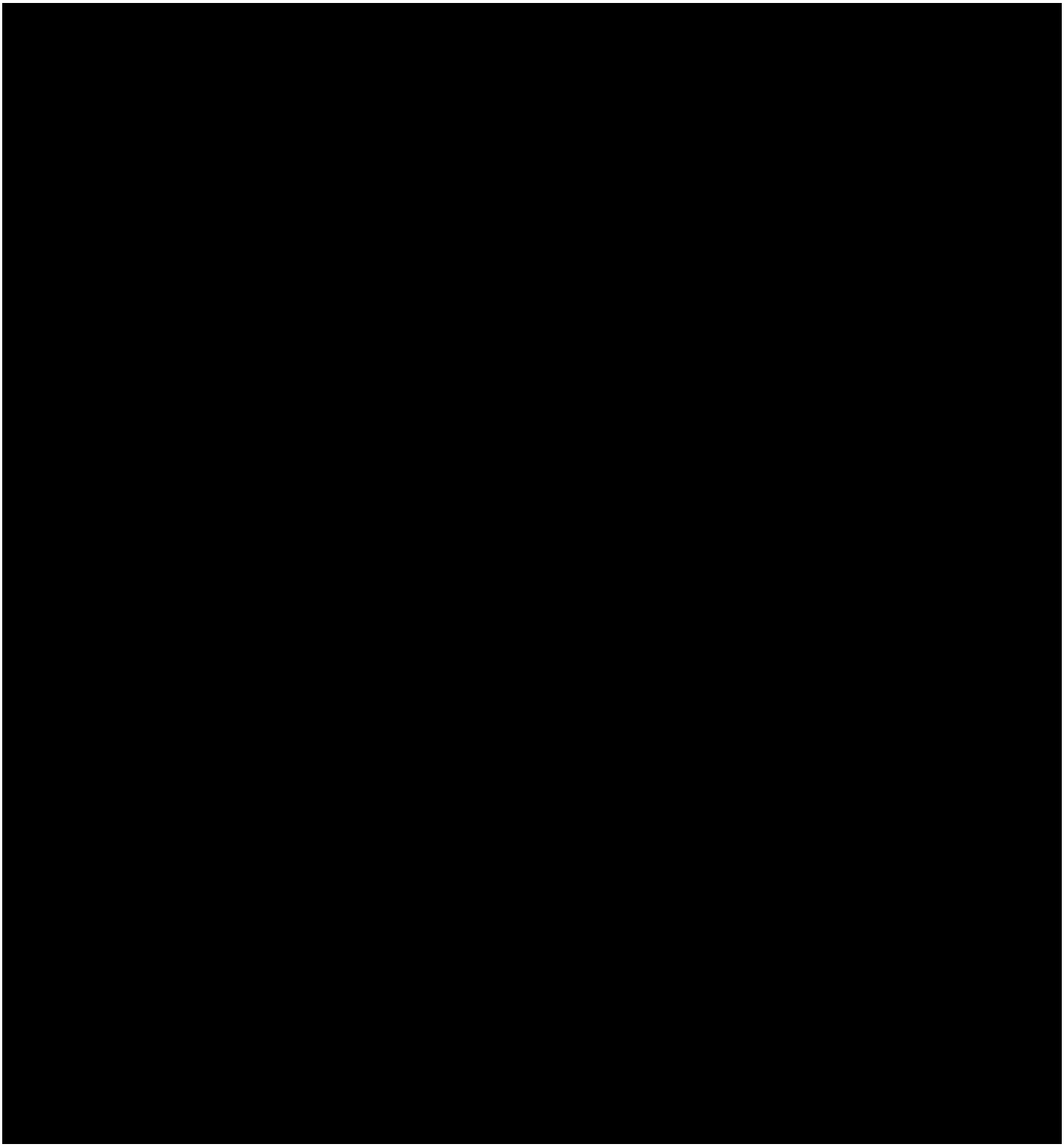


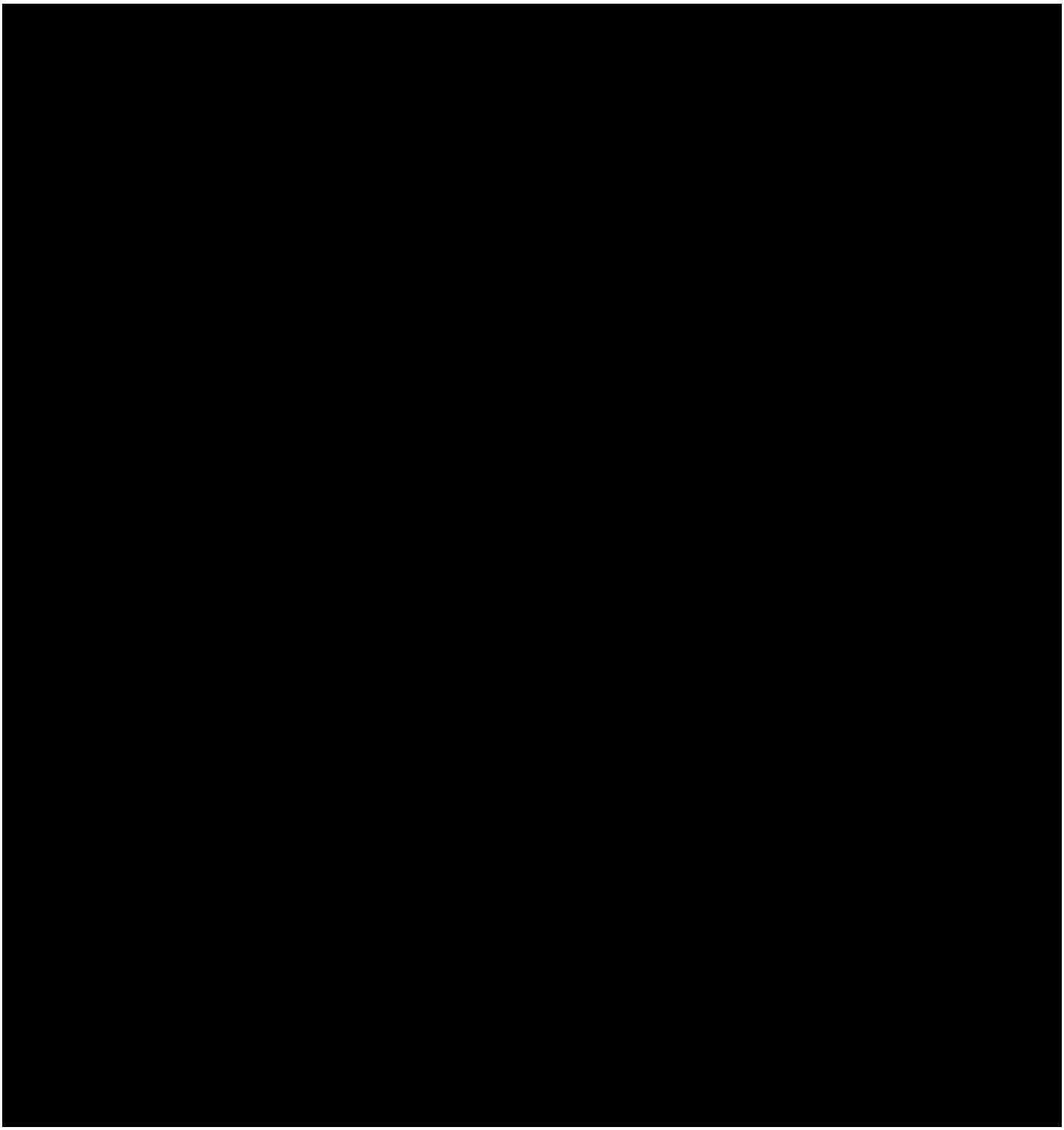
# Vignette executive summary





# OTUS tables





# References found through the epidemiological SLR

# CMV infection - SOT

**Khurana, MP., et al.** Risk factors for failure of primary (val) ganciclovir prophylaxis against cytomegalovirus infection and disease in solid organ transplant recipients. *Open Forum Infect Dis.* 2019, Vol. 6, 6.

**Reekie, J. and al, et.** The risk of CMV infection and recurrence among SOT recipients - Poster 1079. *IDWeek2020.* 2020.

**Navarro, D., et al.** Preventive CMV strategies: A center's experience. *Transplant International.* 2015, Vol. 28, p. 752.

**Serrano-Alonso, M., et al.** Reduction in mortality associated with secondary cytomegalovirus prophylaxis after solid organ transplantation. *Transplant Infectious Disease.* 2018, Vol. 20, 3.

**Serrano-Alonso, M., et al.** Extended versus standard cytomegalovirus prophylaxis in solid organ transplantation. *European Journal of Hospital Pharmacy.* 2018, Vol. 25, S1, p. A87.

**Molina-Ortega, A., et al.** Impact of pretransplant CMV-specific T-cell immune response in the control of CMV infection after solid organ transplantation: a prospective cohort study. *Clinical Microbiology and Infection.* 2019, Vol. 25, 6, pp. 753-8.

**Hensler, D., et al.** Impact of electronic health record-based, pharmacist-driven valganciclovir dose optimization in solid organ transplant recipients. *Transplant Infectious Disease.* 2018, Vol. 20, 2, p. e12849.

**Byrns, JS., Pilch, N. W. and Taber, D. J.** Impact of Pharmacist Involvement in Early Identification and Enrollment in Patient Assistance Programs on CMV Outcomes in Transplantation. Journal of Pharmacy Practice. 2016, Vol. 29, 2, pp. 97-102.

**Toyoda, MS., et al.** Impact of Desensitization on Antiviral Immunity in HLA-Sensitized Kidney Transplant Recipients. *Journal of Immunological Research.* 2017.

**Fayek, SA., et al.** Extended Low-Dose Valganciclovir Is Effective Prophylaxis Against Cytomegalovirus in High-Risk Kidney Transplant Recipients With Near-Complete Eradication of Late-Onset Disease. *Transplantation Proceedings.* 2016, Vol. 48, 6, pp. 2056-64.

**Sheldon, AT. and Clancy, M.** Patterns of CMV infection post-renal transplant. *Transplant International.* 2015, Vol. 28, p. 553.

**Hemmersbach-Miller, M., et al.** Age matters: older age as a risk factor for CMV reactivation in the CMV serostatus-positive kidney transplant recipient. *European Journal of Clinical Microbiology and Infectious Diseases.* 2020, Vol. 39, 3, pp. 455-63.

**Strakosha, A., Pasko, N. and Cadri, V.** Cytomegalovirus infection in renal transplant recipient. *Transplant International.* 2017, Vol. 30, S2, pp. 494-5.

**Ritta, M., et al.** Pre-transplant assessment of CMV-specific immune response by Elispot assay in kidney transplant recipients. *New Microbiologica.* 2015, Vol. 38, 3, pp. 329-35.

**Lollinga, WT., et al.** High human cytomegalovirus DNAemia early post-transplantation associates with irreversible and progressive loss of renal function – a retrospective study. *Transplant International.* 2017, Vol. 30, pp. 817-26.

**Tague, LK., et al.** Lung transplant outcomes are influenced by severity of neutropenia and granulocyte colony-stimulating factor treatment. *Am J Transplant.* 2020, Vol. 20, pp. 250-61.

**Beam, E., et al.** Cytomegalovirus disease is associated with higher all-cause mortality after lung transplantation despite extended antiviral prophylaxis. *Clin Transplant.* 2016, Vol. 30, pp. 270-8.

**Monforte, V., et al.** Risk factors, survival, and impact of prophylaxis length in cytomegalovirus-seropositive lung transplant recipients: A prospective, observational, multicenter study. *Transplant Infectious Disease.* 2017, Vol. 19, 3.

**Jewani, PK., Pouch, S. M. and Kissling, K. T.** Incidence of cytomegalovirus in cardiac transplant recipients receiving induction immunosuppression with antithymocyte globulin. *Clinical Transplantation.* 2018, Vol. 32, 11, p. e13420.

**Schneider, M., et al.** Clinical significance of the single nucleotide polymorphism TLR2 R753Q in heart transplant recipients at risk for cytomegalovirus disease. *Journal of Clinical Virology.* 2016, Vol. 84, pp. 64-9.

**Mahr, S., et al.** Cmv complications after heart transplantation-a single center analysis. *Transplant International.* 2015, Vol. 28, p. 253.

**Eriksson, M., et al.** Low-dose valganciclovir prohylaxis is efficacious and safe in cytomegalovirus seropositive heart transplant recipients with anti-thymocyte globulin. *Transplant Infectious Disease.* 2018, Vol. 20, 3, p. e12868.

**Durante-Mangoni, E., et al.** Effect of the immunosuppressive regimen on the incidence of cytomegalovirus infection in 378 heart transplant recipients: A single centre, prospective cohort study. *Journal of Clinical Virology.* 2015, Vol. 68, pp. 37-42.

**Timpone, JG., et al.** Resistant cytomegalovirus in intestinal and multivisceral transplant recipients. *Transplant Infectious Disease.* 2016, Vol. 18, 2, pp. 202-9.

**Nagai, S., et al.** Cytomegalovirus Infection After Intestinal/Multivisceral Transplantation: A Single-Center Experience With 210 CasesTransplantation. *Transplantation.* 2016, Vol. 100, 2, pp. 451-60.

**Liu, A.W., Jutivorakool, K. and Fisher, C. E., et al.** Comparison of Preemptive Therapy and Antiviral Prophylaxis for Prevention of Cytomegalovirus in Seropositive Liver Transplant Recipients. *Transplantation.* 2017.

**Shah, AP., Chen, JM. and Fridell, JA.** Incidence and outcomes of cytomegalovirus in pancreas transplantation with steroid free immunosuppression. *Clin Transplant.* 2015, Vol. 29, pp. 1221-9.

**Jaamei, N., et al.** Clinical significance of post-prophylaxis cytomegalovirus infection in lung transplant recipients. *Transplant Infectious Disease.* 2018, Vol. 20, 4, p. e12893.

**Mengelle, C., et al.** Prophylaxis versus pre-emptive treatment for prevention of cytomegalovirus infection in CMV-seropositive orthotopic liver-transplant recipients. *Journal of Medical Virology.* 2015, Vol. 87, 5, pp. 836-44.

# Refractory CMV – SOT

**Fisher, CE., et al.** Risk Factors and Outcomes of Ganciclovir-Resistant Cytomegalovirus Infection in Solid Organ Transplant Recipients. *Clinical Infectious Diseases.* 2017, Vol. 65, 1, pp. 57-63.

**Nagai, S., et al.** Cytomegalovirus Infection After Intestinal/Multivisceral Transplantation: A Single-Center Experience With 210 CasesTransplantation. *Transplantation.* 2016, Vol. 100, 2, pp. 451-60.

# Resistent CMV – SOT

**Gardiner, BJ., et al.** The impact of recurrent cytomegalovirus infection on long-term survival in solid organ transplant recipients. *Transplant Infectious.* 2019, Vol. 21, 6, p. e13189.

**Hensler, D., et al.** Impact of electronic health record-based, pharmacist-driven valganciclovir dose optimization in solid organ transplant recipients. *Transplant Infectious Disease.* 2018, Vol. 20, 2, p. e12849.

**Young, PG., et al.** Ganciclovir-resistant cytomegalovirus infection in solid organ transplant recipients: a single-center retrospective cohort study. *Transplant Infectious Disease.* 2016, Vol. 18, 3, pp. 390-5.

**Shah, AP., Chen, JM. and Fridell, JA.** Incidence and outcomes of cytomegalovirus in pancreas transplantation with steroid free immunosuppression. *Clin Transplant.* 2015, Vol. 29, pp. 1221-9.

**Timpone, JG., et al.** Resistant cytomegalovirus in intestinal and multivisceral transplant recipients. *Transplant Infectious Disease.* 2016, Vol. 18, 2, pp. 202-9.

**Nagai, S., et al.** Cytomegalovirus Infection After Intestinal/Multivisceral Transplantation: A Single-Center Experience With 210 CasesTransplantation. *Transplantation.* 2016, Vol. 100, 2, pp. 451-60.

**Grewal, H., et al.** Cytomegalovirus (CMV) Infection in Small Intestinal and Multivisceral Transplant Recipients: The Role of Donor Selection on CMV Incidence and Outcomes. *Am J Transplant.* 2018, Vol. 18, S4.

**Khurana, MP., et al.** Risk factors for failure of primary (val) ganciclovir prophylaxis against cytomegalovirus infection and disease in solid organ transplant recipients. *Open Forum Infect Dis.* 2019, Vol. 6, 6.

**Lollinga, WT., et al.** High human cytomegalovirus DNAemia early post-transplantation associates with irreversible and progressive loss of renal function – a retrospective study. *Transplant International.* 2017, Vol. 30, pp. 817-26.

**Durante-Mangoni, E., et al.** Effect of the immunosuppressive regimen on the incidence of cytomegalovirus infection in 378 heart transplant recipients: A single centre, prospective cohort study. *Journal of Clinical Virology.* 2015, Vol. 68, pp. 37-42.

**Mengelle, C., et al.** Prophylaxis versus pre-emptive treatment for prevention of cytomegalovirus infection in CMV-seropositive orthotopic liver-transplant recipients. *Journal of Medical Virology.* 2015, Vol. 87, 5, pp. 836-44.

**Ambrose, TS, L. M., et al.** Cytomegalovirus Infection and Rates of Antiviral Resistance Following Intestinal and Multivisceral Transplantation. *Transplantation Proceedings.* 2016, Vol. 48, 2, pp. 492-6.

# Recurrent CMV – SOT

**Gardiner, BJ., et al.** The impact of recurrent cytomegalovirus infection on long-term survival in solid organ transplant recipients. *Transplant Infectious.* 2019, Vol. 21, 6, p. e13189.

**Devresse, A., et al.** Reduction in late onset cytomegalovirus primary disease after discontinuation of antiviral prophylaxis in kidney transplant recipients treated with de novo everolimus. *Transplant Infectious Disease.* 2018, Vol. 20, 2, p. e12846.

**Nagai, S., et al.** Cytomegalovirus Infection After Intestinal/Multivisceral Transplantation: A Single-Center Experience With 210 CasesTransplantation. *Transplantation.* 2016, Vol. 100, 2, pp. 451-60.

**Durante-Mangoni, E., et al.** Effect of the immunosuppressive regimen on the incidence of cytomegalovirus infection in 378 heart transplant recipients: A single centre, prospective cohort study. *Journal of Clinical Virology.* 2015, Vol. 68, pp. 37-42.

# CMV infection – HSCT

**Slade, MG, S., et al.** Epidemiology of infections following haploidentical peripheral blood hematopoietic cell transplantation. *Transplant Infectious Disease.* 2017, Vol. 19, 1.

**Schuster, M., et al.** Infections in Hematopoietic Cell Transplant Recipients: Results From the Organ Transplant Infection Project, a Multicenter, Prospective, Cohort Study. *Open Forum Infect Dis.* 2017.

**Marchalik, R., et al.** Cytomegalovirus (CMV) infection and disease incidence and risk factors across diverse hematopoietic cell transplantation (HCT) platforms using a standardized monitoring and treatment approach: A comprehensive evaluation from a single institution. *Biology of Blood and Marrow Transplantation.* 2018, Vol. 24, 3 S1, pp. S377-S8.

**Tandra, A., et al.** Low dose antithymocyte globulin (ATG) for graft-versus-host disease (GVHD) prophylaxis. *Blood Conference: 58th Annual Meeting of the American Society of Hematology, ASH.* 2016, Vol. 128, 22.

**Saullo, JL., et al.** Cytomegalovirus in Allogeneic Hematopoietic Transplantation: Impact on Costs and Clinical Outcomes Using a Preemptive Strategy. *Biol Blood Marrow Transplant.* 2020, Vol. 26, pp. 568-80.

**Webb, BJ., et al.** The clinical and economic impact of cytomegalovirus infection in recipients of hematopoietic stem cell transplantation. *Transplant Infectious Disease.* 2018, Vol. 20, 5, p. e12961.

**Hakimi, Z., et al.** Burden of cytomegalovirus disease in allogeneic hematopoietic cell transplant recipients: a national, matched cohort study in an inpatient setting. *Current Research in Translational Medicine.* 2018, Vol. 66, 4, pp. 95-101.

**Balan, AM., et al.** Molecular monitoring of Herpesviridae family members after allogeneic hematopoietic stem cell transplantation - a single center experience. *Bone Marrow Transplantation - 41st Annual Meeting of ESBMT: Physicians Poster Sessions.* 2015.

**Tischer, J., et al.** Virus infection in HLA-haploidentical hematopoietic stem cell transplantation: incidence in the context of immune recovery in two different transplantation settings. *Annals of Hematology.* 2015, Vol. 94, 10, pp. 1677-88.

**Robin, C., et al.** Economic burden of preemptive treatment of CMV infection after allogeneic stem cell transplantation: a retrospective study of 208 consecutive patients. *BMC Infectious Diseases.* 2017, Vol. 17, 1.

**Verduyn Lunel, FM., et al.** Cytomegalovirus status and the outcome of T cell-replete reduced-intensity allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2016, Vol. 22, 10, pp. 1883-7.

**Koldehoff, M., et al.** Early CMV-replication after allogeneic stem cell transplantation is associated with a reduced relapse risk in lymphoma. *Leukemia & Lymphoma.* 2017, Vol. 58, 4, pp. 822-33.

**Reekie, J. and al, et.** Absolute lymphocyte count as a predictor of CMV infection and recurrence in HSCT recipients - Poster 1075. *IDWeek2020.* 2020.

**Panagou, E., et al.** Cytomegalovirus pre-emptive therapy after hematopoietic stem cell transplantation in the era of real-time quantitative PCR: comparison with recipients of solid organ transplants. *Transplant Infectious Disease.* 2016, Vol. 18, 3, pp. 405-14.

**Aparicio, ES, Cardenoso L, Pereira PL, Fernandez PC, Torrecillas SG, Caso BF, de la Camara R.** Impact of cmv replication in overall survival in allogeneic HSCT recipients. *45th Annual Meeting of the EBMT - Physicians - Poster Session.* 2019, Vol. 54.

**Crocchiolo, R., et al.** Infections after T-replete haploidentical transplantation and high-dose cyclophosphamide as graft-versus-host disease prophylaxis. *Transplant Infectious Disease.* 2015, Vol. 17, 2, pp. 242-9.

**Servais, S., et al.** Response to antiviral therapy in haematopoietic stem cell transplant recipients with cytomegalovirus (CMV) reactivation according to the donor CMV serological status. *Clinical Microbiology & Infection.* 2016, Vol. 22, 3, p. 289.

**Baltadakis, I., et al.** Viral Reactivation after T Cell Replete Haploidentical Stem Cell Transplantation: Increased Incidence in Association with Immune Reconstitution. *Biology of Blood and Marrow Transplantation.* 2020, Vol. 26, S3.

**Camargo, JF., et al.** Impact of Cytomegalovirus Viral Load on Probability of Spontaneous Clearance and Response to Preemptive Therapy in Allogeneic Stem Cell Transplantation Recipients. *Biology of Blood & Marrow Transplantation.* 2018, Vol. 24, 4, pp. 806-14.

**Green, ML., et al.** Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. *The Lancet Haematology.* 2016, Vol. 3, 3, pp. e119-27.

Zavras, P., Su, Y. and Fang, J et al. Impact of Preemptive Therapy for Cytomegalovirus on Toxicities after Allogeneic Hematopoietic Cell Transplantation in Clinical Practice: A Retrospective Single-Center Cohort Study. Biol Blood Marrow Transplant. 2020, Vol. 26, pp. 1482-91.

**Hammerstrom, AE., et al.** Prevention of Cytomegalovirus Reactivation in Haploidentical Stem Cell Transplantation. *Biology of Blood & Marrow Transplantation.* 2018, Vol. 24, 2, pp. 353-8.

**Rinehart, M., et al.** Evaluation of cytomegalovirus reactivation and tolerability in seropositive umbilical cord transplant patients after implementation of an intensive prevention strategy. *Hematol Oncol Stem Cell Ther.* 2016, Vol. 9, 3, pp. 105-111.

**Kim, SJ., et al.** Cytomegalovirus resistance in CD34+ selected hematopoietic cell transplant recipients. *Transplant Infectious Disease.* 2018, Vol. 20, 3, p. e12881.

**Huang, YT., et al.** Cytomegalovirus Infection in Allogeneic Hematopoietic Cell Transplantation Managed by the Preemptive Approach: Estimating the Impact on Healthcare Resource Utilization and Outcomes. *Biology of Blood & Marrow Transplantation.* 2019, Vol. 25, 4, pp. 791-9.

**Ramanathan, M., Teira, P., Battiwalla, M., et al.** Impact of Early Cytomegalovirus Reactivation in Cord Blood Stem Cell Recipients in the Current Era. *Bone Marrow Transplant.* 2016, Vol. 51, 8, pp. 1113-20.

**Hilal, T., et al.** Cytomegalovirus reactivation is associated with a lower rate of early relapse in myeloid malignancies independent of in-vivo T cell depletion strategy. *Leukemia Research.* 2017, Vol. 57, pp. 37-44.

# Refractory CMV – HSCT

**Camargo, JF., et al.** Impact of Cytomegalovirus Viral Load on Probability of Spontaneous Clearance and Response to Preemptive Therapy in Allogeneic Stem Cell Transplantation Recipients. *Biology of Blood & Marrow Transplantation.* 2018, Vol. 24, 4, pp. 806-14.

**Tan, S., Waggoner, J. and Pinsky, B.** Cytomegalovirus load at treatment initiation is predictive of time to resolution of viremia and duration of therapy in hematopoietic cell transplant recipients. *J Clin Virol.* 2015, Vol. 69, pp. 179-83.

**Aparicio, ES, Cardenoso L, Pereira PL, Fernandez PC, Torrecillas SG, Caso BF, de la Camara R.** Impact of cmv replication in overall survival in allogeneic HSCT recipients. *45th Annual Meeting of the EBMT - Physicians - Poster Session.* 2019, Vol. 54.

**Servais, S., et al.** Response to antiviral therapy in haematopoietic stem cell transplant recipients with cytomegalovirus (CMV) reactivation according to the donor CMV serological status. *Clinical Microbiology & Infection.* 2016, Vol. 22, 3, p. 289.

# Resistent CMV – HSCT

**Slade, MG, S., et al.** Epidemiology of infections following haploidentical peripheral blood hematopoietic cell transplantation. *Transplant Infectious Disease.* 2017, Vol. 19, 1.

**Camargo, JF., et al.** Impact of Cytomegalovirus Viral Load on Probability of Spontaneous Clearance and Response to Preemptive Therapy in Allogeneic Stem Cell Transplantation Recipients. *Biology of Blood & Marrow Transplantation.* 2018, Vol. 24, 4, pp. 806-14.

**Zavras, P., Su, Y. and Fang, J et al.** Impact of Preemptive Therapy for Cytomegalovirus on Toxicities after Allogeneic Hematopoietic Cell Transplantation in Clinical Practice: A Retrospective Single-Center Cohort Study. *Biol Blood Marrow Transplant.* 2020, Vol. 26, pp. 1482-91.

**Saullo, JL., et al.** Cytomegalovirus in Allogeneic Hematopoietic Transplantation: Impact on Costs and Clinical Outcomes Using a Preemptive Strategy. *Biol Blood Marrow Transplant.* 2020, Vol. 26, pp. 568-80.

**Webb, BJ., et al.** The clinical and economic impact of cytomegalovirus infection in recipients of hematopoietic stem cell transplantation. *Transplant Infectious Disease.* 2018, Vol. 20, 5, p. e12961.

**Kim, SJ., et al.** Cytomegalovirus resistance in CD34+ selected hematopoietic cell transplant recipients. *Transplant Infectious Disease.* 2018, Vol. 20, 3, p. e12881.

**Servais, S., et al.** Response to antiviral therapy in haematopoietic stem cell transplant recipients with cytomegalovirus (CMV) reactivation according to the donor CMV serological status. *Clinical Microbiology & Infection.* 2016, Vol. 22, 3, p. 289.

**Aparicio, ES, Cardenoso L, Pereira PL, Fernandez PC, Torrecillas SG, Caso BF, de la Camara R.** Impact of cmv replication in overall survival in allogeneic HSCT recipients. *45th Annual Meeting of the EBMT - Physicians - Poster Session.* 2019, Vol. 54.

# Recurrent CMV – HSCT

**Baltadakis, I., et al.** Viral Reactivation after T Cell Replete Haploidentical Stem Cell Transplantation: Increased Incidence in Association with Immune Reconstitution. *Biology of Blood and Marrow Transplantation.* 2020, Vol. 26, S3.

**Saullo, JL., et al.** Cytomegalovirus in Allogeneic Hematopoietic Transplantation: Impact on Costs and Clinical Outcomes Using a Preemptive Strategy. *Biol Blood Marrow Transplant.* 2020, Vol. 26, pp. 568-80.

**Reekie, J. and al, et.** Absolute lymphocyte count as a predictor of CMV infection and recurrence in HSCT recipients - Poster 1075. *IDWeek2020.* 2020.

**Aparicio, ES, Cardenoso L, Pereira PL, Fernandez PC, Torrecillas SG, Caso BF, de la Camara R.** Impact of cmv replication in overall survival in allogeneic HSCT recipients. *45th Annual Meeting of the EBMT - Physicians - Poster Session.* 2019, Vol. 54.

**Camargo, JF., et al.** Use of maintenance therapy and incidence of recurrent Cytomegalovirus DNAemia among allogeneic hematopoietic cell transplant recipients. *Transplant Infectious Disease.* 2019, Vol. 21, 2, p. e13054.

**Camargo, JF., et al.** Impact of Cytomegalovirus Viral Load on Probability of Spontaneous Clearance and Response to Preemptive Therapy in Allogeneic Stem Cell Transplantation Recipients. *Biology of Blood & Marrow Transplantation.* 2018, Vol. 24, 4, pp. 806-14.

**Servais, S., et al.** Response to antiviral therapy in haematopoietic stem cell transplant recipients with cytomegalovirus (CMV) reactivation according to the donor CMV serological status. *Clinical Microbiology & Infection.* 2016, Vol. 22, 3, p. 289.

**Balan, AM., et al.** Molecular monitoring of Herpesviridae family members after allogeneic hematopoietic stem cell transplantation - a single center experience. *Bone Marrow Transplantation - 41st Annual Meeting of ESBMT: Physicians Poster Sessions.* 2015.