NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Takeda UK

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Anthony Nolan and Leukaemia Care
   b. British Association for the Study of the Liver
   c. UK Renal Pharmacy Group

4. **Evidence Review Group report** prepared by BMJ Group

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from Takeda UK

7. **Technical engagement responses & expert statements from experts:**
   a. Dr Sophie Gillett, Consultant Medical Virologist – clinical expert, nominated by UK Clinical Virology Network
   b. Dr Joanna Moore, Consultant Hepatologist and Honorary Senior Clinical Lecturer – clinical expert, nominated by nominated by British Association for the Study of the Liver / British Liver Transplant Group
   c. Steve Rothberg – patient expert, nominated by Anthony Nolan
   d. Tim Wright - patient expert, nominated by Anthony Nolan

8. **Evidence Review Group critique of company response to technical engagement** prepared by BMJ

9. **Technical engagement follow-up response from company,** Takeda UK

10. **Evidence Review Group follow-up critique** prepared by BMJ

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant ID3900

Document B
Company evidence submission

File name	Version	Contains confidential information	Date
Maribavir for RR CMV ID3900_Document B_(18 Feb REDACTED)	1	Yes	12 January 2022

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List of abbreviations

Acronym	Definition
AE	Adverse event
AESI	Adverse events of special interest
ANC	Absolute neutrophil count
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BSBMT	British Society of Blood and Marrow Transplantation
BSH	British Society for Haematology
BTS	British Transplantation Society
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Conformité Européenne
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
CRD	Centre for Reviews and Dissemination
csCMV	Clinically significant cytomegalovirus
CSR	Clinical study report
cs-recurrence	Clinically significant-recurrence
CUA	Cost-utility analysis
DBD	Donor after brain death
DCD	Donation after circulatory death
DNA	Deoxyribonucleic acid
EAC	Endpoint Adjudication Committee
EBMT	European Society for Blood and Marrow Transplantation
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ER	Endoplasmic reticulum
ERG	Evidence Review Group
FACT-BMT	Functional Assessment of Cancer Therapy - Bone Marrow Transplantation
GORD	Gastro-oesophageal reflux disease
GvHD	Graft-versus-host disease
HCST	Hematopoietic stem cell transplant
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRG	Healthcare resource group
HRU	Healthcare resource utilization
HSCT	Haematopoietic stem cell transplant
HTA	Health technology assessment
IAT	Investigator-assigned anti-CMV treatment
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IPD	Individual patient data
IQR	Interquartile range
IRR	Incidence rate ratio
ITT	Intention-to-treat
IV	Intravenous
LLOQ	Lower limit of quantification
LOS	Length of stay
LYG	Life years gained
MBV	Maribavir
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Multiple myeloma

Acronym	Definition
NHS	National Health Service
NHSBT	National Health Service Blood and Transplant
NICE	National Institute for Health and Care Excellence
NR	Not reported
ns-csCMV	Non-clinically significant Cytomegalovirus
ONS	Office of National Statistics
OTUS	Outcomes, treatment patterns and healthcare resource utilization studies
PAS	Patient access scheme
PCR	Polymerase chain reaction
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Oral
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	Short form-36
SF-36v2	Short form-36 Version 2
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SOT	Solid organ transplant
TEAE	Treatment emergent adverse events
TTO	Time-trade off
UK	United Kingdom
US	United States
WTP	Willingness-to-pay

Executive summary

Decision problem, description of the technology and clinical care pathway

- The submission covers the technology's full marketing authorisation for this indication
- Maribavir is a first-in-class (benzimidazole riboside) anti-cytomegalovirus (CMV) agent, with a novel mechanism of action that has multi-targeted anti-CMV activity

Disease overview

- CMV is a common viral pathogen of the Herpesviridae family.[1] While CMV infection is generally asymptomatic or mild, when the host immunity is weakened, latent CMV can reactivate causing a severe infection, tissue invasive disease, or a severe debilitating condition[1,2]
- 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

Burden

- CMV infections that are refractory or resistant to currently available antivirals are a major cause of morbidity and mortality among solid organ transplant (SOT) and allogeneic haematopoietic stem cell transplant (HSCT) recipients[3]
- Given the shortage of organs, transplant failure is a costly and tragic outcome which wastes a precious resource; patients with transplant failures are generally eligible to receive another transplant, retransplant is not guaranteed

Care pathway

- For the treatment of patients with refractory or resistant CMV post-transplant (SOT and HSCT), the available options include ganciclovir (Cymevene®), valganciclovir (Valcyte ®), or foscarnet (Foscavir®) retreatment with initial or another antiviral can be used, depending on safety profile. All are used off-label in the United Kingdom (UK)

Clinical effectiveness – SOLSTICE

- SOLSTICE was a Phase III, multicentre, randomised (2:1 ratio), open-label, active-controlled, 20-week study which evaluated the efficacy, safety and tolerability of maribavir 400 mg twice daily (BID), compared with investigator-assigned anti-CMV treatment (IAT) (ganciclovir [intravenous; IV], valganciclovir [oral], foscarnet [IV], or cidofovir [IV]) in transplant recipients with CMV infections that are refractory or resistant to treatment

Efficacy

- 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%), a difference of 32.8% (95% confidence interval [CI]: 22.8%, 42.7%; p<0.001)

Safety

- Maribavir had a favourable safety profile and was generally well-tolerated compared to IAT in patients with refractory or resistant CMV in SOLSTICE

Cost-effectiveness

- Maribavir is a cost-effective treatment option compared to current standard of care (IAT)
- In the base case, for the intention-to-treat (ITT) population (SOT and HSCT combined), the deterministic incremental cost-effectiveness ratio (ICER) was £15,337 with higher incremental costs (£2,004), higher incremental quality-adjusted life years (QALYs) (0.131) and life years (0.160)
- The probability that maribavir is cost-effective compared with IAT was 51.83% at a willingness-to-pay (WTP) threshold of £20,000 and 61.72% at a WTP threshold of £30,000

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

This decision problem addressed in this submission is summarised in Table 1.

Table 1: The decision problem

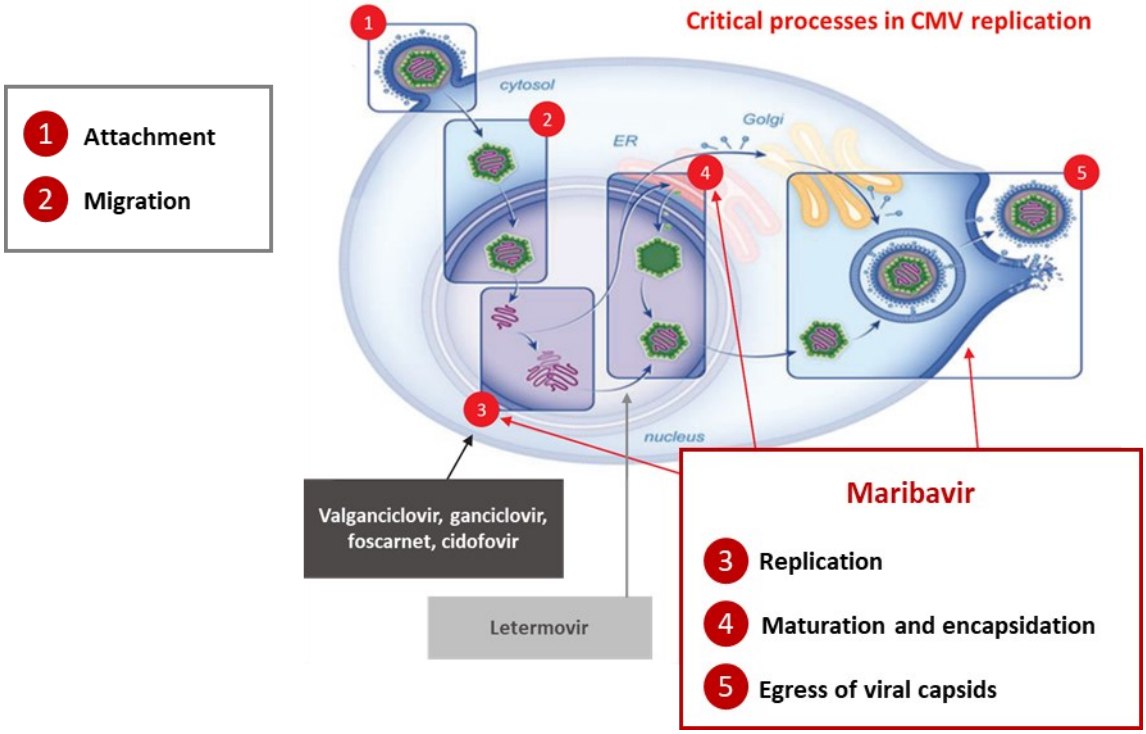
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Intervention(s)	Maribavir	Maribavir	
Population(s)	People with cytomegalovirus infection that is refractory or resistant to treatments after haematopoietic stem cell transplantation or solid organ transplant	As per the final NICE scope	N/A
Comparators	• Ganciclovir • Valganciclovir • Foscarnet • Cidofovir • Ganciclovir with foscarnet • Ganciclovir with hyperimmune globulins • Cytotoxic lymphocytes *None of the listed comparators currently have a marketing authorisation in the UK for this indication.*	• Ganciclovir • Valganciclovir • Foscarnet • Cidofovir *None of the listed comparators currently have a marketing authorisation in the UK for this indication.*	Cytotoxic lymphocytes and hyperimmune globulins are not included within the decision problem as they are not used in regular clinical practice within the UK. No evidence of their efficacy has been identified by an SLR (Appendix D.1)
Outcomes	The outcome measures to be considered include: • CMV infection symptom improvement or reduction • Length of hospital stay • Mortality • Tissue invasive disease • Transplant graft function • Viral load • Adverse effects of treatment • Health-related quality of life	As per the final NICE scope	N/A
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • People who have had HSCT • People who have had SOT The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The NICE submission includes Study 303 data for HSCT and SOT population	N/A

CMV=Cytomegalovirus; HSCT=Haematopoietic stem cell transplant; IAT=Investigator-assigned anti-CMV treatment; N/A=Not applicable; NICE=National Institute for Health and Clinical Excellence; SLR=Systematic literature review; SOT=Solid organ transplant; UK=United Kingdom

B.1.2 Description of the technology being appraised

Maribavir is a first-in-class (benzimidazole riboside) anti-cytomegalovirus (CMV) agent, with a novel mechanism of action that has multi-targeted anti-CMV activity, through the inhibition of the UL97 protein kinase and its natural substrates. UL97 kinase is involved in several important processes in the CMV life cycle including phosphorylation of CMV viral and host proteins which modulate the cell-cycle to support viral deoxyribonucleic acid (DNA) synthesis, the regulation of viral gene expression, and the induction of nuclear lamina disruption to facilitate nuclear egress of viral particles.[4] By targeting the UL97 enzyme, maribavir acts at multiple stages of the CMV lifecycle, inhibiting both replication and encapsulation of CMV DNA as well as preventing the escape of viral capsules from infected cells.[5] This multisite action makes maribavir less susceptible to mutations of the viral DNA polymerase which can cause resistance in other therapies used for the treatment of CMV (Figure 1).[6-9]

Figure 1: Stages of CMV replication and sites of action of currently used antivirals



CMV=Cytomegalovirus; ER=Endoplasmic reticulum
Source: Maertens J, et al. 2019; Takeda 2019.[10,11]

Table 2: Technology being appraised

UK approved name and brand name	Maribavir (LIVTENCITY)[a]
Mechanism 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.[6-9]
Marketing authorisation/CE mark status	Maribavir does not currently have a marketing authorisation in the UK. An application for marketing authorisation was submitted to the EMA on 31 May 2021, with an application to the MHRA (via the reliance route) planned for September 2021. EMA and MHRA approval is expected in November 2022.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	At present, Takeda anticipates maribavir to be indicated for the treatment of adults with post-transplant CMV infection and/or disease who are resistant and/or refractory to prior therapy including ganciclovir, valganciclovir, cidofovir or foscarnet
Method of administration and dosage	Oral administration 400 mg BID, (200 mg x 2 tablets in the morning and 200 mg x 2 in the evening with or without food for 8 weeks
Additional tests or investigations	Not anticipated
List price and average cost of a course of treatment[b]	Cost per 56 x 200 mg pack: £[redacted] Cost per 8-week treatment cycle: £[redacted]
Patient access scheme (if applicable)	Simple discount Cost per 56 x 200 mg pack [redacted] Cost per 8-week treatment cycle: [redacted]

BID=Twice daily; CE=Conformité Européenne; CMV=Cytomegalovirus; DNA=Deoxyribonucleic acid; EMA=European Medicines Agency; mg=Milligram; MHRA=Medicines and Healthcare products Regulatory Agency; SmPC=Summary of product characteristics; UK=United Kingdom

[a] Proposed product name in the UK pending MHRA approval

b The list price of maribavir has been submitted to the Department of Health and Social care and is subject to approval. Takeda UK Ltd offer a simple discount on the submitted list price which has been accepted by PASLU.

B.1.3 Health condition and position of the technology in the treatment pathway

Disease overview

- CMV is a common viral pathogen (prevalent in 60–70% of the general population) of the Herpesviridae family.[1] While CMV infection is generally asymptomatic or mild, when the host immunity is weakened, latent CMV can reactivate causing a severe infection, tissue invasive disease, or a severe debilitating condition[1,2]
- 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
    - There are two phases of post-transplant care: acute and chronic
        - Acute phase (1–3 months): Immunosuppression therapy will be higher during this phase; therefore, patients are at higher risk of CMV infection
        - Post-transplant chronic phase (3–6 months): Immunosuppression therapy is decreased as a result of the patients innate immunity becoming more robust; therefore, are less likely to result in morbidity and mortality

Epidemiology

- In the 2019–2020 financial year, there were over 4,700 solid organ transplant (SOT) procedures in the United Kingdom (UK)[12]
- In 2019, there were 1,726 allogeneic haematopoietic stem cell transplant (HSCT) procedures in the UK[13]
- Due to the lack of UK-specific epidemiology evidence in the literature, Takeda has estimated the total number of patients eligible for maribavir using available UK data and validated this with expert English clinicians. It is estimated there are [redacted] patients post-transplant who are refractory or resistant to CMV per year in the UK[14]

Burden

- CMV infections that are refractory or resistant to currently available antivirals are a major cause of morbidity and mortality among SOT and allogeneic HSCT recipients[3]
- Generally, CMV manifests as CMV infection (asymptomatic) or CMV disease (symptomatic, presents as fever in combination with either neutropenia, thrombocytopenia, or bone marrow suppression); patients can experience severe outcomes when not treated and when resistant or refractory to treatment, including:[15,16]
    - When CMV infects an end-organ in SOT patients, it causes tissue injury that results in organ dysfunction and leads to tissue invasive disease such as CMV pneumonia, gastrointestinal CMV disease, CMV central nervous system disease, and CMV retinitis[15,16]
    - CMV infection after allogeneic HSCT also leads to tissue invasive disease (e.g. esophagitis, gastroenteritis, hepatitis, retinitis, pneumonia, encephalitis)[17]
- Various studies indicate that any level of CMV is associated with an increased risk of mortality post-transplant in both SOT and HSCT patients[18-21]
- Given the shortage of organs, transplant failure is a costly and tragic outcome which wastes a precious resource; patients with transplant failures are generally eligible to receive another transplant, but retransplant is not guaranteed
    - An effective treatment regimen to prevent CMV infection can reduce the risk of transplant failure and improve success

Care pathway

• For both SOT and HSCT, the management of CMV post-transplant can be separated into two stages:[22,23]
  ○ Prophylaxis is administered prior to detectable CMV viral load and ensures patients remains at undetectable levels[22]
  ○ Pre-emptive therapy is administered once patients have a detectable CMV viral load; these patients can be symptomatic or asymptomatic[22]
• SOT treatment pathway:[22]
  ○ There are no treatments approved for the management of CMV post-SOT, the most commonly used treatments: ganciclovir, valganciclovir, foscarnet, and cidofovir are used off-label
  ○ Pre-emptive therapies for the treatment of patients with refractory or resistant CMV post-transplant include retreatment with valganciclovir or ganciclovir; or the use of foscarnet. However, treatments are often limited due to toxicity associated with valganciclovir and ganciclovir (e.g. neutropenia) and foscarnet (e.g. nephrotoxicity)
• Allogeneic HSCT treatment pathway:[23]
  ○ Letermovir is the only product approved for the management of CMV post-HSCT; however, it is used as prophylaxis through the first 100 days post-transplant and cannot be used for pre-emptive treatment in the population of interest - refractory or resistant post-transplant
  ○ For the treatment of patients with refractory or resistant CMV post-transplant, the available options include ganciclovir, valganciclovir, or foscarnet, retreatment with initial or another antiviral can be used, depending on safety profile

B.1.3.1 Disease overview

Human CMV is a common viral pathogen of the Herpesviridae family.[1] While CMV infection is generally asymptomatic or mild, when the host immunity is weakened or suppressed, latent CMV can reactivate causing a severe infection (Table 3).[24] In immunocompromised patients (e.g. post-transplant), an asymptomatic CMV infection can quickly progress to CMV syndrome and tissue invasive disease, a severe debilitating condition.[1,2] SOT and allogeneic HSCT require the use of potent immunosuppressive chemotherapy, which reduces the patient's protection to CMV; consequently, CMV is a frequent complication after transplantation.[25,26]

Table 3: Definitions of CMV manifestations

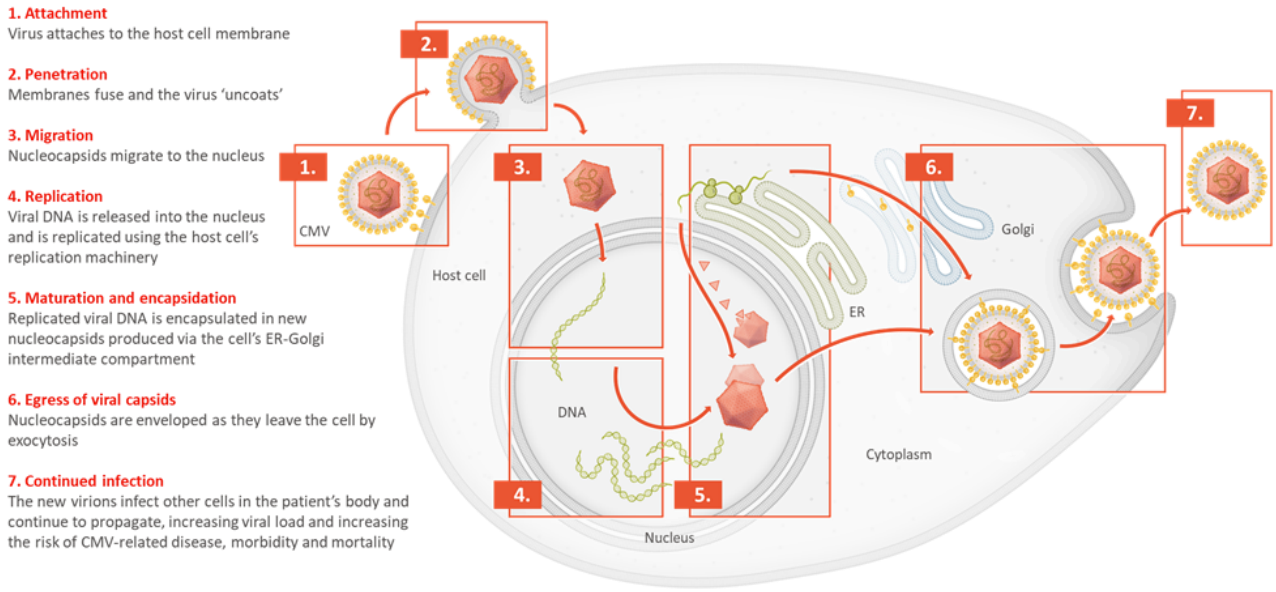
Terminology	Definition
CMV infection	Prescence of detectable CMV viral particles. A CMV infection can be asymptomatic
CMV disease	A symptomatic CMV infection. CMV disease can be classified as CMV syndrome or tissue invasive disease
CMV syndrome	• For SOT patients, CMV syndrome is defined as fever (>38 ºC) for at least 2 days within a 4-day period, CMV detection in blood and either neutropenia or thrombocytopenia • For allogeneic HSCT patients, the definition for CMV syndrome is broader and is defined as a combination of fever and bone marrow suppression
CMV tissue invasive disease	Combination of CMV detection or CMV syndrome, plus an end-organ disease (e.g. CMV pneumonia, CMV gastrointestinal disease, CMV hepatitis, CMV nephritis, CMV cystitis, CMV myocarditis, CMV retinitis)

CMV=Cytomegalovirus; HSCT=Haematopoietic stem cell transplant; SOT=Solid organ transplant
Source: Danziger-Isakov, LA. 2021; Ljungman P, et al. 2002; Ramanan P, et al. 2013.[16,27,28]

B.1.3.2 Pathogenesis of post-transplant CMV

CMV is a double-stranded DNA virus which depends on its ability to hijack host cells to produce additional copies of itself within the immunocompromised patient environment.[24,29] The lifecycle of CMV in a human host cell is illustrated in Figure 2.

Figure 2: CMV life-cycle in a human host cell



DNA=Deoxyribonucleic acid; ER=Endoplasmic reticulum; CMV=Cytomegalovirus
Source: Crough T. 2009.[24]

Due to the immunosuppression required to prevent organ rejection following SOT and allogeneic HSCT, patients 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.[30] In addition, in rare cases, if both the recipient and donor are CMV-negative, primary CMV infection can occur.[31]

CMV reactivation occurs when CMV-seropositive patients reactivate their CMV infection; in this case, the prior and current CMV strains are indistinguishable.[30] In addition, CMV-seropositive recipients may acquire a new CMV infection strain, and CMV-seronegative recipients may acquire a new or primary CMV infection from the donor or blood products used during the transplant.[15,16,32]

Patients are at higher risk of CMV infection progressing to CMV disease during the initial period after transplantation, when high levels of immunosuppression are used. As patients move to the post-transplant maintenance phase (3–6 months), the dose of immunosuppression is reduced.[33] As a result, the patient's own immune system is more able to combat viral replication in most cases.[34]

B.1.3.3 Epidemiology

CMV infection is highly prevalent, present in approximately 60% to 70% of the population.[1] However, the incidence rates of CMV infection and CMV disease post-transplantation vary considerably in the literature.[1,35] Given the lack of UK-specific epidemiology data, Takeda developed and validated a patient flow pathway with expert English clinicians. Based on this, Takeda estimates that [redacted] patients with refractory and/or resistant CMV infection after transplant would be eligible for treatment with maribavir in 2022 (See Section B.1.3.3.3 for additional details).

B.1.3.3.1 Literature estimates of SOT epidemiology

In the 2019–2020 financial year, there were over 4,700 SOT procedures in the UK.[12] The latest figures for SOT procedures in the UK (2021) have been impacted by COVID-19; therefore, Takeda believes the 2019–2020 data are the most accurate representation of the number of SOTs performed. SOT procedures included renal (69.4%), liver (19.1%), pancreas (4.4%), cardiothoracic (6.7%), and intestinal (0.4%) transplants.[12] CMV infection occurs in approximately 18% of SOT patients overall.[36] However, the rate of infection varies according to recipient serostatus.[37-42] Of the patients with a CMV infection, 4% to 12% of patients progress to CMV disease.[37-39,42-44] There is limited evidence on the number of patients who are refractory or resistant to current antiviral treatments post-transplantation and no evidence is available from the UK. In Europe, available studies estimate 0.7% to 8.4% of patients who have a CMV infection after treatment develop treatment resistance.[35,37,45,46] Expert clinicians have recommended that, in the case of data paucity, renal transplants can be used as a proxy for overall SOT as it represents a large portion of SOTs.

B.1.3.3.2 Literature estimates of allogeneic HSCT epidemiology

In 2019, there were 1,726 allogeneic HSCT procedures in the UK.[13] As with SOT, the latest figures for HSCT procedures in the UK (2020) have been impacted by COVID-19; therefore, Takeda believes the 2019 data are the most accurate representation of the number of HSCTs performed. CMV infection occurs in approximately 50% of allogeneic HSCT patients, with 5 to 10% of patients who have CMV infection progressing to CMV disease.[44] There is limited evidence on the number of patients who are refractory or resistant to current antiviral treatments post-transplantation and no UK-specific evidence is available. In Europe, studies conducted prior to the availability of letermovir indicate that between 9.0% and 25.5% of allogeneic HSCT patients with a CMV infection are refractory to treatment, and between 1.8% and 2.2% of patients who receive treatment develop drug resistance.[47,48] The number of patients with a CMV infection post-HSCT has decreased since July 2019, due to the availability of letermovir (TA591) for prophylaxis of CMV in allogeneic HSCT patients.[49]

B.1.3.3.3 Eligible population for maribavir

Given the lack of UK-specific epidemiology data, Takeda developed and validated a patient flow pathway with expert English clinicians. Based on publicly available data supplemented with input from these clinicians, Takeda estimates that [redacted] patients with refractory and/or resistant CMV infection after transplant would be eligible for treatment with maribavir in 2022.

A summary of the relevant sources used to estimate the size of the eligible population of patients with refractory and/or resistant CMV infection after transplant is provided in Table 4.

Table 4: Epidemiology data used in estimating number of patients eligible for maribavir for treating refractory or resistant CMV infection after transplant

	SOT		HSCT	
	Number of patients	**Source**	**Number of patients**	**Source**
Number of transplant patients in the UK	4,733	NHSBT Organ Donation and Transplantation for the UK as of 9 April 2020	1,714	BSBMT for the UK as of 2019
Number of transplant patients with R/R CMV in the UK	[redacted]	Expert clinical advice	[redacted]	Expert clinical advice
Number of transplant patients with R/R CMV in England	[redacted]	ONS population estimates[a]	[redacted]	ONS population estimates[a]
Total number of patients eligible for maribavir in England	[redacted]			

[a] The number of SOT/HSCT patients with R/R CMV in England has been calculated by multiplying the number of transplant patients with R/R CMV in the UK by 0.843 (the general population of England/the general population of UK)
BSBMT=British Society of Blood and Marrow Transplantation; HSCT=Haematopoietic-cell transplant; NHSBT=National Health Service Blood and Transplant; ONS=Office of National Statistics; R/R=Refractory or resistant; SOT=Solid organ transplant
Sources: NHS Blood and Transplant. 2020; BSBMTCT Registry. 2019; Office of National Statistics. 2021.[12,13,50]

B.1.3.4 Clinical burden

CMV infections that are refractory or resistant to currently available antivirals are a major cause of morbidity and mortality among SOT and allogeneic HSCT recipients.[3] 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 (See Section B.1.3.1 for CMV disease definitions).[15] 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.[15,16] CMV infection

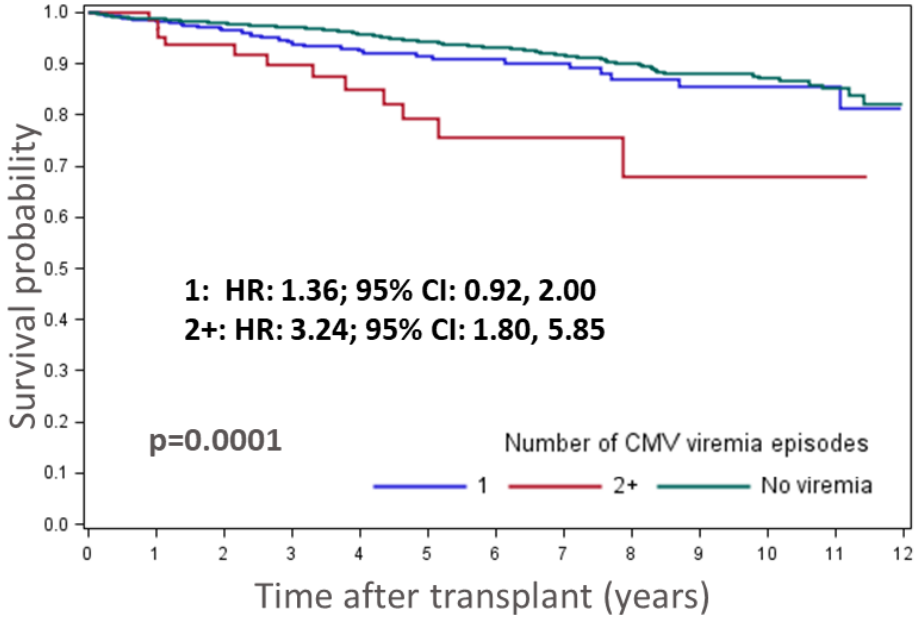
after allogeneic HSCT can also lead to tissue invasive disease (e.g. oesophagitis, gastroenteritis, hepatitis, retinitis, pneumonia or encephalitis). The direct effects of tissue invasive disease or CMV syndrome are accompanied by indirect effects, including increased incidence of concurrent bacterial and/or fungal infections, potential graft-versus-host disease (GvHD), graft rejection post-transplantation and increased risk of mortality.[22,51-54]

B.1.3.4.1 Graft loss

Given the lack of UK-specific evidence in the literature, international data have been used to support the impact of viraemia on graft loss.

In a Canadian retrospective study including 2,466 renal transplant recipients, it was found that death-censored graft loss was significantly increased in recipients with increasing number of CMV viraemia episodes. Patients who had two or more episodes of CMV viraemia, which are reflective of the refractory/resistant CMV population, had an increased risk of graft loss compared with patients without CMV viraemia episodes (hazard ratio [HR]:3.24; 95% confidence interval [CI]: 1.80 to 5.85) (Figure 3).[36]

Figure 3: Death censored graft loss in renal patients by viraemia episodes



CI=Confidence interval; CMV=Cytomegalovirus; HR=Hazard ratio
Note: 1=patients with only one episode of CMV; 2+=patients who had had two or more episodes of CMV
Source: Dobrer S, et al. 2021.[36]

B.1.3.4.2 GvHD and CMV infection

After an allogeneic HSCT, the donor's stem cells (graft) may react against the host cells, termed GvHD. GvHD can manifest within the first 100 days after transplant (acute) or more than 100 days after transplant (chronic).[55] GvHD affects many different areas of the body, most commonly the skin, gut (including the bowel and stomach) or liver.[55] In some cases, GvHD can be life threatening.[56] Although a causal relationship

in which CMV may lead to GvHD is not well evidenced in the literature, a single study has suggested that CMV infection may lead to the development of GvHD. However, for more severe grades of GvHD, the association was not significant.[56] In addition, the study suggested that GvHD increases the probability of CMV viraemia.[56] There is inconclusive evidence to demonstrate if CMV infection increases the probability of GvHD or vice versa.

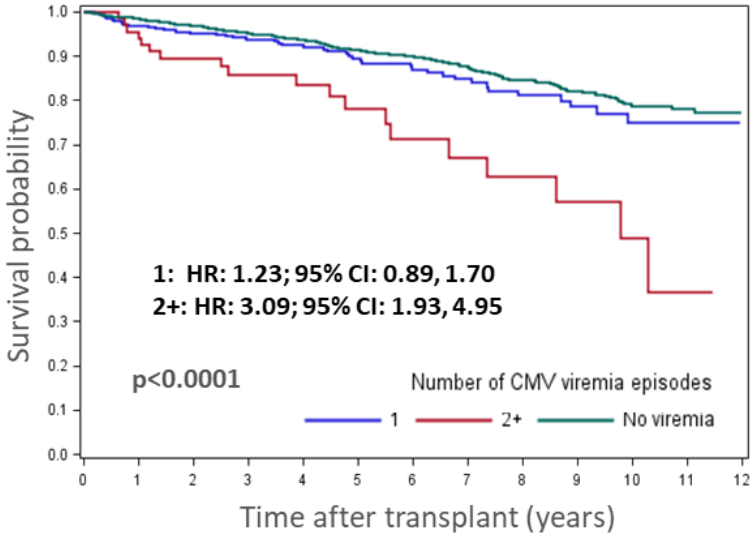
B.1.3.4.3 Mortality and CMV infection

Various studies indicate that any level of CMV is associated with an increased risk of post-transplant mortality in both SOT and HSCT patients.[18-21]

B.1.3.4.3.1 Mortality in SOT

In a Canadian retrospective study including 2,466 renal transplant recipients, patients with two or more episodes of CMV viraemia (reflective of the proposed resistant/refractory CMV population) had a statistically significant increased risk of mortality compared with patients without CMV viraemia episodes (HR: 3.09; 95% CI: 1.93, 4.95) (Figure 4).[36]

Figure 4: Patient survival over time by number of CMV viraemia episodes



CI=Confidence interval; CMV=Cytomegalovirus; HR=Hazard ratio
Note: 1=patients with only one episode of CMV; 2+=patients who had had two or more episodes of CMV
Source: Dobrer S, et al. 2021.[36]

In response to the limited published mortality data, two multinational CMV outcomes, treatment patterns and healthcare resource utilisation studies (OTUS) following either SOT or HSCT have been conducted by Takeda.[57,58] The interim analyses of OTUS SOT included [redacted] patients, of whom [redacted] were European patients with refractory or resistant CMV who had undergone an SOT between January 2014 and September 2021. The subgroup of European patients (N=58) had an incidence rate of all-cause and CMV-related mortality of [redacted] and [redacted] cases per 1,000 person-years, respectively.[59] The risk of mortality was greater among patients who had a subsequent

recurrence (N=7): the incidence rate of all-cause mortality was [redacted] cases per 1,000-person-years for patients who had at least two recurrent CMV episodes.[59] The expected date of completion of OTUS-SOT is April 2022.

B.1.3.4.3.2 Mortality in allogeneic HSCT

The interim analyses of OTUS HSCT for Cohort 1 included [redacted] patients, of whom [redacted] were European patients with refractory of resistant CMV who had undergone an allogeneic HSCT from January 2017 to October 2021. The subgroup of European patients had an incidence rate of all-cause and CMV-related mortality of [redacted] and [redacted] cases per 1,000 person-years, respectively.[60] In patients who had undergone an allogeneic HSCT who had at least two recurrent CMV episodes (N=9), the incidence rate of all-cause mortality increased to [redacted] cases per 1,000 person-years.[60] The expected date of completion of OTUS-HSCT is April 2022. Final analyses are yet to be performed, but the majority of data were likely collected after the availability of letermovir.

B.1.3.5 Humanistic burden

The effect of CMV infection on health-related quality of life (HRQoL) is extremely challenging to isolate from the effects of antiviral treatment, the tolerability of the medications used and/or the underlying medical condition.[61] A systematic literature review (SLR), conducted by Takeda (see Appendix H), identified no UK studies which quantitatively described the effect of CMV infection on HRQoL in a refractory or resistant post-transplant population; however, clinical experts are in agreement that *"reducing CMV reactivation rates and the need for CMV therapy would improve quality of life".*[14]

One Australian study in patients who had undergone HSCT, found that the European Organisation for Research and Treatment of Cancer (EORTC) global quality of life (QoL) score was significantly lower in patients who had CMV compared with those who did not (67 vs. 75 respectively, p=0.02) with a higher fatigue score (44 vs. 33 respectively, p=0.018) and lower social functioning score (67 vs. 83 respectively, p=0.02).[62]

In response to the challenge of directly collecting meaningful HRQoL data, a vignette study was carried out in 2021 by Takeda to identify appropriate health-related utilities data. Health state descriptions were developed in conjunction with UK clinicians before valuation by a sample of the UK public (N=[redacted]). Overall, the sample acknowledged the substantial impact of CMV on utility in both SOT and allogeneic HSCT patients with CMV infection. The utility for SOT and allogeneic HCST patients with a CMV infection that did not require treatment was [redacted]; this reduced to [redacted] in asymptomatic patients who required treatment and [redacted] in patients with symptomatic CMV who required treatment.[63]

B.1.3.6 Patient burden

In response to the limited evidence on patient burden, Takeda conducted a patient advisory board in December 2021 to better understand the patient voice.[64] Where possible, data from the literature has been provided to support this perspective. Having a transplant is a huge and challenging event in a patient's life. Patients are given a life-changing diagnosis with impending mortality, and those who require an SOT must often wait years before a matched organ is available. In the UK, there is a chronic shortage of organs with 6,213 people waiting for an SOT in December 2021.[65] While patients await an organ, they must manage the symptoms of their underlying condition and the accompanying management of the condition (i.e. dialysis), which is often burdensome. In the financial year 2019–2020, 372 patients died while on the active list waiting for their SOT, and a further 746 were removed from the transplant list as a result of deteriorating health and ineligibility for transplant.[12] The number of patients dying while on the waitlist has likely increased during the COVID-19 pandemic as waitlisted SOT recipients have higher rates of mortality after testing positive for COVID-19,[66] so the number of patients dying while on the waitlist has likely increased during the COVID-19 pandemic. Given the shortage of donors, a second transplant may in principle be offered to patients, but there is no guarantee of the availability of a suitable second transplant.[67] Matching donors becomes increasingly difficult as patients are exposed to more antigens, making tissue typing challenging. The average waiting time for a deceased donor kidney transplant in the UK is 2–3 years.[68]

> *"I've been on dialysis for five years. For me, it's the most difficult part of the wait. Dialysis keeps me alive whilst I wait for a transplant; but that's all it does. I'm in limbo"* (patient quote)[64]

With many patients waiting such a long time for their transplant, it is a huge relief once they are able to receive an organ; however, this may be short lived as patients learn the organ is at risk of failure due to CMV infection or reactivation. This is a major concern for patients, particularly in the case of live donor transplants where the donor is potentially known to the recipient. This makes the organ donation even more *"precious"* to the recipient.[64]

CMV infection has a significant impact on long-term HRQoL. For recipients of allogeneic HSCT who received treatment for CMV infection, fatigue is common and social functioning is affected.[62] For SOT recipients, patients can experience long-term fatigue, lethargy, breathlessness and an inability to think clearly/process information post-CMV diagnosis.[64] Furthermore, clinical expert opinion suggests the increasing use of a prophylaxis regimen has turned CMV from an acute-stage life threatening infection into a late-stage chronic and often recurring infection for those that are impacted by it, resulting in further detriment to patients' HRQoL.

From discussions with six English patients, we understand anxiety increases as the future is uncertain. Patients feel they'll never be cured of CMV, and dread seeing the hospital number appear on their phone.[64]

> *"I don't want to go back and experience everything again"* (patient quote)[69]
>
> *"I'm anxious that the lab tests might go wrong"* (patient quote)[69]
>
> *"it's hard to find a balance, and I seem to be in a circle of hell"* (patient quote)[69]

Post-transplant CMV infection has a significant impact on work and lifestyle, with the need for increased hospital visits/blood tests. Due to chronic health issues and frequent visits and follow-ups to the clinic, patients may be unable to maintain full-time employment. This burden makes it difficult to resume work and maintain lifestyle activities that patients had prior to the transplant.[64,69]

> *"wouldn't stray too far from a toilet"* [due to gastrointestinal issues] (patient quote)[69]
>
> *"combined effects of the infection and the treatment made me just want to get rid of it!"* (patient quote)[69]
>
> *"to sum it all up, great that the transplant finally came through but the CMV hit me like a hammer, it's no joke"* (patient quote)[69]
>
> *"some friends died, and I couldn't tell them goodbye as it was dangerous for my health to have contact with them"* (patient quote)[69]

There is lack of information provided to patients about the risk of CMV. Some patients with documented recurrent CMV episodes, symptoms and treatments are unaware of the relationship of their symptoms with CMV.[64] Whilst there are dedicated patient organisation groups in the UK, they are primarily focused on congenital CMV and provide little education on CMV post-transplant.[64]

> *"People don't know about CMV. Since the beginning, there is bad information, and I feel so lonely"* (patient quote)[69]
>
> *"I was told that CMV could not come back, and that was on the top of my mind. I'm a bit confused"* (patient quote)[69]

Clinical experts have highlighted the difficulty in isolating the impact of CMV in transplant recipients due to various burdens post-transplant patients experience. Recipients must endure the burden of taking medication intravenously, the stress and anxiety from having an infection, re-hospitalisation, and antiviral therapy toxicity, all without proper education of their disease. Furthermore, these burdens are emphasised due to the uncertainty in their diagnosis and the potential for transplant rejection.[69,70]

B.1.3.7 Economic burden

In the proposed patient population for maribavir, patients have previously undergone an SOT or allogeneic HSCT. In addition to the substantial clinical burden the transplant places on the patient, these transplants represent a significant cost to the healthcare system; within the national schedule of National Health Service (NHS) costs, transplants represent 13 of the top 20 most expensive healthcare resource group (HRG) costs.[71] Depending on organ type, an adult SOT costs between £12,000 (kidney) and £87,000 (complex heart); while allogeneic HSCT ranges from £28,000 to £90,000, depending on the donor.[71]

CMV infection adds to the already large economic burden associated with transplants. Regardless of the severity of disease, the most commonly used anti-CMV viral therapies in the UK often require patients to be hospitalised during treatment as many are administered intravenously multiple times per day.[72-76] This means that transplant recipients with a CMV infection incur higher costs and use more resources due to the increased length of hospitalisation compared with transplant recipients who do not have a CMV infection.[20,21,77,78] For every recurrence of CMV, the length of hospitalisation is amplified.[59,60]

B.1.3.7.1 Economic burden in SOT

In the interim analyses of OTUS SOT, of European patients with one CMV episode who had undergone an SOT ([redacted]), the combined rate of emergency department visits and hospitalisations related to CMV was [redacted] cases per 1,000 person-years. In European patients who had undergone an SOT and had experienced two or more episodes of CMV ([redacted]), the combined rate of emergency department visits and hospitalisations related to CMV was [redacted] cases per 1,000 person-years. In patients who had undergone an SOT ([redacted]), the median length of stay (LOS) for CMV-related hospitalisations was [redacted] days.[59,60]

B.1.3.7.2 Economic burden in allogeneic HSCT

In the interim analyses of OTUS HSCT, of European patients with one CMV episode who had undergone an allogeneic HSCT ([redacted]), the combined rate of emergency department visits and hospitalisations related to CMV was [redacted] cases per 1,000 person-years. In patients who had undergone an allogeneic HSCT and had at least two or more episodes of CMV ([redacted]), the incidence doubled to [redacted] per 1,000 person-years. The median LOS for CMV-related hospitalisations in patients who had undergone an allogeneic HSCT ([redacted]),was [redacted] days.[59,60]

B.1.3.8 Care pathway

There is no NICE clinical guidance for the treatment of patients who are refractory or resistant to treatments after SOT or allogeneic HSCT. TA591 – letermovir for prophylaxis of allogeneic HSCT recipients – does not include refractory/resistant CMV and is therefore not relevant to this population.[49]

The management of CMV post-transplant can be separated into two stages, prophylaxis and pre-emptive therapy (Table 5).[22,23] The goal of prophylaxis is to maintain low or no CMV viraemia during the early post-transplant stage when there is no evidence of infection,[22] while pre-emptive therapy is administered to patients with detectable CMV viraemia (who may be asymptomatic or symptomatic).[22] The following information focuses on pre-emptive therapy, which is the proposed use of maribavir.

Table 5: Definition of therapy in CMV

Therapy	Definition
Prophylaxis	Administered prior to detectable CMV viral load and ensures CMV remains at undetectable levels
Pre-emptive	Administered once patients have a detectable CMV viral load; these patients can be symptomatic or asymptomatic. Pre-emptive therapy includes first-line or second-line plus therapy

CMV=Cytomegalovirus
Source: British Transplantation Society. 2015; Emery V, et al. 2013.[22,23]

There are currently no licensed medications to treat CMV in patients after SOT or allogeneic HSCT who are refractory or resistant to CMV treatment in the UK; although there are common antiviral therapies that are used off-label valganciclovir (Valcyte®), ganciclovir (Cymevene®), foscarnet (Foscavir®), and cidofovir.[72-76]

B.1.3.8.1 Care pathway for SOT

B.1.3.8.1.1 Guidelines for management of CMV infection after SOT

In the UK, there is one set of guidelines for prevention and treatment of post-transplant CMV in SOT, published by the British Transplantation Society (BTS) (Table 6).[22] However, these were published in 2015 and Takeda has been advised by external clinical experts that the guidelines are outdated, and that the treatment pathway has evolved.[14]

The BTS guidelines recommend ganciclovir and valganciclovir as pre-emptive first-line treatments and foscarnet and cidofovir as second-line treatments for CMV in SOT.[22] Valganciclovir and ganciclovir are currently approved for the prevention of CMV after SOT.

Table 6: Guidelines for management of CMV infection after SOT (BTS 2015)

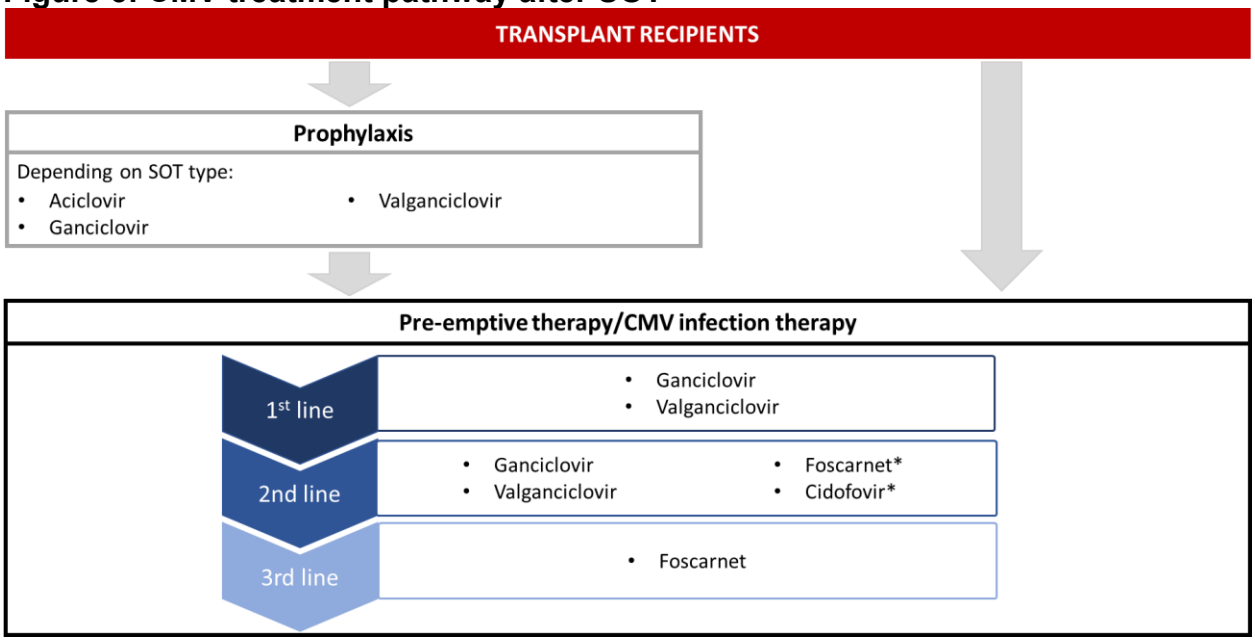
Recommendations
Pre-emptive treatment Patients with CMV disease should receive: • IV ganciclovir or oral valganciclovir until resolution of symptoms and for a minimum of 14 days • Foscarnet and cidofovir are second-line therapeutic options unless ganciclovir resistance has been demonstrated • Consideration should be given to a reduction in immunosuppression • After treatment doses have been administered, an additional 1–3 months of appropriate prophylaxis should be considered to minimise the risk of recurrent infection • The duration and efficacy of treatment should be determined using PCR monitoring of viral load

CMV=Cytomegalovirus; DNA=Deoxyribonucleic acid; IV=Intravenous; PCR=Polymerase chain reaction; SOT=Solid organ transplant
Source: British Transplantation Society. 2015.[22]

B.1.3.8.1.2 Treatment pathway for patients with SOT

In the UK, intravenous (IV) ganciclovir and oral valganciclovir are the most common first-line treatments for patients with CMV who have undergone an SOT. UK clinical experts have advised foscarnet and cidofovir are not commonly used as they are associated with nephrotoxicity, despite recommendations per guidelines as a second-line option. Additionally, experts have advised patients must demonstrate ganciclovir resistance to receive cidofovir or foscarnet. Generally, patients will be retreated with ganciclovir or valganciclovir in the second-line setting if recurrence occurs. The treatment pathway is summarised in Figure 5.

Figure 5: CMV treatment pathway after SOT



CMV=Cytomegalovirus; SOT=Solid organ transplant
*Requires monitoring of renal function

B.1.3.8.2 Care pathway for allogeneic HSCT

B.1.3.8.2.1 Guidelines for management of CMV infection after HSCT

In the UK, there is one set of guidelines for prevention and treatment of patients post-transplant CMV in HSCT, published by the British Society of Blood and Marrow Transplantation (BSBMT) and British Society for Haematology (BSH) (Table 7).[23] However, these were published in 2013 and Takeda has been advised by external clinical experts that the guidelines are outdated, and that the treatment pathway has evolved (e.g. the guidelines do not reflect the availability of letermovir for prophylaxis).

The BSH guidelines recommend ganciclovir as first-line pre-emptive therapy, foscarnet as a second-line agent upon ganciclovir treatment failure (or alternative first-line treatment if neutropenia is present), and cidofovir as a third-line treatment if patients are intolerant to other treatments.[23]

Table 7: Guidelines for management of CMV infection after HSCT (BSH 2013)

Recommendations
Pre-emptive therapy • Ganciclovir is recommended as first-line pre-emptive therapy for CMV in HSCT patients • Oral valganciclovir is a valid alternative when gastrointestinal absorption is normal or only minimally impaired • Foscarnet is recommended as an alternative first-line agent if neutropenia is present or for ganciclovir treatment failure • Pre-emptive therapy with cidofovir can be considered as third-line in patients unresponsive to, or intolerant of, both a ganciclovir preparation and foscarnet • In patients in whom CMV DNA loads in blood increase by 1 $\log^{10}$ over 2 weeks of pre-emptive therapy with a first-line drug, an alternative agent and drug resistance profiling should be considered • Drug resistance should start to be suspected if CMV loads in the blood fail to respond after 14 days of therapy, especially in non-lymphopaenic or multiply pre-treated patients

Note: The BSH 2013 guidelines were written prior to the availability of letermovir. Clinical practice has evolved since the availability
CMV=Cytomegalovirus; DNA=Deoxyribonucleic acid; HSCT=Haematopoietic stem cell transplant; PCR=Polymerase chain reaction; SOT=Solid organ transplant
Source: Emery V 2013.[23]

B.1.3.8.2.2 Treatment pathway for patients with HSCT

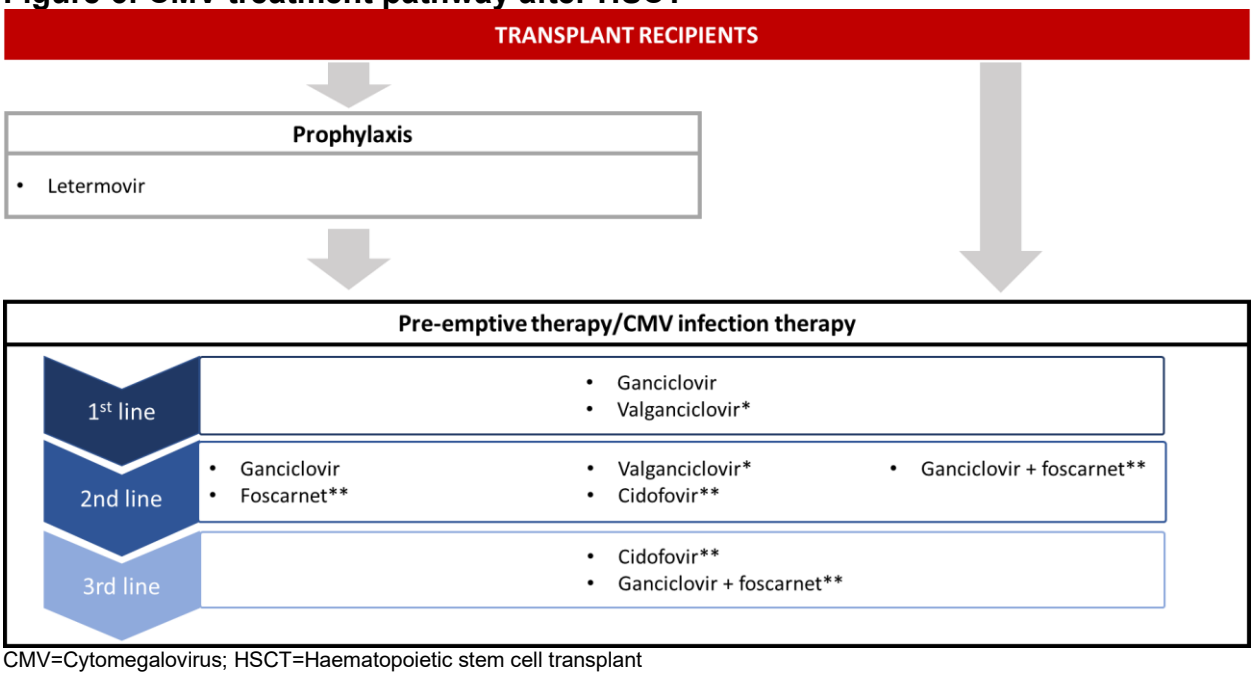
Currently, letermovir is the only treatment with a marketing authorisation for the prevention of CMV disease in patients after an allogeneic HSCT, and is used for prophylaxis.[79]

Ganciclovir (IV) and oral valganciclovir are the most common first-line treatments for patients with CMV who have undergone an HSCT; foscarnet is generally not used as a first-line therapy due to the poor safety and tolerability profile.[14,73,74,80,81] In the second-line setting, patients are often retreated with ganciclovir or valganciclovir if recurrence occurs. There is no approved therapy available for the treatment of patients with refractory or resistant CMV.

Clinicians tend to follow their local standard operating procedure (SOP), based upon the BSBMT guidelines, BSH guidelines, and European Society for Blood and Marrow Transplantation (EBMT) guidance with adaptations.[82]

In summary, in line with the BSH guidelines, clinical experts have advised Takeda that IV ganciclovir and oral valganciclovir are the most common first-line treatments for patients with CMV who have undergone an HSCT; foscarnet is generally not used as a first-line therapy. In the second-line setting, patients will often be retreated with ganciclovir or valganciclovir if a recurrence occurs. The treatment pathway is summarised in Figure 6.

Figure 6: CMV treatment pathway after HSCT



CMV=Cytomegalovirus; HSCT=Haematopoietic stem cell transplant
*For patients without severe gastrointestinal graft-versus-host-disease
**Requires monitoring of renal function

B.1.3.8.3 Limitations of the current standard of care

Current medications used to treat post-transplant CMV infection who are refractory or resistant to antiviral treatment in the UK (valganciclovir, ganciclovir, cidofovir and foscarnet) are used off-label and have substantial drawbacks associated with their use. IV treatments (ganciclovir, foscarnet, cidofovir) require several administrations per day and for patients to be closely monitored for the duration of treatment, often necessitating the hospitalisation of patients for the duration of antiviral treatment.[72-76]

Moreover, these treatments are associated with significant toxicities which may limit their appropriateness for use.[72-76] Valganciclovir and ganciclovir are associated with neutropenia as one of the most common adverse events (AEs), which can result in life-threatening bacterial and/or fungal infections.[83,84] Foscarnet is associated with nephrotoxicity resulting in kidney injury, and is therefore challenging to use in patients

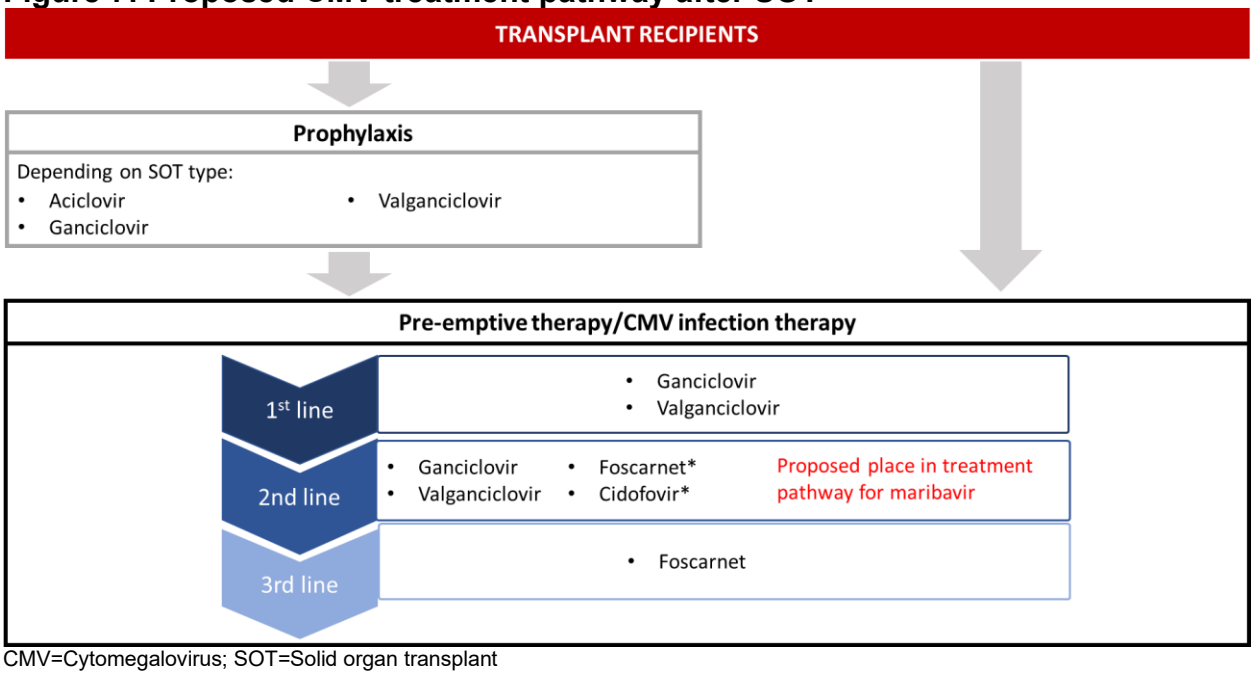
who have undergone a renal transplant or have impaired renal function.[7,83-85] Additionally, cidofovir has been associated with neutropenia and other renal dysfunctions.[75] These CMV drug-induced toxicities can lead to treatment discontinuation, treatment switching or dose adjustment, which in turn may lead to sub-optimal dosing and the risk of resistant CMV infection/disease.[3,84,86-88]

Treatment resistance is a major issue in the refractory or resistant population as there are few available treatments for CMV in transplant patients. Drug resistance may develop as a consequence of CMV mutation, and may lead to viraemia breakthrough, necessitating therapy switching and further increasing the risk of morbidity and mortality.[3,89] The currently available anti-CMV agents for pre-emptive therapy act at the same stage within the cell replication pathway: inhibiting DNA polymerase and hence viral DNA synthesis. Therefore, viral mutation at this stage can lead to cross-resistance; where resistance to one of the four anti-virals used for the treatment of CMV infection confers resistance to the other three, resulting in decreased efficacy and necessitating a reduction in immunosuppression. Maribavir acts at multiple stages of the CMV lifecycle, inhibiting both replication and encapsulation of CMV DNA, as well as preventing the escape of viral capsules from infected cells, limiting the potential for development of resistance (Section B.1.2).[5,90]

B.1.3.8.4 Maribavir's proposed place in the treatment pathway

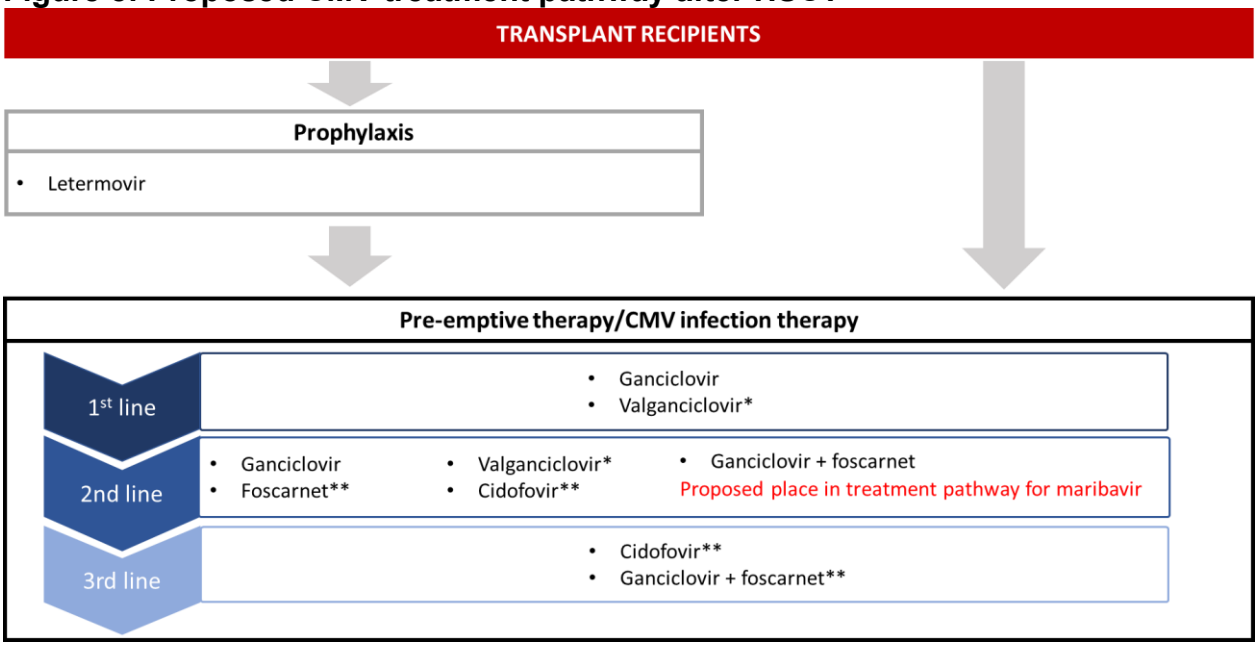
The context for the proposed use of maribavir is summarised in Figure 7 (SOT) and Figure 8 (HSCT). Within this submission, maribavir is positioned as a second-line agent in the treatment of CMV in patients who have received SOT or HSCT. This will place maribavir alongside other second-line treatments including cidofovir and foscarnet, as well as retreatment with ganciclovir and/or valganciclovir. The new management strategy would provide an effective second-line therapy and avoid common toxicities associated with current treatments.

Figure 7: Proposed CMV treatment pathway after SOT



CMV=Cytomegalovirus; SOT=Solid organ transplant
*Requires monitoring of renal function

Figure 8: Proposed CMV treatment pathway after HSCT



CMV=Cytomegalovirus; HSCT=Haematopoietic stem cell transplant
*For patients without severe gastrointestinal graft-versus-host-disease
**Requires monitoring of renal function

B.1.4 Equality considerations

Patients from minority ethnic groups are more likely develop conditions such as high blood pressure, diabetes and certain forms of hepatitis than white people.[91] This makes them more likely to need a transplant; 35% of UK kidney transplants in 2019–

20 were in minority ethnic groups,[92] compared with 14.6% in the general English population.[93] However, there is an imbalance between the numbers of minority ethnic donors and those patients in need of a lifesaving transplant. People from these communities represented 7% of all deceased donors in 2019–20 compared with 32% of those on the transplant waiting list.[94] While many minority ethnic group patients are able to receive a transplant from a white donor, the best match will typically be obtained from a donor of similar ethnic background.[92,93] A less than optimal match may result in higher levels of immunosuppression resulting in an increased risk of CMV.[95] Patients from these backgrounds continue to wait longer for an organ, 20% of black, Asian and minority ethnic patients have received a transplant one year after being listed for a kidney, the most commonly transplanted organ, compared with 31% of white patients.[94]

Age is a consideration when selecting who is most eligible for a kidney transplant via the National Kidney Allocation Scheme. Points are awarded based on level of tissue match, time spent waiting for transplant and the age of the recipient (with a progressive reduction in points given after the age of thirty). The majority of patients developing end-stage renal disease who are eligible for kidney transplantation are between 45 and 65 years of age despite evidence to show that age should not be a contra-indication for transplantation.[96,97]

Older patients have less treatment options due to toxicity, some patients receive a transplant which is not a complete match. A less than optimal match may result in higher levels of immunosuppression resulting in an increased risk of CMV and graft rejection. Given the chronic shortage of transplants, there is a need to optimise post-transplant maintenance to ensure graft rejection does not occur.

B.2 Clinical effectiveness

Trial design – SOLSTICE

- SOLSTICE was a Phase III, multicentre, randomised (2:1 ratio), open-label, active-controlled, 20-week study
- The aim was to establish the efficacy, safety profile, 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 transplant recipients with CMV infections that are refractory or resistant to treatment
- Patients were randomised 2:1 (maribavir: IAT) and treatment duration was 8 weeks
- The primary outcome was proportion of confirmed clearance of plasma CMV DNA (confirmed CMV viraemia clearance) at the end of Study Week 8 vs. IAT
- Secondary and exploratory outcomes included confirmed CMV viraemia clearance and CMV infection symptom control at Week 16, mortality, recurrence of CMV viraemia, CMV viral load over time, transplant graft function, EuroQoL Group 5-Dimension 5-Level (EQ-5D), Short Form-36 version 2 (SF-36), hospitalisations
- In SOLSTICE, 350/352 (99.4%) patients received treatment and 73.4% completed the study

Efficacy

- In the randomised 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%), a 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%
  - Hospitalisations: Reduction of [redacted]% in hospitalisations (p=0.021) and [redacted] in LOS (p=0.029)

Safety

- The safety set (N=350) was used for safety analyses in SOLSTICE and consisted of all randomised patients who received at least one dose of study medication
- Within the safety population, the mean exposure to maribavir ([redacted]; standard deviation [SD]: [redacted]) was approximately 50% 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%)
- Similar percentages of patients in the maribavir and IAT groups reported serious TEAEs despite the fact that the duration of exposure to maribavir was approximately [redacted] longer than to IAT
  - Acute kidney injury was among the most frequently reported serious adverse events (SAE) overall, reported in [redacted] of patients in each treatment group
- A total of 40 subject 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

B.2.1 Identification and selection of relevant studies

A clinical SLR was conducted to identify, evaluate, and summarise the clinical efficacy and safety of anti-CMV agents for the treatment of refractory or resistant CMV infection/disease in SOT or HSCT recipients.

The SLR is a compilation of one original SLR (1 January 2020 to 27 April 2020) and one SLR update (28 April 2020 to 21 September 2021). Results were compiled for studies identified across both reviews and are presented in this section for RCTs and in Appendix D.1.3 for observational studies.

B.2.2 List of relevant clinical effectiveness evidence

Overall, 11 studies were identified: two RCTs,[98] one prospective observational study[5,99] and eight retrospective observational studies.[3,100-106] A full list of included studies in the clinical SLR is provided in Table 8. No evidence was identified for ganciclovir with hyperimmune globulins or cytotoxic lymphocytes.

Table 8: Summary of the key study characteristics included in the clinical SLR

Study name	Sample size details			Phase	Blinding	Study setting (Country)	Follow-up duration	Treatments compared
	Eligible	Intervention	Analysed					
Randomised controlled trials								
Duarte 2021 (SOLSTICE)[98]	352	235 maribavir 117 IAT (ganciclovir, valganciclovir, foscarnet, cidofovir)	352[a]	Phase III	Open label	Multicentre International (North America, Europe, Asia)	8 weeks treatment + 12 weeks follow-up	Maribavir vs. IAT
Papanicolaou 2019 (TAK-620-202)[5]	120	40 maribavir 400 mg 40 maribavir 800 mg 40 maribavir 1,200 mg	120	Phase II	Double-blind	Multicentre (US)	12 weeks treatment + 12 weeks follow-up	Maribavir (low-dose) vs. maribavir (high-dose)
Prospective observational study								
Hantz 2010[99]	37	Foscarnet	37	N/A	Open label	Multicentre (France)		N/A
Retrospective observational studies								
Yin 2020[100]	31	Cidofovir	31	N/A	N/A	NR	43.45 weeks	N/A
Veit 2021[101]	28	Letermovir	28	N/A	N/A	Single centre (Germany)	NR	N/A
Pierce 2018[102]	31	Foscarnet	31	N/A	N/A	Single centre (US)	NR	N/A
Avery 2016[103]	39	Foscarnet	39	N/A	N/A	Single centre (US)	NR	N/A
Myhre 2011[104]	27	Foscarnet[b]	27	N/A	N/A	Single centre (Norway)	NR	N/A
Fisher 2017[3]	37	Foscarnet Control arm	37 109	N/A	N/A	Single centre (US)	208.57 (IQR: 99.94-338.92) weeks 178.15 (IQR: 95.59-330.23] weeks	Treatment arm vs. controlled arm
Foresto 2018[105]	28	Foscarnet	28	N/A	N/A	NR	NR	N/A
Kohlschmidt 2019[106]	30	Ganciclovir + Foscarnet	30	N/A	N/A	Single centre (Germany)	NR	N/A

IAT=Investigator-assigned anti-CMV treatment; RCT=Randomised controlled trial; N/A=Not applicable; NR=Not reported; US=United States

[a] Overall, 350/352 patients received treatment as two randomised subjects (one in each treatment group) were not dosed

[b] 10/27 patients were treated with foscarnet

Of the two RCTs identified, one study, SOLSTICE (TAK-620-303), was the pivotal trial which forms the main evidence base for the efficacy, safety and tolerability of maribavir in the population relevant to the decision problem, and is presented within this section. The other study, TAK-620-202, a Phase II multicentre, randomised, dose-ranging, parallel-group study also provides non-comparative data for maribavir; a summary of this data can be found within Appendix D.4.2.1 (Clinical effectiveness results).

The observational studies identified in the clinical SLR included six studies that included foscarnet,[3,99,102-105] one observational study each included cidofovir,[100] letermovir,[101] and ganciclovir plus foscarnet.[106] These observational studies identified in the clinical SLR are not further considered as no comparative data was collected and the relevant comparators are included in SOLSTICE.

Table 9: Clinical effectiveness evidence

Study	SOLSTICE (TAK-620-303; NCT02931539)	TAK-620-202 (NCT01611974)
Study design	Phase III, multicentre, randomised, open-label, active-controlled study	Phase II, multicentre, randomised, dose-ranging, parallel-group study
Population	Post-transplant CMV infection and disease in patients who are resistant/refractory to ganciclovir, valganciclovir, cidofovir or foscarnet	Post-transplant CMV infection and disease in patients who are resistant/refractory to ganciclovir, valganciclovir or foscarnet
Intervention(s)	Maribavir 400 mg (2× 200 mg oral tablets) BID for 8 weeks	Maribavir BID for up to 24 weeks • 400 mg (2× 200 mg oral tablets) BID • 800 mg (4× 200 mg oral tablets) BID • 1200 mg (6× 200 mg oral tablets) BID
Comparator(s)	IAT (ganciclovir [IV], valganciclovir [oral], foscarnet [IV], or cidofovir [IV])	N/A
Indicate if trial supports application for marketing authorisation	Yes	Yes
Indicate if trial used in the economic model	Yes	No
Rationale for use/non-use in the model	SOLSTICE is the pivotal trial for maribavir	The data from TAK-620-202 are superseded by the Phase III comparative trial SOLSTICE
Reported outcomes specified in the decision problem	• CMV clearance • CMV infection symptom improvement or reduction • Mortality • Recurrence rates • Tissue invasive disease • Viral load	• CMV clearance • Adverse effects of treatment • CMV recurrence

	• Adverse effects of treatment • HRQoL	
All other reported outcomes	See Table 11	• PK

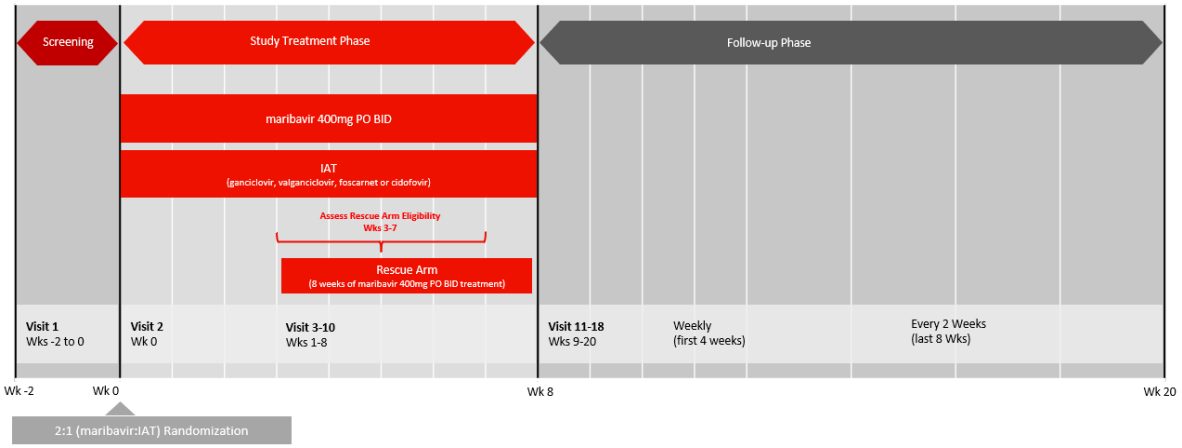
BID=Twice daily; CMV=Cytomegalovirus; HRQoL=Health-related quality of life; IAT=Investigator-assigned anti-CMV treatment; IV=Intravenous; mg=Milligrams; PK=Pharmacokinetics
Source: Avery RK, et al. 2021; Papanicolaou GA, et al. 2019.[5,107]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design

SOLSTICE was a Phase III, multicentre, randomised, open-label, active-controlled study to evaluate the efficacy and safety of maribavir compared to IAT in transplant recipients with CMV infections refractory or resistant to ganciclovir, valganciclovir, foscarnet or cidofovir.[107,108] The design of SOLSTICE is summarised in Figure 9.

Figure 9: SOLSTICE design schematic



BID=Twice daily; IAT=Investigator-assigned anti-CMV treatment; mg=Milligrams; PO=Oral; Wk=Week
Note: Eligibility to enter the maribavir rescue arm was assessed starting at Visit 5/Week 3 up to Visit 9/Week 7
Source: Avery RK, et al. 2021.[107]

B.2.3.2 Trial drugs and concomitant medications

Following stratification, patients were randomised in a 2:1 allocation ratio to receive open-label maribavir 400 mg BID or IAT (ganciclovir [IV], valganciclovir [oral], foscarnet [IV], or cidofovir [IV]), as per the investigator's prescribed dosing for 8 weeks.[107] 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. 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.[107] 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.

Concomitant medications taken during the on-treatment observation period were similar to medications used prior to the trial and was consistent between treatment arms: immunosuppressants (maribavir: 92.3%; IAT: 94.0%), drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD) (maribavir: 81.2%; IAT: 79.3%), corticosteroids for systemic use (maribavir: 75.6%; IAT: 72.4%), and sulphonamides and trimethoprim (maribavir: 54.3%; IAT: 65.5%). Antimycotics for systemic use were used concomitantly by 42.0% of patients (maribavir: 41.0%; IAT: 44.0%).[107]

B.2.3.3 Locations where the data were collected

The study was conducted across 12 countries: Canada, US, UK, Belgium, Germany, Denmark, Spain, France, Croatia, Italy, Singapore and Australia.[109]

B.2.3.4 Eligibility criteria

The key eligibility criteria are presented below.[109]

Key inclusion criteria:[109]

1. Recipients of HSCT or SOT aged ≥12 years at the time of consent
2. Current CMV infection with a screening value of ≥2,730 IU/mL in whole blood or ≥910 IU/mL in plasma, and refractory to the most recently administered of the four anti-CMV treatment agents (defined as 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)
3. Screening laboratory assessments:
   a. Absolute neutrophil count (ANC) ≥1,000/mm^3 (1.0 × 10^9/L)
   b. Platelet count ≥25000 mm^3 (25 × 10^9/L)
   c. Haemoglobin ≥8 g/dL
   d. Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2
4. Life expectancy of ≥8 weeks

Exclusion Criteria:[109]

1. Current CMV infection considered refractory or resistant due to inadequate adherence to prior anti-CMV treatment
2. Required ganciclovir, valganciclovir, foscarnet, or cidofovir administration for conditions other than CMV when study treatment was initiated or needed a coadministration with maribavir for CMV infection. A patient who was not continuing with the same antiviral drug(s) (ganciclovir, valganciclovir, or foscarnet) for the study treatment (when randomised to the IAT arm), must have discontinued their use before the first dose of IAT. If the patient was currently being treated with cidofovir and was assigned by the investigator to another anti-CMV therapy as IAT, the patient must have discontinued use of cidofovir at least 14 days prior to randomisation at Visit 2/Day 0 and the first dose of IAT
3. Received leflunomide, letermovir, or artesunate when study treatment was initiated (leflunomide must have discontinued ≥14 days prior to randomisation

at Visit 2/Day 0 and the first dose of study treatment; letermovir must have been discontinued ≥3 days prior to the first dose of study treatment; artesunate must have been discontinued prior to the first dose of study treatment)
4. Tissue invasive CMV disease with central nervous system involvement, including the retina (e.g. CMV retinitis)
5. Known positive results for human immunodeficiency virus (HIV)
6. Active malignancy, with the exception of non-melanoma skin cancer. Patients who had a HSCT and who had experienced relapse or progression of the malignancy, as per investigator's opinion were not to be enrolled

B.2.3.5 Patient characteristics

Overall, treatment groups were well balanced with respect to the demographics and baseline characteristics.[107] A total of 136 patients (38.6%) were enrolled from Europe, of which 14 patients were enrolled in UK sites.[109] The majority of patients had received SOT prior to enrolment (59.0% vs. 60.4%, in the IAT and maribavir arms, respectively).[107] The most common SOT types were kidney (46.4% vs. 52.1%), lung (31.9% vs. 28.2%), and heart (13.0% vs. 9.9%). The demographics and baseline characteristics are summarised in Table 10. UK clinical experts have validated the whole trial population as generalisable to the UK.[80]

Table 10: Demographics and baseline disease characteristics by treatment group (randomised set)

Characteristic	IAT (N=117)	Maribavir 400 mg BID (N=235)
Age (year)		
Median (range)	54.0 (19, 77)	57.0 (19, 79)
Male sex, n (%)	65 (55.6)	148 (63.0)
Weight, n	115	232
Median (range)	70.0 (39, 131)	74.1 (36, 124)
Race, n (%)		
White	87 (74.4)	179 (76.2)
Black or African American	18 (15.4)	29 (12.3)
Asian	7 (6.0)	9 (3.8)
Other	5 (4.3)	16 (6.8)
Missing	0	2 (0.9)
Region, n (%)		
North America	71 (60.7)	134 (57.0)
Europe	39 (33.3)	97 (41.3)
Asia	7 (6.0)	4 (1.7)
SOT, n (%)	69 (59.0)	142 (60.4)
Kidney	32 (46.4)	74 (52.1)
Lung	22 (31.9)	40 (28.2)
Heart	9 (13.0)	14 (9.9)
Multiple	5 (7.2)	5 (3.5)
Liver	1 (1.4)	6 (4.2)
Pancreas	0	2 (1.4)
Intestine	0	1 (0.7)
HSCT, n (%)	48 (41.0)	93 (39.6)
Allogeneic	48 (100.0)	92 (98.9)

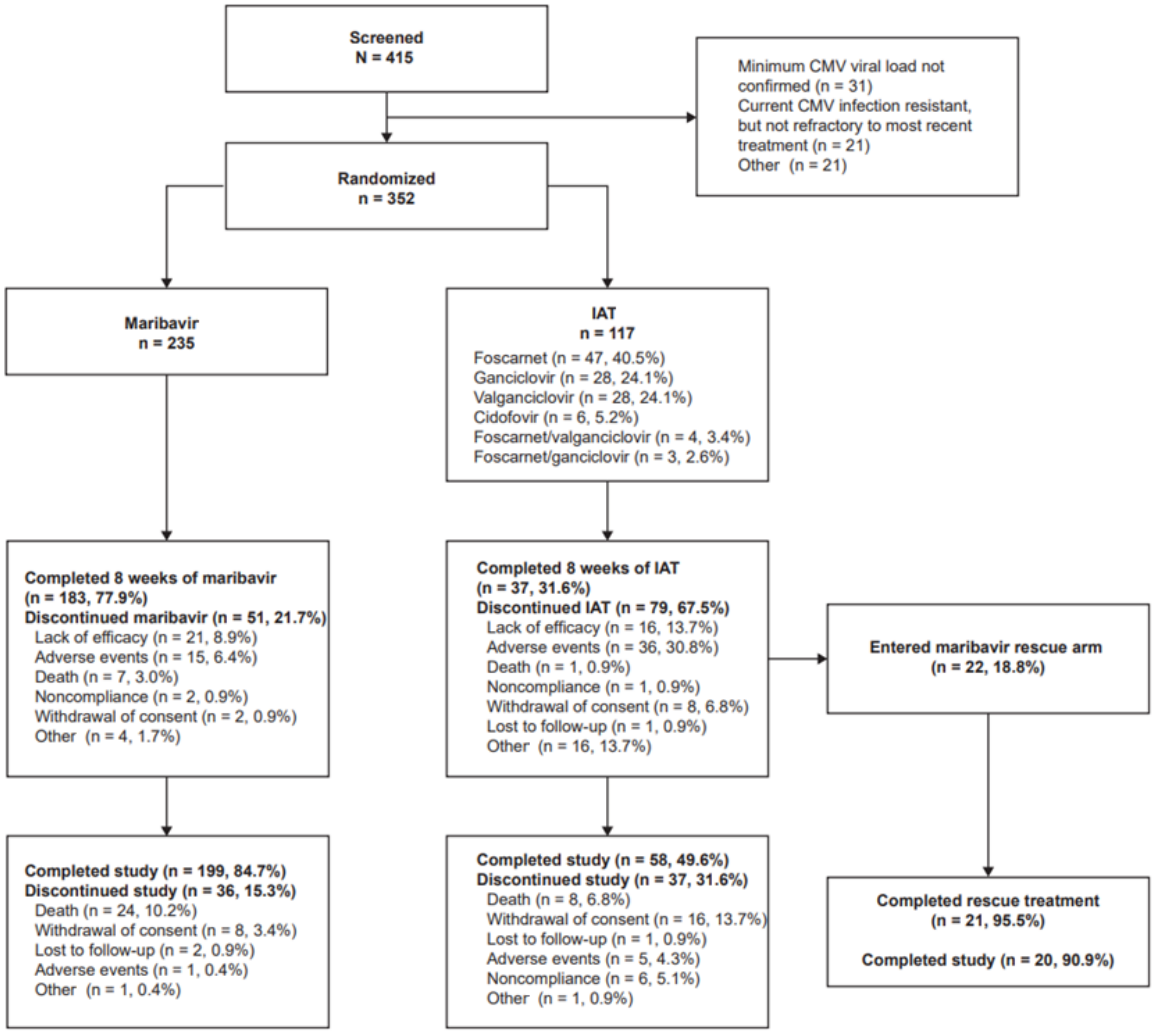
Characteristic	IAT (N=117)	Maribavir 400 mg BID (N=235)
Donor type,		
HLA identical sibling	2 (4.2)	13 (14.1)
HLA matched other relative	10 (20.8)	12 (13.0)
HLA mismatched relative	7 (14.6)	11 (12.0)
Unrelated donor	29 (60.4)	56 (60.9)
Stem cell source		
Peripheral blood stem cell	30 (62.5)	71 (77.2)
Bone marrow	13 (27.1)	16 (17.4)
Cord blood	5 (10.4)	5 (5.4)
Presence of acute GvHD confirmed for HSCT recipients	8 (17.0)	23 (25.0)
Presence of chronic GvHD confirmed for HSCT recipients	5 (10.6)	6 (6.5)
CMV DNA levels by central laboratory at baseline, IU/mL		
Median (IQR)	2869.0 (927, 11,636)	3377.0 (1036, 12,544)
Patients with or without CMV mutations known to confer resistance to ganciclovir, foscarnet, and/or cidofovir, n (%)		
Refractory CMV infection with resistance	69 (59.0)	121 (51.5)
Refractory CMV infection without resistance	34 (29.1)	96 (40.9)
Missing resistance results	14 (12.0)	18 (7.7)
Prior use of CMV prophylaxis, n (%)	45 (38.5)	100 (42.6)
Current CMV infection is the first episode post-transplant, n (%)	78 (66.7)	162 (68.9)
Most recent anti-CMV agent prior to randomisation, n (%)		
Ganciclovir/Valganciclovir	98 (83.8)	204 (86.8)
Foscarnet	18 (15.4)	27 (11.5)
Cidofovir	1 (0.9)	4 (1.7)
Prior direct-acting anti-CMV agents at any time, n (%)	n=116	n=234
Valganciclovir	96 (82.8)	178 (76.1)
Ganciclovir	82 (70.7)	147 (62.8)
Foscarnet	37 (31.9)	49 (20.9)
Letermovir	5 (4.3)	12 (5.1)
Cidofovir	5 (4.3)	7 (3.0)

BID=Twice daily; BMI=Body mass index; CMV=Cytomegalovirus; DNA=Deoxyribonucleic acid; GvHD=Graft-versus-host-disease; HSCT=Haematopoietic stem cell transplant; HLA=human leukocyte antigen; IAT=Investigator-assigned anti-CMV treatment; IQR=Interquartile range; LLOQ=Lower limit of quantification; max=Maximum; mg=Milligrams; min=Minimum; N=Number of patients; SD=Standard deviation; SOT=Solid organ transplant
Source: Avery RK, et al. 2021; Avery RK, et al. 2021.[107,109]

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 10). 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 10).[107,108]

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]).[108] 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]).[108] SOT patients were more commonly treated with ganciclovir/valganciclovir, whilst HSCT patients were more commonly treated with dual therapy or cidofovir.[110]

Figure 10: Patient flow



CMV=Cytomegalovirus; IAT=Investigator-assigned anti-CMV treatment; MBV=Maribavir; N=Number of patients
Source: Avery RK, et al. 2021.[107]

B.2.3.6 Outcomes used in the economic model/specified in the scope and primary outcome

A list of the primary, secondary, exploratory and safety outcomes of the SOLSTICE trial can be found in Table 11. Outcomes highlighted in bold are reported in this

submission and/or are included within the economic model. Responder criteria for key outcomes included within the submission are presented in Table 12**.**

Table 11: Outcomes from the SOLSTICE trial

Endpoint	Description
Primary	• **Confirmed clearance of plasma CMV DNA (confirmed CMV viraemia clearance) at the end of Study Week 8**
Key secondary	• **Confirmed CMV viraemia clearance and CMV infection symptom control at Week 8 with the benefit maintained through Week 16**

Additional secondary	• Achievement of the confirmed CMV viraemia clearance after 8 weeks of receiving study-assigned treatment
	• Achievement of the 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**
	  ○ **Clinically relevant 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	• CMV viral load 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	• 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
HRQoL	• EQ-5D-5L • SF-36v2

AE=Adverse event; CMV=Cytomegalovirus; DNA=Deoxyribonucleic acid; EQ-5D-5L=EuroQoL Group 5-Dimension 5-Level; HRQoL=Health-related quality of life; SF-36v2=Short Form-36 version 2
Source: Avery RK, et al. 2021; Takeda. 2021.[107,108]

Table 12: Responder criteria for key outcomes reported in this submission and/or included within the economic model

Endpoint	Criteria for response
Primary endpoint	
Confirmed CMV viraemia clearance at the end of Study Week 8	Confirmed CMV viraemia clearance at the end of Study Week 8 was defined as plasma CMV DNA concentrations <LLOQ (i.e., <137 IU/mL), when assessed by central specialty laboratory, in two consecutive post-baseline samples separated by at least 5 days.
Key secondary endpoint	
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	To qualify as a responder for the key secondary efficacy endpoint, patients were required to meet the following criteria: • Primary endpoint responder (i.e., CMV viraemia clearance at end of Study Week 8) • 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) • 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 Symptom status for tissue invasive disease or CMV syndrome was the adjudicated status per the EAC. Patients were not required to complete the stipulated 8 weeks of study-assigned treatment.
Other secondary endpoints	
Recurrence of CMV viraemia	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
Clinically relevant recurrence of CMV viraemia	Recurrence of CMV viraemia (as defined above) after Week 8 that required alternative anti-CMV treatment
All-cause mortality	N/A
Exploratory endpoints	
CMV viral load over time	Plasma CMV DNA concentration assessed by the central laboratory
Graft outcomes	N/A
Safety endpoints	
AEs	An AE was any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product that may not necessarily have a causal relationship with that treatment. The primary analysis of safety was based on the "treatment-emergent" principle. The on-treatment observation period starts at the date of study treatment initiation through seven days after the last dose of study treatment, or through 21 days after the last dose of cidofovir (if cidofovir is the IAT).

AE=Adverse event; CMV=Cytomegalovirus; DNA=Deoxyribonucleic acid; EAC=Endpoint Adjudication Committee; IAT=Investigator-assigned anti-CMV treatment; LLOQ=Lower limit of quantification; N/A=Not applicable
Source: Avery RK, et al. 2021.[109]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis populations

The primary objective of SOLSTICE was to evaluate the efficacy of maribavir in clearing CMV viraemia compared with IAT, in transplant recipients who were refractory or resistant to prior anti-CMV treatment. The primary analysis was conducted in the randomised (ITT) set, with data collected until 17 August 2020. Definitions of the analysis sets are summarised in Table 13.[107]

Table 13: Definition and number of participants by analysis population in SOLSTICE

Analysis population	Definition	SOLSTICE, N (%)		
		Maribavir	IAT	All
Enrolled	All patients who had signed informed consent and some study procedures had begun (e.g., dispensed study-assigned treatment, current drug had been withdrawn)	-	-	415 (100.0)
Randomised set	All patients in the enrolled set who had been randomised to the study. Patients were analysed in the treatment group to which they were randomised	235 (100.0)	117 (100.0)	352 (100.0)
Safety Set	All patients who took any dose of study-assigned treatment Patients were analysed according to the treatment actually received	234 (99.6)	116 (99.1)	350 (99.4)

CMV=Cytomegalovirus; IAT=Investigator-assigned anti-CMV treatment; N=Number of patients
Source: Avery RK, et al. 2021.[107]

Subgroup analyses were performed for the primary and key secondary efficacy endpoints for the following subgroups:[107]

- Transplant type (SOT, HSCT, kidney transplant)
- CMV DNA viral load (high, intermediate, low)
- Symptom status (symptomatic, asymptomatic) 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)

B.2.4.2 Statistical analyses and approach to missing data

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 and baseline plasma CMV DNA concentration as two stratification factors. All statistical tests and CIs were 2-sided at α=0.05. 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 α=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 analysed statistically at α=0.05 (2-sided), without adjustment for multiple comparisons.[107,109]

A summary of the statistical analyses and approach to missing data used for assessment of key endpoints included in the SOLSTICE trial relevant to this submission is presented in Table 14.

Table 14: Statistical analyses and approach to missing data for endpoints in the SOLSTICE trial relevant to the submission

Endpoint	Statistical analysis	Analysis population relevant to this submission	Primary missing data approach
Primary endpoint			
Confirmed CMV viraemia clearance at the end of Study Week 8	CMH	Randomised set	If a patient took alternative anti-CMV treatment or maribavir as rescue treatment before Study Week 8 they were assumed to be non-responders If a patient had missing data due to early discontinuation to confirm viraemia clearance at Study Week 8 they were assumed to be non-responders
Key secondary endpoint			
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	CMH	Randomised set	If a patient took alternative anti-CMV treatment or maribavir as rescue treatment before Study Week 16, they were assumed to be non-responders If a patient discontinued study early before Study Week 16 without data to confirm the maintenance of viraemia clearance and CMV infection symptom control at Study Week 16, they were assumed to be non-responders
Other secondary endpoints			
Recurrence of CMV viraemia	N/A	Randomised set	All CMV DNA measurements after achieving confirmed CMV viraemia clearance regardless of rescue or alternative treatment were included in the assessment
All-cause mortality	Time to event analysis; Kaplan-Meier	Randomised set	Included all deaths reported on study regardless of receipt of alternative anti-CMV treatment or maribavir rescue therapy
Exploratory endpoints			
CMV viral load over time	N/A	Randomised set	All CMV viral load data collected after the initiation of rescue or alternative anti-CMV treatment was included
Graft outcomes	N/A	Randomised set	All outcomes after receiving study-assigned treatments before rescue or alternative anti-CMV treatment were included
Safety endpoints			
AEs	N/A	Safety set	For patients who transferred from the study treatment to either maribavir rescue or to a non-study anti-CMV treatment, the on-treatment observation period ended at the seven days after the last dose of study treatment or through 21 days if cidofovir is used, or until initiation of maribavir rescue treatment or non-study anti-CMV treatment, whichever was earlier. Safety analyses for the maribavir rescue arm were analysed separately using the Rescue Set

AE=Adverse event; CMH=Cochran-Mantel-Haenszel; CMV=Cytomegalovirus; DNA=Deoxyribonucleic acid; mL=millilitres; N/A=Not available/not applicable
Source: Avery RK, et al. 2021; Takeda. 2021.[107,108]

B.2.4.3 Sample size calculation

Based on the Phase II Study 202, it was assumed that at least 60% of maribavir-treated patients (at Visit 9/Week 7) and 40% of IAT-treated patients (Visit 10/Week 8) would have achieved undetectable plasma CMV DNA when calculating the sample size for SOLSTICE. A total of 315 patients were required in the ratio of 2:1 (210 patients in maribavir group and 105 patients in the IAT group) to provide 90% power in hypothesis testing at α=0.05 (2-sided test). The sample size was estimated based on a 2-group continuity corrected Chi-square test of equal proportions.[107]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

An assessment of the quality of the relevant clinical effectiveness evidence is presented in Table 15. SOLSTICE was a well-performed RCT with a low risk of bias.

Table 15: Quality assessment of studies identified by SLR

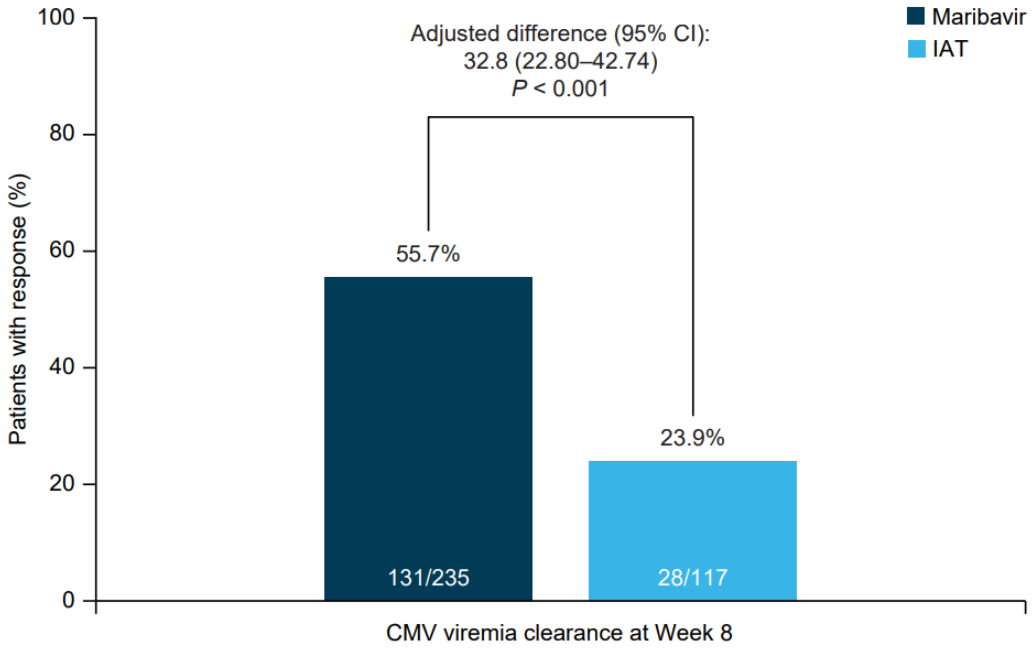
Trial	SOLSTICE (TAK-620-303; NCT02931539)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind 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

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Primary endpoint

SOLSTICE demonstrated that maribavir is a highly effective treatment for the clearance of CMV compared with IAT. In the ITT population, a greater proportion of patients in the maribavir group (55.7%) achieved confirmed CMV viraemia clearance at the end of study Week 8 compared with IAT (23.9%). 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 32.8% (95% CI: 22.8%, 42.7%; p<0.001) (Figure 11).[107] 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)

Figure 11: Primary efficacy endpoint analysis: confirmed CMV viraemia clearance at Week 8 by treatment group (randomised set)



CI=Confidence interval; CMV=Cytomegalovirus; IAT=Investigator-assigned anti-CMV treatment
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
Source: Avery RK, et al. 2021.[107]

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 16. Overall, the results of the sensitivity analyses were consistent with the primary analysis (Table 16).[109] 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. Additional analyses are presented within the Appendix E.1.2.

Table 16: Sensitivity analyses of the primary efficacy endpoint analysis: confirmed CMV viraemia clearance at Week 8 (randomised set)

CMV viraemia clearance at end of Week 8 (Response)	IAT (N=117)	Maribavir 400 mg BID (N=235)	Adjusted difference in percentage of responders (95% CIs)
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 (%)	39 (33.3%)	137 (58.3%)	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 (%)	61 (52.1%)	174 (74.0%)	23.6% (13.2%, 33.9%)
Patients in the IAT group, but not in the maribavir group, who initiated alternative anti-CMV treatment before Week 8 were included as a responder, n (%)	41 (35.0%)	131 (55.7%)	21.7% (11.0%, 32.5%)

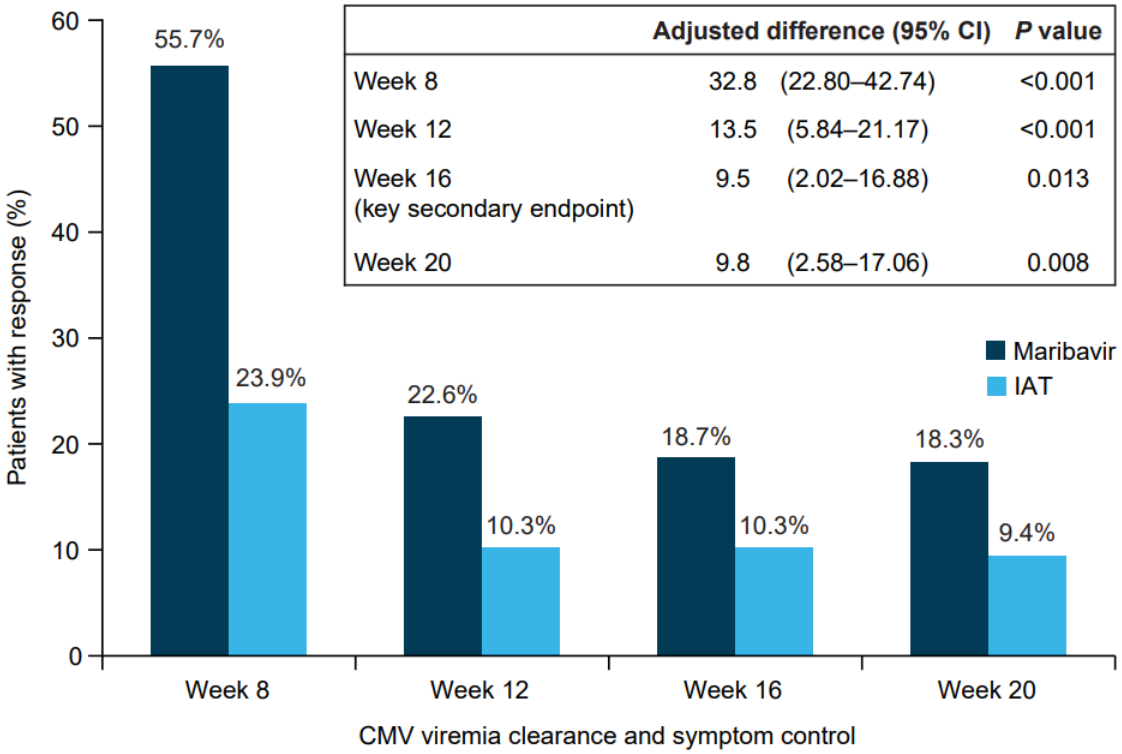
BID=Twice daily; CI=Confidence interval; CMV=Cytomegalovirus; IAT=Investigator-assigned anti-CMV treatment; Mg: Milligram; N=Number of patients
Source: Avery RK, et al. 2021.[109]

B.2.6.2 Secondary outcomes included in the scope

B.2.6.2.1 Confirmed CMV viraemia clearance and CMV infection symptom control

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.[107] In the randomised population, a greater proportion of patients in the maribavir group (18.7%) achieved this composite outcome compared with IAT (10.3%). 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: 2.0%, 16.9%; p=0.013) was statistically significant (Figure 12).[107]

Figure 12: Analysis of achieving confirmed CMV viraemia clearance and CMV infection symptom control followed by maintenance through Week 16 by treatment group (randomised set)



CI=Confidence interval; CMV=Cytomegalovirus; IAT=Investigator-assigned anti-CMV 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.
Source: Avery RK, et al. 2021.[107]

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 discontinued, took alternative anti-CMV treatment or was administered maribavir as rescue treatment during this time, they were considered non-responders. Non-response does not equal a clinically relevant recurrence that requires retreatment; clinically relevant recurrence (i.e., recurrence among responders, after Week 8, who received alternative anti-CMV treatment) occurred less frequently in patients randomised to maribavir (26.0%) than IAT (35.7%) (See Table 14 for the responder definitions).

Maintaining CMV clearance and symptom control in the refractory or resistant population while keeping the antiviral dose low enough to reduce toxicity and prevent discontinuation is an issue with conventional antiviral treatments currently used to treat patients with refractory or resistant CMV.[72-76] Patients are more at risk of CMV infection progressing to CMV disease during the initial period after transplantation when high levels of immunosuppression are used. As patients move to the post-transplant maintenance phase (3–6 months), the dose of immunosuppression is reduced.[33] As a result of this the immune system is more able to combat viral replication.[34]

B.2.6.2.2 All-cause mortality

Maribavir was associated with a similar rate of all-cause mortality in the randomised population 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.[107] 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.[108] The time to all-cause mortality by treatment group is shown in Table 17.

Table 17: Time to all-cause mortality by treatment group (randomised set)

Time to all-cause mortality by treatment group	IAT (N=117)	Maribavir 400 mg BID (N=235)
Number of patients who died, n (%)	13 (11.1)	27 (11.5)
Number of patients censored, n (%)	104 (88.9)	208 (88.5)
Observed event time for those who died, days, median (min, max)	[redacted]	[redacted]
Kaplan-Meier estimates of time to death		
25th, days (95% CI)	[redacted]	[redacted]
50th, days (95% CI)	[redacted]	[redacted]
75th, days (95% CI)	[redacted]	[redacted]
p-value	[redacted]	
HR (95% CI)		
Treatment Group: Maribavir vs. IAT	[redacted]	

BID=Twice daily; CI=Confidence interval; HR=Hazard ratio; IAT=Investigator-assigned anti-CMV treatment; Max=Maximum; Mg=Milligram; Min=Minimum; N=Number of patients; NR=Not reached
Source: Avery RK, et al. 2021; Takeda 2021.[107,108]

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.

B.2.6.2.3 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 randomised to maribavir (26.0%) than IAT (35.7%). Among the 22 patients who initially received IAT and subsequently received maribavir rescue treatment due to lack of response, 11 (50.0%) achieved confirmed CMV viraemia clearance at Week 8 of the maribavir rescue treatment phase (Table 18).[107] 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 18.

Table 18: Analysis of recurrence of CMV viraemia (randomised set)

CMV viraemia recurrence during the first 8 weeks, the follow-up period, and any time on study	IAT (N=117)	Maribavir 400 mg BID (N=235)
Number of patients with clinically relevant recurrence (recurrence among responders, after week 8 who received alternative anti-CMV treatment), n/N (%)[a]	[redacted] (35.7)	[redacted] (26.0)
CMV viraemia clearance after study-assigned treatment at any time on study, n (%)[b]	[redacted]	[redacted]
Patients with CMV viraemia recurrence		
During the first 8 weeks, n (%)	[redacted]	[redacted]
During the follow-up weeks, n (%)	[redacted]	[redacted]
Any time on study, n (%)	[redacted]	[redacted]

BID=Twice daily; CI=Confidence interval; CMV=Cytomegalovirus; IAT=Investigator-assigned anti-CMV treatment; Mg=Milligram; N=Number of patients

[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

Source: Avery RK, et al. 2021; Takeda 2021.[107,108]

B.2.6.2.4 CMV viral load over time

The CMV viral load of patients over time (i.e., plasma CMV DNA concentration assessed by the central laboratory) was an exploratory efficacy endpoint.[108] Maribavir appeared to elicit a stronger response at 4 weeks, reducing the Log_{10} plasma CMV viral load by [redacted], compared with [redacted] in the IAT arm. Although by 20 weeks the results in the maribavir arm and the IAT arm appeared similar, this is likely due to the lower number of patients in the IAT arm with measurements compared with the maribavir arm. The patients without a measurement are more likely to have not achieved viral clearance.[108] For full details on this secondary endpoint, please refer to the Appendix D.4.1.1.

B.2.6.2.5 Transplant graft function

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.[108] In both treatment groups, few patients experienced adverse graft outcomes during the study up to 20 weeks.[108]

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 GvHD was reported during the study for [redacted] ([redacted]) HSCT recipients in the maribavir group and [redacted] ([redacted]) HSCT recipients in the IAT group.[108]

Table 19: Graft status at baseline (randomised set)

	IAT (N=117)	Maribavir 400 mg BID (N=235)	Total (N=352)
SOT			
Functioning with complications, n (%)	[redacted]	[redacted]	[redacted]
Functioning, n (%)	[redacted]	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]	[redacted]
HSCT			
Partially engrafted, n (%)	[redacted]	[redacted]	[redacted]
Functioning with complications, n (%)	[redacted]	[redacted]	[redacted]
Functioning, n (%)	[redacted]	[redacted]	[redacted]

BID=Twice daily; HSCT=Haematopoietic stem cells transplant; IAT=Investigator-assigned anti-CMV treatment; N=Number of patients; SD=Standard deviation; SOT=Solid organ transplant
Source: Takeda 2021.[108]

Table 20: Transplant graft status (randomised set)

	SOT		HSCT	
	IAT (N=69)	Maribavir 400 mg BID (N=142)	IAT (N=48)	Maribavir 400 mg BID (N=93)
Acute rejection [a]				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Chronic rejection [a]				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Graft loss [a]				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
New GvHD [a]				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Time to acute rejection for those with the event (days)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Time to chronic rejection for those with the event (days)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Time to graft loss for those with the event (days)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Time to new GvHD among HSCT patients (days)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]

BID=Twice daily; GvHD=Graft-versus-host disease; HSCT=Haematopoietic Stem Cell Transplant; IAT=Investigator-assigned anti-CMV treatment; Max=Maximum; Mg=Milligram; Min=Minimum; N=Number of patients; NR=Not reached; Q=Quartile; SD=Standard deviation; SOT=Solid organ transplant

[a] Percentages are based on the number of patients in the subset

Source: Takeda 2021.[108]

B.2.6.2.6 Health-related quality of life

The EuroQoL 5-Dimension 5-Level (EQ-5D-5L) and Short Form-36 version 2 (SF-36v2) instruments were used to assess HRQoL. Overall, there was xxxxxxxxxxxxxxx in health states over the treatment and follow-up phases for all patients. The changes in EQ-5D-5L were [redacted].[108] Based on the SF-36v2, there was [redacted] from baseline to the end of both treatments.[108] Patients treated with maribavir demonstrated [redacted] in physical and mental sub-domains of the SF-36 (Table 21).[108]

Table 21: Summary of SF-36v2 domain score (randomised set)

Domains	IAT (N=117)		Maribavir 400 mg BID (N=235)	
	Baseline Mean (SD)	Change from baseline at Week 8 Mean (SD)	Baseline Mean (SD)	Change from baseline at week 8 Mean (SD)
Patients	[redacted]	[redacted]	[redacted]	[redacted]
Physical component score	[redacted]	[redacted]	[redacted]	[redacted]
Mental component score	[redacted]	[redacted]	[redacted]	[redacted]

BID=Twice daily; IAT=Investigator-assigned anti-CMV treatment; Mg=Milligram; N=Number of patients; SD=Standard deviation; SF-36v2=Short form 36 Version 2
Source: Takeda 2021.[108]

B.2.6.2.7 Hospitalisation

For patients on treatment, those receiving maribavir were [redacted] less likely to be hospitalised compared with patients receiving IAT (p= [redacted]). Over the full study period, patients receiving maribavir were [redacted] less likely to be hospitalised (p= [redacted]) (Table 22).[111]

Table 22: Incidence of hospitalisation for patients receiving maribavir or IAT (randomised set)

	IAT (N=117)	Maribavir 400 mg BID (N=235)	Adjusted difference in rates of hospital admissions, IRR (95% CI)
On-treatment phase[a]			
Adjusted incidence rate, admissions/person/year (95% CI)	[redacted]	[redacted]	[redacted]
Adjusted incidence rate of hospitalisation admissions, incidence rate (95% CI)	[redacted]	[redacted]	[redacted]
Full study period[b]			
Adjusted incidence rate, admissions/person/year (95% CI)	[redacted]	[redacted]	
Adjusted incidence rate of hospitalisation admissions, incidence rate (95% CI)	[redacted]	[redacted]	[redacted]

BID=Twice daily; CI=Confidence interval; IAT=Investigator-assigned anti-CMV treatment; IRR=Incidence rate ratio; Mg=Milligram; N=Number of patients; SD=Standard deviation
[a] On-treatment adjusted rates are adjusted for duration of time on treatment (52 days for maribavir, 35.7 days for IAT)
[b] 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)
Source: Takeda 2021.[111]

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

Table 23: LOS for patients receiving maribavir or IAT (randomised set)

	IAT (N=117)	Maribavir 400 mg BID (N=235)	Adjusted difference in LOS, IRR (95% CI)
On-treatment phase[a]			
Adjusted duration of LOS, days/person/year (95% CI)	[redacted]	[redacted]	[redacted]
Full study period[b]			
Adjusted duration of LOS, days/person/year (95% CI)	[redacted]	[redacted]	[redacted]

BID=Twice daily; CI=Confidence interval; IAT=Investigator-assigned anti-CMV treatment; IRR=Incidence rate ratio; Mg=Milligram; LOS=Length of stay; N=Number of patients; SD=Standard deviation
[a] On-treatment LOS are adjusted for duration of time on treatment (52 days for maribavir, 35.7 days for IAT)
[b] LOS for the full study period are adjusted for duration of time in study (132.1 days for maribavir, 92.9 days for IAT)
Source: Takeda 2021.[111]

B.2.7 Subgroup analysis

Subgroup analyses were performed for patients who had SOT or HSCT. Overall, in patients who had undergone an SOT, the benefits of treatment with maribavir were consistent with the benefits seen in the overall population (Table 24).[108,110]

Table 24: Efficacy endpoint analysis in SOT patients

Endpoint	IAT (N=48)	Maribavir 400 mg BID (N=93)	Adjusted difference in proportion (95% CI); p-value
Primary endpoint			
Confirmed CMV viraemia clearance at Week 8, n (%)[a]	18 (26.1)	79 (55.6)	30.5 (17.3, 43.6); [redacted]
Secondary endpoint			
Number of patients who died, n (%)[b]	[redacted]	[redacted]	**HR (95% CI)** [redacted]

BID=Twice daily; CI=Confidence interval; CMV=Cytomegalovirus; DNA=Deoxyribonucleic acid; HR=Hazard ratio IAT=Investigator-assigned anti-CMV treatment; N=Number of patients; SOT=Solid organ transplant
Note: Percentages are based on the number of patients in the Randomised Set
[a] Analysis was pre-specified
[b] Post-hoc analysis
Source: Avery RK, et al. 2021; Takeda 2021.[107,110]

Similarly, patients treated with maribavir who had received HSCT demonstrated consistent benefits across the majority of the primary and secondary outcomes. However, mortality rates were higher among HSCT patients than the overall population (Table 25).[108,110]

Table 25: Efficacy endpoint analysis in HSCT patients

Endpoint	IAT (N=48)	Maribavir 400 mg BID (N=93)	Adjusted difference in proportion (95% CI); p-value
Primary endpoint			
Confirmed CMV viraemia clearance at Week 8, n (%)[a]	10 (20.8)	52 (55.9)	36.1 (21.1, 51.2); [redacted]
Secondary endpoints			
Number of patients who died, (%)[b]	[redacted]	[redacted]	[redacted]

BID=Twice daily; CI=Confidence interval; CMV=Cytomegalovirus; HR=Hazard ratio; HSCT=Haematopoietic stem cells transplant; IAT=Investigator-assigned anti-CMV treatment; N=Number of patients
[a] Analysis was pre-specified
[b] Post-hoc analysis
Source: Avery RK, et al. 2021; Takeda 2021.[107,110]

B.2.8 Meta-analysis

As SOLSTICE is the only Phase III trial supporting the application, a meta-analysis is not required.

B.2.9 Indirect and mixed treatment comparisons

As the key trial (SOLSTICE) provided a comparison between maribavir and the relevant comparators, an indirect treatment comparison is not required.

B.2.10 Adverse reactions

B.2.10.1 Safety analysis population

The safety set (N=350) was used for safety analyses in SOLSTICE and consisted of all randomised 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.

B.2.10.2 Adverse effects of treatment

B.2.10.2.1 Treatment exposure

Within the safety population, the mean exposure to maribavir ([redacted]; SD: [redacted]) was approximately 50% longer than IAT due to early discontinuation of treatment in the IAT group ([redacted]) (Table 26).[108]

Table 26: Treatment exposure of the safety population

	IAT (N=116)	Maribavir 400 mg BID (N=234)
Exposure duration[a]		
n[b]	[redacted]	[redacted]
Mean (SD), days	[redacted]	[redacted]
Median, days	34.0	57.0
Min, max, days	4, 64	2, 64
Actual exposure to study-assigned treatment[c]		
n[b]	[redacted]	[redacted]
Mean (SD), days	[redacted]	[redacted]
Median, days	[redacted]	[redacted]
Min, max, days	[redacted]	[redacted]

BID=Twice daily; IAT=Investigator-assigned anti-CMV treatment; max=Maximum; min=Minimum; N=Number of patients; 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

Source: Avery RK, et al. 2021; Takeda 2021.[107,108]

B.2.10.2.2 Treatment-emergent adverse events

The majority of patients in both treatment groups had at least one treatment-emergent AE (TEAE) in the on-treatment observation period, reflecting the medical complexity of this patient population.[108] Dysgeusia (altered sense of taste) was the most frequently reported TEAE in the maribavir group (maribavir: 37.2%; IAT: 3.4%). Dysgeusia this was reported as mostly mild (88.5%), usually resolved either on treatment or shortly after the last dose of maribavir, and rarely led to treatment discontinuation (0.9% of patients in maribavir group). 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 diarrhoea (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 27).[107,108]

An overall summary of treatment related TEAEs during the on-treatment observation period by treatment group can be found in Appendix F.1.1. Frequently occurring TEAEs occurring in ≥5% of patients during the on-treatment observation period by treatment group can be found in Appendix F.1.2.

Table 27: Frequently occurring TEAEs in ≥10% of patients in the maribavir or IAT group[a] (safety set)

System organ class preferred term	IAT (N=116)	IAT Type[b]			Maribavir 400 mg BID (N=234)
		Ganciclovir/ Valganciclovir (N=56)	Foscarnet (N=47)	Cidofovir (N=6)	
Any related TEAE, n (%)	106 (91.4)	51 (91.1)	43 (91.5)	5 (83.3)	228 (97.4)
Blood and lymphatic system disorders, n (%)					
Anaemia	14 (12.1)	4 (7.1)	9 (19.1)	0	29 (12.4)
Leukopenia	8 (6.9)	7 (12.5)	1 (2.1)	0	7 (3.0)
Neutropenia	26 (22.4)	19 (33.9)	7 (14.9)	0	22 (9.4)
Gastrointestinal disorders, n (%)					
Diarrhoea	24 (20.7)	13 (23.2)	9 (19.1)	1 (16.7)	44 (18.8)
Nausea	25 (21.6)	8 (14.3)	14 (29.8)	1 (16.7)	50 (21.4)
Vomiting	19 (16.4)	7 (12.5)	8 (17.0)	2 (33.3)	33 (14.1)
General disorders and administration site conditions, n (%)					
Fatigue	10 (8.6)	7 (12.5)	3 (6.4)	0	28 (12.0)
Oedema peripheral	9 (7.8)	3 (5.4)	5 (10.6)	0	17 (7.3)
Pyrexia	17 (14.7)	6 (10.7)	9 (19.1)	2 (33.3)	24 (10.3)
Infections and infestations, n (%)					
CMV viraemia[c]	6 (5.2)	4 (7.1)	1 (2.1)	0	24 (10.3)
Metabolism and nutrition disorders, n (%)					
Hypokalaemia	11 (9.5)	1 (1.8)	9 (19.1)	1 (16.7)	8 (3.4)
Hypomagnesemia	10 (8.6)	2 (3.6)	7 (14.9)	1 (16.7)	9 (3.8)
Hypophosphatemia	5 (4.3)	0	5 (10.6)	0	4 (1.7)
Nervous system disorders, n (%)					
Dysgeusia	4 (3.4)	2 (3.6)	0	1 (16.7)	87 (37.2)
Headache	15 (12.9)	6 (10.7)	8 (17.0)	0	19 (8.1)
Taste disorder	5 (4.3)	0	5 (10.6)	0	4 (1.7)
Renal and urinary disorders, n (%)					
Acute kidney injury	11 (9.5)	1 (1.8)	10 (21.3)	0	20 (8.5)
Vascular disorders, n (%)					
Hypertension	8 (6.9)	1 (1.8)	6 (12.8)	0	9 (3.8)

BID=Twice daily; IAT=Investigator-assigned anti-CMV treatment; Mg=Milligram; N=Number of patients; TEAE=Treatment-emergent adverse event

[a] The cidofovir group was not considered in the application of the 10% cutoff due to low patient numbers (n=6)

[b] Overall, 7 patients received a combination of valganciclovir/ganciclovir and foscarnet (not included in the table)

[c] Events such as worsening of CMV viraemia were coded to the preferred term of CMV viraemia

Source: Avery RK, et al. 2021.[109]

B.2.10.2.3 TEAEs leading to discontinuation

During the on-treatment observation period, 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. Treatment discontinuation due to TEAEs by IAT type was highest for foscarnet, following cidofovir, and ganciclovir/valganciclovir.[108]

Table 28: TEAEs leading to discontinuation by treatment (safety set)

System Organ Class Preferred Term, n (%)	IAT (N=116)	IAT Type		Maribavir 400 mg BID (N=234)
		Ganciclovir/ Valganciclovir (N=56)	Foscarnet (N=47)	
Any TEAE leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
CMV infection	[redacted]	[redacted]	[redacted]	[redacted]
CMV infection reactivation	[redacted]	[redacted]	[redacted]	[redacted]
CMV viraemia	[redacted]	[redacted]	[redacted]	[redacted]
Encephalitis CMV	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]
Acute lymphocytic leukaemia recurrent	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]	[redacted]	[redacted]

BID=Twice daily; CMV=Cytomegalovirus; IAT=Investigator-assigned anti-CMV treatment; TEAE=Treatment-emergent adverse event
Source: Takeda 2021.[108]

B.2.10.2.4 Adverse events of special interest

B.2.10.2.4.1 Tissue invasive disease

Most patients did not have CMV tissue invasive disease or CMV syndrome at baseline (maribavir: [redacted]; IAT: [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 29).[108]

Table 29: Tissue invasive disease during on-treatment observation period (safety set)

AESI Class Preferred Term	IAT (N=116)	Maribavir 400 mg BID (N=234)
Tissue invasive CMV disease/syndrome, n (%)	[redacted]	[redacted]
CMV chorioretinitis, n (%)		
CMV colitis, n (%)		
CMV enteritis, n (%)		
CMV gastrointestinal infection, n (%)		
CMV mucocutaneous ulcer, n (%)		
CMV syndrome, n (%)		

AESI=Adverse event of special interest; BID=Twice daily; CMV=Cytomegalovirus; IAT=Investigator-assigned anti-CMV treatment; Mg=Milligram; N=Number of patients
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.
Source: Takeda 2021.[108]

Additional data on other AESI can be found in Appendix F.1.3.

B.2.10.2.4.2 Deaths due to TEAEs

A total of 40 deaths were reported in SOLSTICE. This included two patients in the maribavir group who died within the first week of initiating treatment (before receiving a sufficient course of therapy) as well as four patients (two 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).[109]

The most common SAEs leading to death were due to respiratory failure or relapse or progression of underlying disease. Details are presented in the Appendix F.1.4.[109]

B.2.11 Ongoing studies

B.2.11.1 SOLSTICE long term follow-up

In order to evaluate long-term efficacy and safety outcomes in patients who are refractory or resistant to prior anti-CMV treatments, patients enrolled within the maribavir arm of the SOLSTICE trial are being followed up for 12 months after trial initiation. Outcomes include all-cause mortality, overall survival and graft outcomes (including the proportion of patients with graft failure, time to graft failure and proportion of patients with re-transplantation). The final results for the SOLSTICE long term follow-up trial are expected Q2 2022.

B.2.12 Innovation

Maribavir is an efficacious treatment option that addresses the considerable clinical unmet need that remains in patients with post-transplant CMV infection and/or disease who are refractory or resistant to CMV treatment. Furthermore, the potential prevention of transplant loss due to CMV infection reduces the economic burden associated with this disease. However, there are several benefits associated with maribavir which are not captured in the economic model.

In 2013, maribavir was granted an orphan drug designation, with the European Medicines Agency (EMA) recognising the effectiveness in the prevention of CMV in patients at risk. Maribavir will be the first drug approved for the treatment of patients with refractory or resistant CMV post-transplant. All pre-emptive anti-CMV treatments used in UK clinical practice are used off-label. The commonly used treatment options have substantial drawbacks associated with their use (e.g., IV treatments [ganciclovir, foscarnet, cidofovir]) require several administrations per day and close monitoring for the duration of treatment, often necessitating the hospitalisation of patients for the duration of antiviral treatment.[72-76]

In contrast, maribavir will be available as an oral formulation; patients will not require hospitalisation to receive treatment, thereby reducing the burden of treatment administration and monitoring. Maribavir can be administered with or without food, resulting in a convenient administration for patients that may aid treatment compliance. In comparison, the only other oral anti-CMV agent, valganciclovir, is recommended to be taken with food, whenever possible.

Maribavir is associated with a favourable safety profile in patients with CMV post-transplant who are refractory or resistant to ganciclovir, valganciclovir, cidofovir or foscarnet. Maribavir, when compared with IAT, has demonstrated reduced discontinuation due to TEAEs (maribavir: 13.2% vs IAT: 31.9%) and discontinuation due to treatment-related TEAEs (maribavir: 4.7% vs IAT 23.3%).[109] Treatments currently used are associated with significant toxicities which may limit the appropriateness.[72-76] Due to the toxicity risks, the available treatment options are associated with risk of suboptimal dosing (e.g., treatment discontinuation, dose reduction) which may reduce efficacy in the real world.

The currently available anti-CMV agents act on one stage within the cell replication pathway: inhibiting DNA polymerase. As a result, resistance to one of the four currently used antivirals can confer resistance to the other three, reducing efficacy and necessitating a reduction in immunosuppression. Maribavir represents a new anti-CMV class (benzimidazole riboside) that has multi-targeted anti-CMV activity across the CMV lifecycle, resulting in maribavir being less susceptible to mutations of the viral DNA polymerase and enabling activity against strains with viral DNA polymerase mutations.[6-9] Due to this, maribavir results in sustained efficacy to allow for patients to build their natural immunity.

Patients who had two or more episodes of CMV viraemia had a higher risk of graft loss compared to patients with no or one CMV viraemia episode in a Canadian study in renal transplant patients (see Section B.1.3.4.1).[36] This impact of CMV viraemia on graft loss was not incorporated in the economic model, as long-term benefits of improved CMV status were not incorporated (see section B.3.2).

In addition to the substantial clinical burden that transplants place on patients, these transplants are a large cost for the healthcare system. Given the chronic shortage of organs, tissues and cells for transplant, patients may be subjected to prolonged waiting times, which may result in death or removal from the transplant list due to deteriorating health.[12,65] Considering the long waiting time, the possibility of transplant

failure due to CMV infection thereby results in further complications for patients, including deteriorations in HRQoL (e.g., increased anxiety).[69] Additionally, considering the large investment required from healthcare systems across the patient's transplant journey, there is a need to ensure transplant loss due to CMV does not occur. The availability of maribavir may help ensure that the investments made by patients and healthcare systems in ensuring successful transplants do not go to waste as a result of CMV infection.

B.2.13 Interpretation of clinical effectiveness and safety evidence

SOLSTICE demonstrates that maribavir 400 mg BID provides clinically relevant benefits over ganciclovir, valganciclovir, cidofovir or foscarnet, for patients with CMV post-transplant who are refractory or resistant to CMV treatment, whilst having a favourable safety profile and the capacity to reduce the amount of time patients spend in hospital. The Phase III, multicentre, randomised design of the trial provides a strong evidence base to evaluate the efficacy and safety of maribavir in the target population. The reported clinical endpoints were aligned to the key post-transplant morbidities and the patient baseline characteristics across both treatment arms were balanced. Despite the wide heterogeneity in local and international CMV management practices, UK clinical experts have verified that the SOLSTICE patient population is generalisable to the UK.[14]

In SOLSTICE, more than twice as many transplant patients with refractory or resistant CMV infection/disease treated with maribavir achieved the primary endpoint of CMV viraemia clearance at Week 8, compared with patients treated with conventional ganciclovir, valganciclovir, foscarnet or cidofovir (maribavir: 55.7% vs. IAT: 23.9%; p<0.001). 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%). No differences in all-cause mortality were observed across treatment groups.[109] For patients on treatment, patients receiving maribavir had a statistically significant reduction in hospitalisations ([redacted]) and LOS ([redacted]) compared with patients receiving IAT.[111]

Overall, the benefits of maribavir are consistent across both patients who have undergone SOT and HSCT.[109] For SOT patients, confirmed CMV viraemia clearance at Week 8 was higher in patients receiving maribavir (55.6%) compared with IAT (26.1%) (adjusted difference: 30.5%; 95% CI: 17.3%, 43.6%; p<0.001). For mortality, rates were lower in SOT population (maribavir: 4.9% vs. IAT: [redacted] compared with the overall study population (maribavir: [redacted] vs. IAT: [redacted] [108,110]

For HSCT patients, confirmed CMV viraemia clearance at Week 8 was numerically higher in the maribavir group (55.9%) compared with IAT (20.8%) (adjusted difference: 36.1%; 95% CI: 21.1%, 51.2%; p<0.001). For mortality, rates were higher in the HSCT population (maribavir: [redacted] vs. IAT: [redacted] than the overall study population (maribavir: [redacted] vs. IAT: [redacted]).[108,110]

Maribavir was well tolerated in patients with CMV post-transplant who are refractory or resistant to ganciclovir, valganciclovir, cidofovir or foscarnet. Nearly five times more

maribavir-treated patients completed the treatment course compared with conventional therapies. In addition, maribavir demonstrated a lower incidence of TEAEs leading to discontinuations compared with IAT (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.[109]

B.2.13.1 Key clinical issues

B.2.13.1.1 No trial results beyond week 20

In SOLSTICE, treatment was administered for a maximum of 8 weeks, with 12 weeks of follow-up.[109] 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. In order to evaluate long-term efficacy and safety outcomes in patients who are refractory or resistant to prior anti-CMV treatments; patients enrolled within the maribavir arm of the SOLSTICE trial are being followed up for 12 months after trial initiation. Outcomes include all-cause mortality, overall survival and graft outcomes (including the proportion of patients with graft failure, time to graft failure and proportion of patients with re-transplantation). Twelve-month follow up data are expected to be available in Q2 2022.

B.2.13.1.2 Use of IAT

SOLSTICE was conducted with an open-label design,[109] principally because of the need for the physician to individualise 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 UK practice for the management of CMV infection.[80] 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 characterised toxicities associated with the anti-CMV agents used as IAT. The distribution of the CMV therapies within SOLSTICE was validated by UK clinical experts and was considered reflective of English clinical practice for difficult-to-treat infections with refractory or resistant CMV.[14]

B.2.13.1.3 Discontinuation

In SOLSTICE, treatment discontinuations were higher with IAT (67.5%) than maribavir (21.7%); largely due to the high risk of AEs associated with the IAT treatments.[109] Overall, 31.9% of patients treated with IAT had a TEAE leading to discontinuation, in contrast with only 13.2% of patients treated with maribavir.[109] In addition a maribavir rescue arm was an option for patients originally assigned IAT after at least 3 weeks of treatment (see Section B.2.3.2). Patients who received maribavir rescue or alternative anti-CMV treatment before the end of Week 8, or failed to achieve confirmed CMV viraemia clearance at Week 8 (including missing virologic data) were considered non-responders.[109] However, the various sensitivity analyses conducted on the primary endpoint (Section B.2.6.1 and Appendix E.1.2.) indicate that discontinuation did not have a large impact on the primary outcome of the trial.

B.3 Cost effectiveness

Model structure and input parameters

- A *de novo* model was developed from a UK payer perspective comparing maribavir with IAT in CMV infection that is refractory or resistant to treatments after SOT or HSCT
- The Markov model has been separated into two stages:
  - Stage 1: 0 to 12 months
    - A three state Markov model: clinically significant CMV infection (csCMV), no clinically significant CMV infection (n-csCMV) and a dead state
  - Stage 2: 12 months to lifetime horizon
    - A two state Markov model with the states being alive or dead
- The time horizon represents a lifetime (up to age 100 years), with 4-week cycles for the first 3 years, then 1-year cycles thereafter. Costs and quality adjusted life years (QALYs) are discounted at an annual rate of 3.5%.
- The economic model utilises the primary endpoint from SOLSTICE, alongside important secondary endpoints, and the outputs from an individual patient data (IPD) analysis of the SOLSTICE data to establish the cost-effectiveness of maribavir compared with IAT
- Health state utility
  - Health state utility values in Stage 1 of the model were derived using the EQ-5D-3L from SOLSTICE. For Stage 2 of the model a disutility value is calculated from the SOLSTICE week 20 utility and the mean UK general population utility at age 53 is applied to the mean age-specific UK population utility values for the remainder of the time horizon
  - The disutility associated with AEs was sourced from UK specific literature, whilst the disutility associated with graft loss was derived from a UK vignette study
- The economic model includes several cost categories:
  - Drug acquisition were adjusted using SOLSTICE time on treatment data
  - Monitoring frequency was estimated from the respective SmPCs
  - Administration (i.e., IV or oral) were in line with NICE's preferred approach in TA591 (letermovir)
  - Health state resource use (hospitalisation) and AE incidence rates were sourced from the IPD analysis of the SOLSTICE trial
  - Costing was sourced from the British National Formulary (BNF) and NHS cost schedule
- The mortality rates applied in the model are dependent on the time point:
  - Stage 1: transplant (week 0-8) and health state specific mortality (week 8-52) were derived from SOLSTICE
  - Stage 2: transplant specific mortality estimates sourced from UK specific literature

Results

- In the base-case, for the ITT population (SOT and HSCT combined), the deterministic incremental cost-effectiveness ratio (ICER) for maribavir compared to IAT was £15,337 with higher incremental costs (£2,004), higher incremental QALYs (0.131), and higher incremental life years (0.160)
- Based on 10,000 sampled probabilistic ICERs, the probability that maribavir is cost-effective compared to IAT is 51.83% at a willingness-to-pay (WTP) threshold of £20,000, and 61.72% at a WTP threshold of £30,000.
- The ICER in the SOT only and HSCT only subgroup was £9,303 and £29,471, respectively. The higher ICER in the HSCT subgroup is driven by the impact of the underlying disease on mortality, resulting in lower life years and lower overall quality-adjusted life-years (QALYs).
- The model was most sensitive to drug acquisition costs, transition probabilities for clearance, and the time point at which stage 2 of the model commences.

B.3.1 Published cost-effectiveness studies

An economic SLR was conducted to identify published economic evaluations (cost-effectiveness analyses) comparing treatments for:

i. CMV in SOT or HSCT recipients that are refractory or resistant to pre-emptive treatment
ii. CMV in SOT or HSCT recipients on pre-emptive treatment.

The economic SLR was a compilation of one original SLR and two sets of updates conducted across multiple timeframes from 2007–2021, with the most recent conducted in September 2021. A summary of the timeframes covered for each SLR and its subsequent updates is presented in Table 30. The results obtained from the included studies identified across all reviews were compiled and are summarised in this section.

Of note, economic studies that included SOT or HSCT recipients that received prophylaxis for CMV were excluded. Prophylaxis aims to prevent a post-transplant CMV infection occurring; in contrast, patients who are refractory or resistant already have a CMV infection that has not responded to prior treatment. As this difference in disease staging requires different modelling considerations, the economic evaluations of products for prophylaxis were considered less relevant and were therefore excluded to focus the SLR on the more directly relevant treatment setting and ensure the number of identified studies was manageable. Further details of the search strategy are provided in Appendix G.2. To ensure that any relevant information from previous NICE appraisals was captured, a targeted search was undertaken to identify any NICE appraisals which evaluated products for CMV. This also included prophylactic treatments , as this was not considered to be a burdensome addition to the review.

Table 30: Summary of the SLRs conducted for economic evaluations (cost-effectiveness analyses) review

Year of search	2017	2020	2021
Version	Original SLR	Update 1	Update 2
Economic/cost-effectiveness analysis SLR search dates	1st January 2007 to 14th November 2017	15th November 2017 to 28th April 2020	29th April 2020 to 21st September 2021

SLR= Systematic literature review

B.3.1.1 CMV R/R to pre-emptive treatment

No studies were identified which evaluated economic/cost-effectiveness for CMV in SOT or HSCT recipients that are refractory or resistant to CMV treatments.

B.3.1.2 CMV on pre-emptive treatment

One economic analysis was identified reporting the cost-effectiveness of a CMV-specific T-cell therapy for the management of CMV in allogeneic HSCT recipients.[112] This study was only presented as an abstract, and reported a Markov model comparing foscarnet (second-line CMV treatment), cidofovir (third-line disease treatment) and standard treatment (no further detail) from the NHS perspective. No details were provided on health states included in the model, cycle length, or time horizon and source of clinical effectiveness. For details, please see Appendix G.4.2.

B.3.1.3 Prophylaxis of CMV

The targeted literature review identified one NICE health technology assessment (HTA), which evaluated a product for the prevention of CMV; letermovir (TA591).[49] This NICE appraisal presented an economic model comparing letermovir with placebo for CMV prophylaxis in allogeneic HSCT patients. The model started with a decision tree followed by a two-state Markov (alive/dead) model. The use of the decision tree was criticised by the Evidence Review Group (ERG) for its over simplified approach and lack of explicit health states to capture differences in QALYs. Outcomes reported were QALYs, life years, costs and the ICER (£/QALY) per patient.

Although not directly applicable to the resistant and refractory setting, the model presented in this NICE appraisal (TA591)[49] included components that are relevant to all settings. Therefore, TA591 was used in part to inform the approach developed for the maribavir model.

B.3.2 Economic analysis

No relevant economic evaluations were identified by the economic SLR and therefore a *de novo* model was developed, incorporating relevant aspects of the model developed for NICE TA591 as appropriate. Expert clinical input from UK SOT and HSCT physicians, as well as expert health economists, was used to define the health states and model structure.[14,113]

B.3.2.1 Patient population

The model population represents patients with CMV that are refractory or resistant to treatment after allogeneic HSCT or SOT. The population is aligned with the inclusion criteria used in SOLSTICE:[107]

- 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
- Documented CMV in whole blood or plasma, with a screening value of ≥2730 IU/mL in whole blood or ≥910 IU/mL in plasma in two consecutive assessments, separated by ≥1 day
- Current CMV infection that is refractory to the most recently administered of the four available anti-CMV treatment agents

This is in line with the final NICE scope, as highlighted in Section B.1.1.

B.3.2.2 Model structure

Based on expert UK clinician and external health economist advice, and a review of previous economic evaluations, a Markov approach was determined to be the most appropriate modelling method for the decision problem of this appriasal.[14] Though the previous model for letermovir (TA591) for prophylaxis used a decision tree and Markov model hybrid,[49] all relevant outcomes and disease states can be captured within a

Markov framework without the need for an initial decision tree. The Markov approach also allows this model to capture a link between explicit health states, defined by CMV status, and the consequential impact on QoL, mortality, and other events (such as CMV recurrence and graft loss) which are drivers of cost-effectiveness.

The model has been separated into two stages:

- **Stage 1:** 0 to 12 months
    - A three state Markov model with the states being clinically significant CMV infection (csCMV), no clinically significant CMV infection (n-csCMV) and a dead state.
- **Stage 2:** 12 months to lifetime horizon
    - A two state Markov model with the states being alive or dead

Clinical experts advised that the treatment for refractory or resistant CMV is for a limited period, and most patients would complete treatment within 12 months. Patients are at higher risk of CMV infection progressing to CMV disease during the initial period after transplantation, when high levels of immunosuppression are used. As patients move to the post-transplant maintenance phase (3–6 months), the dose of immunosuppression is reduced.[33] As a result of this, the patient's own immune system is typically better able to combat viral replication.[34] This results in natural clearance of CMV, which reduces the need for continued intervention. For this reason, the model assumes no further CMV events can occur after 12 months, with any remaining CMV assumed to be controlled by the patient's immune system without the need for further anti-CMV treatment. Therefore, in the second stage of the model (post 12-months), a two-state Markov (alive and dead) is used to model long-term survival for the remainder of the time horizon. Clinical experts advised that continuing treatment beyond 12 months occurs only in rare cases, and that it is therefore a reasonable simplifying assumption to transition to the two-state alive/dead Markov model after 12 months. In addition, this approach is consistent with the methods accepted by the NICE committee in a recent health technology appraisal for letermovir (TA591) for preventing CMV in allogeneic HSCT recipients.[49]

B.3.2.2.1 Markov model (Stage 1; 0–52 weeks)

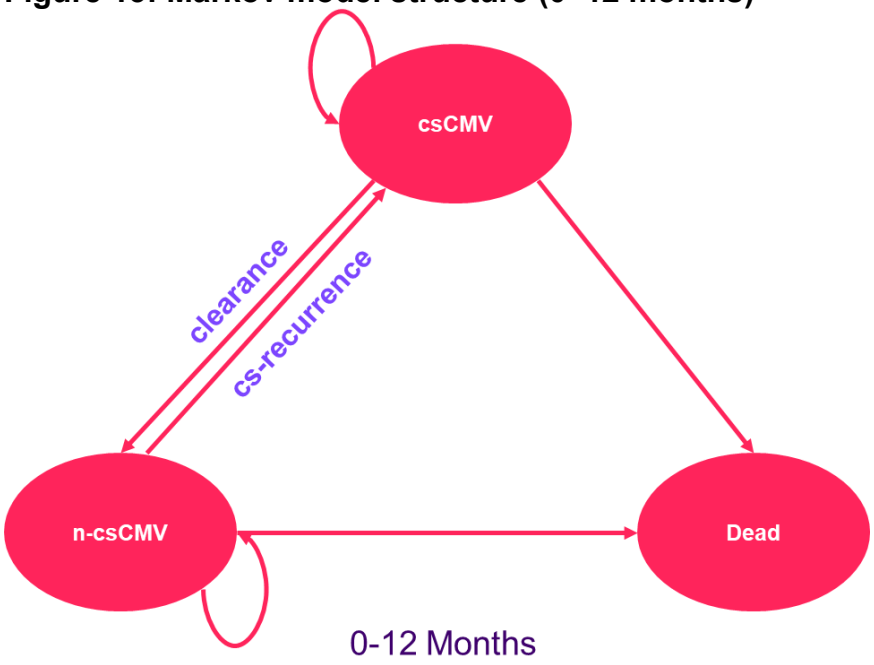
During the first 12 months (52 weeks; Stage 1), a three-state Markov model is used. This approach was selected because it adequately allows the model to capture important distinctions in CMV status and thus the ability to link these states to other important model outcomes (QoL, mortality and incidence of important clinical events). The three health states in the model are:

- **Clinically significant CMV (csCMV)**: All patients enter the model with clinically significant refractory or resistant CMV requiring treatment. This state is occupied by patients who do not achieve CMV viraemia clearance (i.e., clearance defined as plasma CMV DNA concentration below the lower limit of quantification [LLOQ]) or patients who in a previous cycle occupied the non-clinically significant CMV (n-csCMV) health state but then experience a clinically significant recurrence (i.e., plasma CMV DNA concentration >LLOQ which requires treatment).

- **Non-clinically significant CMV (n-csCMV)**: patients who achieve CMV clearance or those who have achieved clearance and do not experience a clinically significant recurrence occupy the n-csCMV health state.
- **Dead**: All patients in the model have a risk of transitioning to the dead state; this is an absorbing final health state.

Clinically significant refractory or resistant CMV requiring treatment was selected as the health state definition rather than any level of CMV viraemia above the LLOQ. Clinical experts advised that that the CMV viraemia LLOQ is a strict criteria that does not necessarily reflect clinical significance,[14] and only recurrences which result in active treatment by a clinician should be considered clinically significant.[14] Clinically significant recurrences allow the model to capture CMV events that have important clinical and cost implications. The Markov model structure is illustrated in Figure 13, where the arrows represent the transitions allowed in the model.

Figure 13: Markov model structure (0–12 months)



csCMV=Clinically significant cytomegalovirus; cs-recurrence=Clinically significant-recurrence; n-csCMV=Non-clinically significant cytomegalovirus

The feasible transitions in the three-state Markov model are:

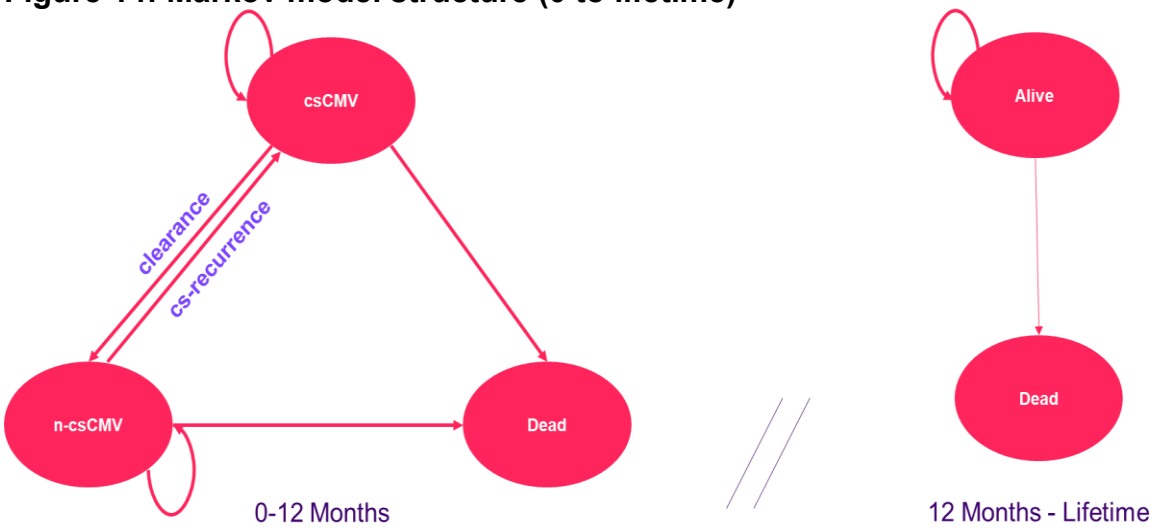
- **csCMV → n-csCMV (clearance)**: patients who respond to treatment and achieve CMV clearance (i.e., plasma CMV DNA concentration <LLOQ in two consecutive readings)
- **csCMV → csCMV (no clearance)**: patients who have no response to treatment and remain in the csCMV health state
- **n-csCMV → csCMV (cs-recurrence):** patients who achieved CMV clearance experience a CMV viral load >LLOQ and require treatment with an anti-CMV agent
- **n-csCMV → n-csCMV (no cs-recurrence)**: patients who maintain CMV clearance and do not have a clinically significant recurrence

- **csCMV → dead** or **n-csCMV → dead:** patients in the csCMV or n-csCMV health states that die.

B.3.2.2.2 Markov model (Stage 2; 52 week – lifetime)

The Markov model structure in Stage 2 (12 months to the lifetime horizon) is illustrated in Figure 14 (alongside the Stage 1 Markov). From 12 months onwards, the model assumes no further CMV events can occur. Instead, the model adopts a two-state approach 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 14: Markov model structure (0 to lifetime)



csCMV=Clinically significant cytomegalovirus; cs-recurrence=Clinically significant-recurrence; n-csCMV=Non-clinically significant cytomegalovirus

The feasible transitions in the two-state Markov model are:

- **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 transplant-specific mortality and general population mortality

B.3.2.2.3 Time horizon

For the base-case analysis, the model uses a lifetime horizon to ensure that all costs and effects of treatment are captured. This method is in alignment with the NICE reference case.[114] A time horizon of 47 years for a starting cohort aged 53 (average age of participants in SOLSTICE) is assumed to represent a lifetime horizon with all patients assumed to be dead at age 100.

B.3.2.2.4 Cycle length

The model uses a 4-week cycle length for the first three years, thereafter, it adopts annual cycles. A 4-week cycle length was chosen for the initial period as SOLSTICE showed evidence that patients treated with maribavir achieved faster clearance

compared with IAT (i.e. before completion of the 8-week treatment duration). A 4-week cycle was deemed a reasonable balance between allowing the model to capture the benefits associated with this earlier clearance, mirroring the average length of treatment in clinical practice, while reducing the computational burden associated with a potential shorter cycle length. In the base-case, after the first year, the model transitions to stage 2 (alive-death model). However, to allow the model to be flexible and have the ability to include further CMV occurrences beyond 12 months, 4-week cycles are used up to year 3. After year 3, the model uses annual cycles to model transitions from the alive state to the dead states only, to ensure the model does not become computationally burdensome.

B.3.2.2.5 Features of the economic analysis

The key features of the economic analysis in the current appraisal, as well as those used in the previous technology appraisal for letermovir for preventing CMV disease after HSCT (TA591), are presented in Table 31. In alignment with the NICE reference case, the cost-effectiveness analysis takes the UK payer perspective. Unit costs and resource use are based on the perspective of the NHS (National Health Service) and PSS (Personal Social Services), while health outcomes for patients are measured using QALYs. Costs and health outcomes are discounted annually, with a (base-case) discount rate of 3.5% for both costs and outcomes, in line with the NICE reference case.[114]

Table 31: Features of the economic analysis

	Previous appraisal	Current appraisal	
Factor	**TA591**	**Chosen values**	**Justification**
Model structure	Decision tree (stage 1; 0–24 weeks) followed by alive/dead Markov (stage 2; 24 weeks -lifetime)	Three-state Markov (stage 1; 0–52 weeks) followed by alive/dead after 1 year (stage 2; 52 weeks – lifetime)	The choice to adopt a two-state model from 12-months onwards was based on discussions with clinical experts and experienced health economists. Clinical experts explained that almost all patients with CMV would be off treatment at 12 months as patients' immunity recovers overtime resulting in natural clearance of CMV without the need for CMV treatment. 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)
Cycle length	not applicable (stage 1) 1 year (stage 2)	4-week (year 0 to 3) 1 year (year 3 to lifetime)	SOLSTICE CSR indicates that patients on treatment with maribavir achieve faster clearance compared with IAT. As a result, a 4-week cycle length was chosen to capture the benefit of this faster clearance
Time horizon	Lifetime	Lifetime	This time horizon is sufficient to ensure that all cost and benefit differences between maribavir and SOT are captured, as suggested by the NICE reference case[114]
Perspective	UK payer perspective (NHS England)	UK payer perspective (NHS England)	In line with the NICE reference case[114]
Discounting	3.5%	3.5%	In line with the NICE reference case[114]
Source of utilities	The sources of utilities were obtained from PN001 trial data and were collected using FACT-BMT and the EQ-5D. The utilities derived from the EQ-5D were applied in the model. Health effects were expressed in QALYs	The sources of utilities were obtained from SOLSTICE and were collected using EQ-5D-5L. The utilities derived from the EQ-5D were applied in the model. Health effects are expressed in QALYs	In line with the NICE reference case[114]
Source of costs	Sourced from the NHS reference costs and PSSRU. The perspective on costs was that of the NHS and PSS	Sourced from the NHS reference costs and PSSRU. The perspective on costs was that of the NHS and PSS	In line with the NICE reference case[114]

CSR=Clinical study report; FACT-BMT= Functional Assessment of Cancer Therapy - Bone Marrow Transplantation; NHS=National Health Service; NICE=National Institute of Health and Care Excellence; PSS=Personal Social Services; PSSRU=Personal Social Services Research Unit; QALY=Quality-adjusted life year
Source: NICE 2019.[49]

B.3.2.3 Intervention technology and comparators

In line with the final scope, the economic analysis presented in this submission is for the use of maribavir in patients with CMV infection that is refractory or resistant to CMV treatments after SOT or HSCT.

The comparator included in the model is IAT, which is a blend of the four most commonly used anti-CMV agents in the UK: ganciclovir, valganciclovir, foscarnet and cidofovir. This is in line with the maribavir pivotal trial SOLSTICE.[107] IAT was selected as the comparator in the SOLSTICE trial principally because of the need for the physician to individualise drug selection for treatment-refractory subjects in the IAT arm, choosing the appropriate therapy based on clinical data and judgment, guidelines and published guidance documents. This is consistent with how anti-CMV agents are provided to refractory or resistant patients in the real-world clinical setting.

In SOLSTICE, 7 out of 116 patients in the IAT arm were treated with a combination therapy (foscarnet/valganciclovir [n=3] and foscarnet/ganciclovir [n=4]). Dual therapy is not routinely used in UK clinical practice and there is a lack of guidance on its use, and in particular, dosing. In order to avoid potential double counting of costs by costing both therapies at a full dose, a conservative assumption was made that these patients should be distributed evenly across the two drugs, effectively equating to half a dose of each drug. The uncertainty in this approach, however, has a negligible impact on the results due to the limited number of patients receiving combination therapy in the SOLSTICE trial. The readjusted percentages are presented in Table 32.

Table 32: Treatment distributions in SOLSTICE and the economic model

	SOLSTICE distribution, n (%)		Model distribution, n (%)	
Drug	**Maribavir**	**IAT**	**Maribavir**	**IAT**
Maribavir	100%		100%	
Ganciclovir		28 (24.1)		29.5 (25.4)
Valganciclovir		28 (24.1)		30 (25.9)
Foscarnet		47 (40.5)		50.5 (43.5)
Cidofovir		6 (5.2)		6 (5.2)
Foscarnet / valganciclovir		4 (3.4)		N/A
Foscarnet / ganciclovir		3 (2.6)		N/A

IAT=Investigator-assigned anti-CMV treatment; N/A=Not applicable
Source: Takeda 2021.[108]

In the intervention arm, patients receive maribavir as their first treatment and IAT as retreatment for patients who do not clear CMV or have clinically significant recurrence. For the comparator arm, patients receive IAT as their first treatment and IAT as a retreatment. In the base-case, it is assumed the IAT distribution is the same as the proportions observed in SOLSTICE, adjusted as per the initial treatment.

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline patient characteristics

The baseline population characteristics of the economic model are derived from the SOLSTICE study (Table 33) to align with the population in which treatment effects were measured. Expert clinical opinion indicated that the baseline characteristics within the trial are broadly aligned with UK clinical practice. For full baseline characteristics in SOLSTICE see Section B.2.3.5 (Table 10).

Table 33: Baseline patient characteristics

Patient characteristic	Value
Age, years (SE)	53 (0.70)[a]
Male, % (SE)	61% (0.03)[b]
Patient weight, kg (SE)	74.80 (0.97)[a]
SOT patients (of HSCT and SOT patients), % (SE)	59.9% [c]
Distribution of SOT types, %	
Heart	11%
Kidney	50%
Lung	29%
Liver	3%
Other	6%

CSR=Clinical study report; HSCT=Hematopoietic stem transplantation; kg=kilogram; SD=Standard deviation; SE=Standard error; SOT=Solid organ transplant

[a] SE is calculated as $\frac{SD}{\sqrt{n}}$, where n is the total number of patients in the trial (352) and the SD is from the SOLSTICE CSR

[b] SE 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] Type of transplant is not included in the probabilistic sensistivity analysis and therefore no SE value is assigned

Source: Avery RK, et al. 2021.[107]

Patient age and gender are used to estimate all-cause mortality rates of the cohort in Stage 2 of the Markov model, using general population lifetables. These lifetables are adjusted to account for the added risk of mortality among transplant recipients (SOT or HSCT), with the risk of mortality dependent on time since transplant (Section B.3.3.2.3).

The patient weight is used to calculate the cost of treatment as certain IAT dosages are defined according to bodyweight.

The model separately models SOT and HSCT patients (i.e., there are separate Markov traces for these patients), therefore, the baseline type of transplant parameter is used to weight the results from these two models to derive weighted average cost-effectiveness results in the ITT population.

B.3.3.2 Transition probabilities

Transition probabilities in the model are defined by three key clinical parameters: clearance, recurrence and mortality. The input values that inform the transition probabilities are described in the sections below.

B.3.3.2.1 Clearance

Clearance (defined as plasma CMV DNA concentration <LLOQ in two consecutive readings, separated by at least five days) is the primary treatment effect associated with an anti-CMV agent, and defines the transition from csCMV to n-csCMV. Clearance probabilities for maribavir and IAT were taken directly from SOLSTICE. As explained in Section B.3.3.2.1, due to evidence of faster clearance with maribavir, the model uses a 4-week cycle length. The clearance observed for both the maribavir arm and IAT at week 4 are derived from IPD analysis of SOLSTICE (Table 34).[110] The IPD analysis also reported the proportion of patients who achieve CMV clearance from week 4 to week 8 in the maribavir and IAT arms (i.e., those who were non-responders at week 4 and achieve a response at week 8). This was used as a transition probability for clearance from week 4 to 8 (transition from csCMV to n-csCMV).

From weeks 8 to 52, patients who occupy the csCMV health state in either the maribavir or IAT arms are assumed to receive IAT retreatment. Therefore, the clearance probabilities utilised from week 8 onwards are derived from the IAT arm of SOLSTICE.[110] Specifically, the clearance observed from week 0 to 8 in the trial has been converted into a 4-week transition probability and used for the remaining cycles of the Stage 1 Markov in the model.

From week 52 onwards (i.e., the start of Stage 2), the model assumes that no further CMV events can occur, and therefore, that all patients are off treatment and natural clearance will occur. Therefore, clearance probabilities are no longer of relevance beyond 52 weeks.

Table 34: 4-week clearance transition probabilities from csCMV to n-csCMV

Time point	Maribavir: Mean (SE)[a]	IAT: Mean (SE)[a]
Week 0 to 4	[redacted]	[redacted]
Week 4 to 8	[redacted]	[redacted]
Week 8 to 52 [b]	[redacted]	[redacted]
Week 52 onwards	N/A	N/A

N/A=Not applicable; SE=Standard error; csCMV=Clinically significant cytomegalovirus; n-csCMV=Non-clinically significant cytomegalovirus; IAT=Investigator assigned treatment

[a] SE is 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

[b] The model retains functionality to incorporate different 4-weekly transition probabilities between week 8 to 20 and then for week 20 onwards.

[c] Assumed same as IAT as retreatment is with IAT

Source: Takeda 2021; Takeda 2021.[108,110]

B.3.3.2.2 Clinically significant recurrence

Clinically significant recurrence (defined as those who after achieving clearance, have a plasma CMV DNA >LLOQ and requires treatment with an anti-CMV agent) defines the transition from n-csCMV to csCMV. Clinically significant recurrence probabilities for maribavir and IAT were taken from an IPD analysis of SOLSTICE.[107,110] Patients are only able to occupy the n-csCMV health state from week 4 onwards, therefore, the first occurrence of clinically significant recurrence occurs at week 8. The IPD analysis reported the number of patients achieving a response at week 4 who then have a

recurrence requiring treatment at week 8, in both the maribavir and IAT arms.[110] This was used as a transition probability for cs-recurrence (transition from n-csCMV to csCMV) from week 4 to week 8.

It should be noted that between weeks 4 and 8, patients who discontinued treatment due to AEs and then initiated a subsequent anti-CMV treatment before, or at, week 8 were classified as patients who had recurrence requiring treatment. Any patient who could not reasonably be assumed to have had a recurrence requiring treatment between weeks 4 and 8 (i.e., due to death or lack of data on CMV viral load) was excluded from the efficacy analysis,[110] and the recurrence probability was adjusted to account for this exclusion. Therefore, the adjusted recurrence rate is equal to the number of patients with response at week 4 and patients with recurrence requiring treatment at week 8, plus those on alternative CMV treatment and those who discontinued due to AEs; this total number of patients is then divided by the number of patients achieving response at week 8 (after excluding patients who did not comply with the study procedure, withdrew from the study, died, or due to another reason but remained in the study).

From week 8 to 52, transition probabilities for cs-recurrence are determined according to treatment history. Patients whose most recent treatment was maribavir (i.e., patients achieved CMV clearance following treatment with maribavir, and have since occupied the n-csCMV health state), have a risk of recurrence defined by converting the recurrence requiring treatment observed in the maribavir arm between week 8 to 20 in SOLSTICE into a 4-week transition probability (Table 35).[110] Those patients who have had IAT as their most recent treatment have a risk of recurrence defined by converting the recurrence requiring treatment observed in the IAT arm between week 8 to 20 in SOLSTICE into a 4-week transition probability.

From week 52 onwards (i.e., the start of Stage 2), the model assumes no further CMV events can occur, all patients are off treatment and natural clearance will occur. Therefore, recurrence probabilities are no longer of relevance beyond 52 weeks.

Table 35: 4-week recurrence transition probabilities from csCMV to n-csCMV

Time point	Most recent treatment maribavir: Mean (SE)[a]	Most recent treatment IAT Mean (SE)[a]
Week 0 to 4	N/A	N/A
Week 4 to 8	[redacted]	[redacted]
Week 8 to 52	[redacted]	[redacted]
Week 52 onwards	N/A	N/A

N/A=Not applicable; SE=Standard error; IAT=Investigator assigned treatment

[a] SE is 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

Source: Takeda. 2021.[110]

B.3.3.2.3 Mortality

As illustrated in the Markov structural diagrams in Section B.3.2.2 (Figure 13 and Figure 14), all patients are at risk of mortality.

B.3.3.2.3.1 Week 0 to 8

Following the completion of IPD analysis, it was observed that neither treatment, health-state nor transplant type had a statistically significant impact on mortality in the first 8 weeks. However, following discussions with clinical experts, it was advised that as the underlying condition for SOT and HSCT patients are different, it would be most appropriate to use transplant specific mortality rates.[14] The IPD analyses reported the risk of mortality by transplant type separately for weeks 0 to 4 and weeks 4 to 8, and these were used directly as transition probabilities in the model, with mortality assumed the same for the csCMV and n-csCMV health state for weeks 0 to 8 (Table 36).[110] In addition to the transplant specific mortality probabilities, background sex- and age-specific general population mortality have been added to the transplant-specific mortality rates.[115] Annual sex- and age- specific mortality probabilities were taken from Office for National Statistics data,[115] converted into 4-week mortality probabilities and added to the transplant-specific mortality probabilities in each cycle.

Table 36: Week 0 to 8 mortality rates

Time point	SOT Mean (SE)[a]	HSCT Mean (SE)[a]
Week 0 to 4	[redacted]	[redacted]
Week 4 to 8	[redacted]	[redacted]

SE=Standard error; HSCT=Hematopoietic stem transplantation; SOT=Solid organ transplant

[a] SE is 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

Source: Takeda 2021; Takeda 2021.[108,110]

B.3.3.2.3.2 Week 8 to 52

From week 8 to 52, health-state specific mortality was incorporated into the model to better reflect the outcomes associated with CMV status. The IPD analysis classified patients into two categories: response (patients achieving clearance) and no response (all patients not achieving clearance) at week 8, as per the primary endpoint of SOLSTICE.[110] 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 could be 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 52 (Table 37). In addition to the transplant-specific mortality probabilities, background sex- and age-specific general population mortality rates have been added to the transplant-specific mortality rates. Annual sex- and age- specific mortality probabilities were taken from Office for National statistics data,[115] converted into 4-week mortality probabilities and added to the transplant-specific mortality probabilities in each cycle.

Table 37: Week 8 to 52 Mortality rates

Time point	csCMV (SE)[a]	n-cCMV (SE)[a]
Week 8 to 52	[redacted]	[redacted]

SE=Standard error; csCMV=Clinically significant cytomegalovirus; n-csCMV=Non-clinically significant cytomegalovirus

[a] SE is 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

Source: Takeda. 2021; Takeda. 2021.[108,110]

The decision to not further categorise patients by health state and transplant type was taken due to sample size, as patient numbers become too low in each respective category to provide robust and plausible estimates. Specifically, in the SOT cohort, [redacted]% and [redacted] % mortality probabilities were observed over 12 weeks in the response and no response groups, respectively (Table 37). When converted into 4-week probabilities, this results in [redacted] % and [redacted] % for the n-csCMV and csCMV health states, respectively (Table 38). Expert clinicians advised Takeda that using the ITT population and health-state specific values provided the most clinically appropriate results.

Table 38: 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]	[redacted]	[redacted]	[redacted]

HSCT=Haematopoietic stem cell transplant; SOT=Solid organ transplant

Source: Takeda. 2021.[110]

B.3.3.2.3.3 Week 52 onwards

Transition probabilities in Stage 2 are governed by long-term mortality estimates. For patients who received SOT, mortality was estimated based on data from the NHS Organ Donation Annual Activity Report.[116] This was chosen as it provides the most up-to-date information on SOT for UK patients. One-, two-, five-, and ten-year post-transplant survival estimates for first non-paediatric heart, lung, liver and kidney transplants of all donor types (shown in Table 39) were converted into their corresponding annual conditional survival probabilities. For lung, Donation after Circulatory Death (DCD) donor types, the survival probabilities were available only for one-, two- and three-year post-transplant, so this organ and donor type was only included in mortality calculations for the first three years post-transplant.

Table 39: 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[a]	N/A
Liver	DBD	94	92	84	68

DBD=Donor after brain death; DCD=Donor after circulatory death, N/A=Not applicable; SOT=Solid organ transplant
[a] 3-year survival estimate as the 5-year survival estimate was not available
Source: NHS Blood and Transplant 2021.[116]

The annual conditional survival probabilities for each organ and year category were converted into annual conditional mortality probabilities shown in Table 40. To account for years where there are no published data available (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 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 years 6, 7, 8 and 9.

Table 40: SOT annual mortality probabilities

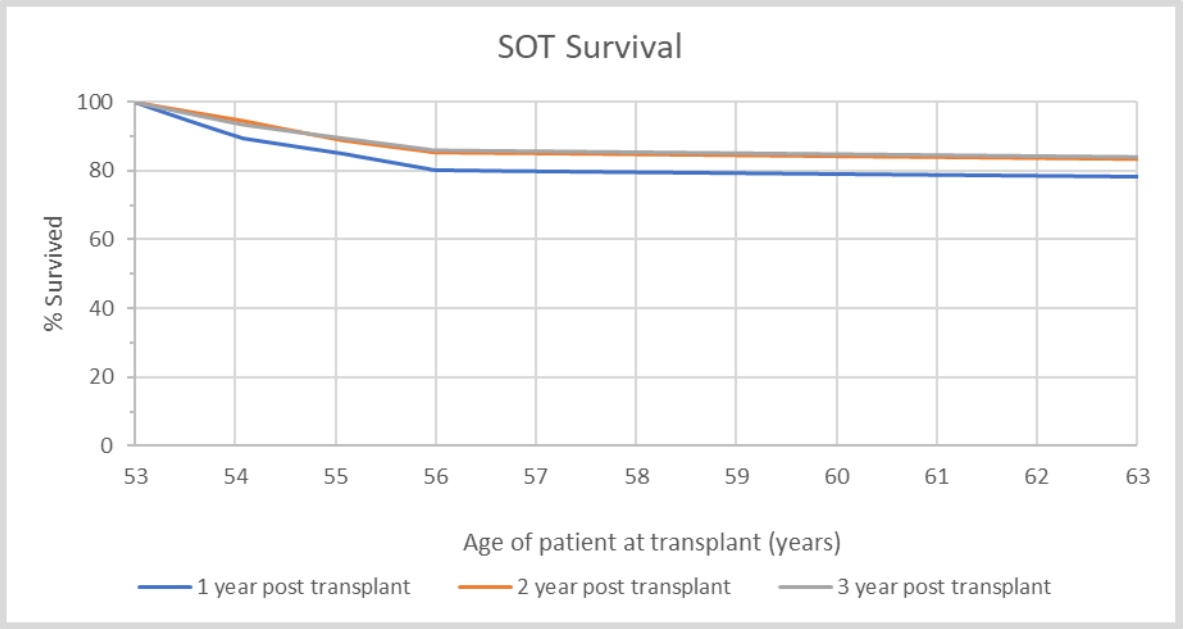
Organ	Donor type	Annual probability at year 1	Annual probability at year 2	Annual probability at year 5	Annual probability at year 10
Kidney	DBD	0.03	0.02	0.02	0.03
Kidney	DCD	0.03	0.02	0.02	0.02
Kidney	Living	0.01	0.01	0.01	0.02
Heart	DBD	0.16	0.07	0.07	0.02
Lung	DBD	0.17	0.10	0.10	0.08
Lung	DCD	0.24	0.11	0.20	N/A
Liver	DBD	0.06	0.02	0.03	0.04
Average	-	0.10	0.05	0.04	0.04

DBD=Donor after brain death; DCD=Donor after circulatory death; N/A=Not applicable; SOT=Solid organ transplant
Source: NHS Blood and Transplant. 2021.[116]

The calculated weighted average annual probabilities across each organ type were then compared to the general population age- and sex-adjusted mortality values, and the largest mortality rate of the two was selected for each age in the model (starting at age 53).[115]

The SOT patient survival curves for patients who are 1-, 2- and 3- year(s) post-transplant and enter the model at age 53, are shown in Figure 15, patients are assumed to be 1-year post transplant on entering the model. The methods used to estimate long-term mortality for SOT patients ensures that long-term mortality is adjusted for the 1 year since patients have had a transplant.

Figure 15: SOT survival curves



SOT=Solid organ transplant
Note: For 1-year post transplant it is assumed that patients received a transplant at age 52 and are still alive at age 53 (starting age in the economic model)
Source NHS Blood and Transplant 2021.[116]

For HSCT, data from the Haematological Malignancy Research Network (HMRN)[49] is used to estimate mortality in the first 5 years post-transplant (Table 41). After year 5, the HMRN data showed high attrition and therefore, the 5-year mortality is continued for the remaining model years. From 5 years post-transplant, the base-case mortality is estimated by comparing the annual mortality probability at 5 years with the age- and sex-adjusted mortality values for the general population, taking the largest of the two at each time point past 5 years post-transplant. [115]

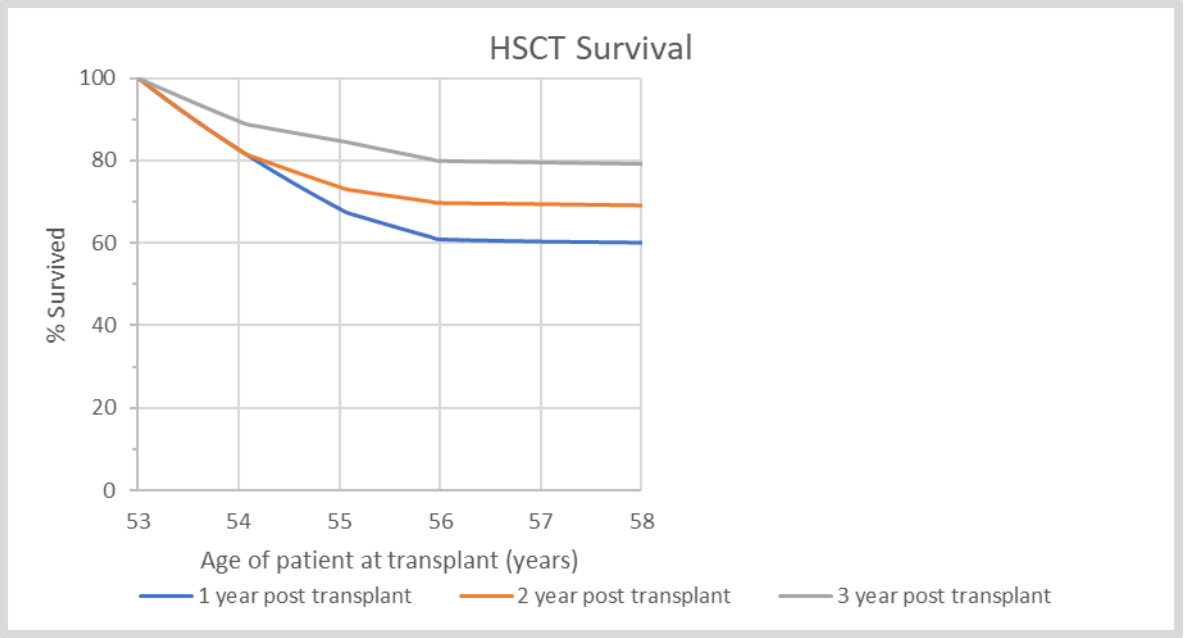
Table 41: HSCT mortality rate and annual probability

Years	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

HMRN=The Haematological Malignancy Research Network; HSCT=Haematopoietic stem cell transplant
Source: NICE 2019.[49]

In years post-transplant where data are unavailable (year 1), it is assumed to be the same as the closest year with available data (year 2). The HSCT patient survival curves for patients who are 1-, 2-, and 3- year(s) post-transplant and enter the model at age 53 are shown in Figure 16, which was derived using the annual probability of mortality in Table 41. Patients are assumed to be 1-year post transplant on entering the model.

Figure 16: HSCT survival curves



HSCT=Haematopoietic stem cell transplant
Note: For 1-year post transplant it is assumed that patients received a transplant at age 52 and are still alive at age 53 (starting age in the economic model)
Source: NICE 2019.[49]

B.3.3.2.4 Disease complications

B.3.3.2.4.1 Graft loss

Although no graft loss events occurred in SOLSTICE (see Table 20), clinical experts indicated that graft preservation is an important factor for the treatment of CMV in SOT patients. Clinical experts also explained that graft loss events would be more likely to be observed over a longer time horizon, and with greater frequency in a CMV cohort. This is supported by the results from a retrospective cohort study of 20,473 patients in France,[20] which reported 2-year probabilities of graft loss of 9.41% in patients who do not have CMV within 3 months of SOT, and 10.81% in those who have CMV in this period. These values were used to derive a RR of graft loss of 1.15 for patients with CMV compared with those without CMV. The 2-year probabilities of graft loss for study participants with CMV were converted into 4-week probabilities (0.44%) and used as a cyclical probability in the model for the csCMV health state. The probabilities for patients in the csCMV health state was then calculated in the model by multiplying the 4-week csCMV probabilities of graft loss by the 1.15 RR (Table 42).

Table 42: Risk of graft loss for patients with csCMV and n-csCMV

Health state	Risk of graft loss: Mean (SE)[a]
csCMV	0.0044 (0.0014)
n-csCMV	0.0038 (0.0013)

csCMV=Clinically significant cytomegalovirus; n-csCMV=Non-clinically significant cytomegalovirus; SE=Standard error,

[a] SE is 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
Source: Hakimi Z, et al. 2017.[20]

When a graft loss event occurs in the model, the distribution of organ transplant at baseline (Table 43) is used to estimate the specific organ impacted during the graft loss (e.g., 11% of graft loss events per cycle are assumed to impact the heart, see Table 43 for other proportions). Patients are only at risk of a single graft loss event in the model; although a second transplant may in principle be offered to patients, given the shortage of matched organs there is no guarantee of a suitable second transplant donor.[67] Studies indicate that patients who have a retransplant have an elevated risk of mortality (Table 43);[117,118] therefore, individuals who suffer from graft loss experience an increased risk of mortality. This increased mortality is applied by multiplying the organ-specific HR sourced from the literature by the relevant annual age- and sex-specific mortality.[108,117,118]

Table 43: Baseline distribution of transplant type and mortality risk for retransplant patients

Baseline transplant type	SOLSTICE, SOT population Proportion of transplant type at baseline: Mean (SE)	HR of mortality for retransplant patients	
		Mean (SE)	Source
Heart transplant	0.11 (0.02)[a]	1.79 (0.20)[b]	Miller et al. 2019[117]
Kidney transplant	0.50 (0.03)[a]	1.25 (0.09)[b]	Panchal et al. 2015[119]
Lung transplant	0.29 (0.02)[a]	1.30 (0.08)[b]	Kawut et al. 2008[120]
Liver transplant	0.03 (0.01)[a]	1.30 (0.13)[b]	Kim et al. 2010[118]
Other	0.06[c] (0.1)[a]	1.33[d] (0.13)[a]	Weighted average

CI=Confidence interval; HR=Hazard ratio; SE=Standard error; SOT=Solid organ transplant

[a] SE is assumed to be 10% of the value.

[b] SE is calculated as $\frac{upper\ 95\%\ CI - lower\ 95\%\ CI}{3.92}$.

[c] 1- sum of all other baseline transplant types.

[d] Weighted average of all other transplant types, weight is the proportion of transplant type at the baseline.

Additionally, clinical experts indicated that patients who have had a failed 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, along with the additional cost of dialysis while waiting for a transplant. The waiting time for retransplant for renal patients is based on a weighted average for deceased (63.47%) and living donors (36.57%), which is 976 days and 313 days, respectively.[121]

Table 44: Dialysis inputs

Baseline transplant type	Base case	Source
Proportion of patients on lifetime dialysis	0.7	Assumption
Annual cost of dialysis	£32,259.00	NICE (NG107) [122]
Years of dialysis	2.01	The British Transplant Society [121]
HR - dialysis mortality	1.39	Rayner et al.[123]
Dialysis disutility	-0.25	Liem et al.[124] (used in NICE NG107)

HR=Hazard ratio; NICE=The National Institute for Heath and Care Excellence
[a] The disutility of dialysis is the difference between the utility of haemodialysis and renal transplantation.

In a Canadian retrospective study including 2,466 renal transplant recipients, it was found that death-censored graft loss was significantly increased in recipients with increasing number of CMV viraemia episodes, with the effect sustained over time (see Figure 3).[36] As the model moves to a two-state Markov model after 12 months, long-term effects on graft survival are not captured. This is, therefore, a conservative approach, as in SOLSTICE, patients treated with maribavir were more likely to achieve CMV clearance compared with IAT.

B.3.3.2.4.2 GvHD

As described in Section B.1.3.4, there is limited clinical evidence of a causal relationship between CMV and GvHD, therefore the incidence of GvHD was not included in the base-case. In a scenario analysis, GvHD is incorporated using published data.[56,125]

B.3.3.4 Adverse events

Treatment emergent adverse events (TEAEs) that had an incidence of ≥10% in either the maribavir or IAT arms, as well as any additional AEs from SOLSTICE considered clinically important by clinical experts, were included in the model. Each individual IAT drug was assumed to have the pooled IAT incidence, which keeps AEs consistent with the pooled IAT treatment efficacy data. It was assumed that SOLSTICE provided rates of AEs over a 20-week time horizon, which were converted into 4-week probabilities and implemented as a treatment-specific cyclical risk in the model (Table 45).

Table 45: Incidence of AEs included within the model – 4-week probability

AE	Maribavir	IAT
Acute kidney injury	0.040	0.042
Anaemia	0.034	0.047
Diarrhoea	0.045	0.052
Dysgeusia	0.080	0.024
Fatigue	0.024	0.017
Febrile neutropenia	0.003	0.010
Headache	0.018	0.027
Leukopenia	0.013	0.022
Nausea	0.050	0.047
Neutropenia	0.079	0.108
Pyrexia	0.024	0.034
Renal impairment	0.002	0.010
Thrombocytopenia	0.019	0.022
Vomiting	0.040	0.034

AE=Adverse event; IAT=Investigator-assigned anti-CMV treatment
Source: Takeda 2021.[110]

B.3.4 Measurement and valuation of health effects

An 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).

B.3.4.1 Health-related quality-of-life data from clinical trials

HRQoL was evaluated in SOLSTICE using the EQ-5D-5L and the SF-36v2. In line with the NICE reference case, EQ-5D-5L values were mapped to EQ-5D-3L using the methodology by van Hout et al. 2012.[126]

B.3.4.2 Health-related quality-of-life studies

The HRQoL SLR is a compilation of one original SLR and two sets of updates conducted across multiple timeframes from 2017–2021, with the most recent conducted in September 2021 (Table 46). See Section B.3.1 for a summary of the timeframes covered for the SLR and the updates. Results were compiled for studies identified across all reviews and are summarised in this section and detailed in Appendix H. The utility values of interest for this HRQoL SLR included:

- Healthy (no viraemia)
- Asymptomatic CMV
- Symptomatic CMV
- Acute graft rejection
- Graft loss
- Acute graft vs. host disease (GvHD)
- Chronic GvHD
- Opportunistic infections
- Dialysis
- Repeat transplantation

Table 46: Summary of the SLRs conducted for health-related utility review

Year of search	2017	2020	2021
Version	Original SLR	Update 1	Update 2
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

SLR: Systematic literature review

AEs were excluded from the scope of this SLR to ensure the number of included studies was manageable. Instead, a targeted UK search was conducted (see Section B.3.4.3) to obtain utility estimates relating to AEs.

B.3.4.2.1 Summary of included studies

Across the three HRQoL SLRs with searches last updated on 21st September 2021, a total of 13 studies and 4 HTAs reporting health-related utility values were identified. All the included studies were cost-utility analyses, and reported utility values. Of these studies, two were conducted in the UK,[127,128] six were conducted in US,[34,129-133] one each was conducted in Spain,[134] Italy,[135] Australia,[136] Hong Kong,[137] and country was not reported for one study.[138] Two HTAs each were retrieved from Canadian Agency for Drugs and Technologies in Health (CADTH)[139,140] and NICE,[49,141] respectively.

No studies were directly relevant for the decision problem, since they did not provide health-related utility values for patients with refractory or resistant CMV who have cleared CMV or are receiving pre-emptive therapy.

Five studies and two HTAs identified included letermovir as prophylaxis in allogeneic HSCT recipients.[137] Another five studies reported utilities for patients receiving valganciclovir as prophylaxis following renal transplant,[34,129-131,136] and one study reported utilities for pre-emptive therapy using ganciclovir following orthoptic liver transplant.[138]

In addition, a cost-effectiveness study reported CMV utilities for patients at risk of developing CMV infection after receiving transfused plasma, that is neither following SOT or HSCT.[134] Three studies did not include patients with CMV but provided utility values for graft loss.[128,140,141] One study investigated utility values for tacrolimus and ciclosporin treatment in liver transplant recipients.[128] Two HTA reports provided information on end stage renal disease in patients with autosomal dominant polycystic disease[140] and everolimus with tacrolimus in liver transplant recipients.[141]

A summary of key findings of relevance to the decision problem is provided below, with additional supplementary detail provided in Appendix H.4.

B.3.4.2.1.1 Transplant and post-transplant utility values

Four publications included utility values for renal transplant recipients[34,130,131,136], two publications included utility values for liver transplant recipients[128,134], while three publications and two HTAs included utility values for allogeneic HSCT recipients.[49,133,135,137,139]

Kidney transplant utility values (on patients with any condition) in the studies were derived from Laupacis et al. (1996), a Canadian study including 168 patients that collected utility values using time-trade off (TTO) before and up to 2-years post renal transplant[142]. Three studies reported that the patients with functioning kidney transplant had a utility value of 0.73.[34,130,131] Tilden et al. reported that patients with functioning graft had a utility value of 0.70.[136]

Babigumira et al. (2018) 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),[134] derived from a TTO study including patients with chronic hepatitis C virus.[143] Muduma et al. (2016) reported the utilities for two health states, derived from a UK-specific study in which an EQ-5D tariff value was elicited from 542 liver transplant recipients.[144] 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.[128]

A cost-utility analysis (CUA) was submitted to CADTH comparing letermovir as prophylaxis of CMV infection, alongside usual care, in adult CMV-seropositive HSCT recipients compared with usual care alone.[139] Treatment-specific utility values in the submission were taken from a CUA (submitted to CADTH) 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).[139] The post-allogeneic HSCT value after the first year was 0.76,[145] and the post-trial utility value in the CADTH Centre for Reviews and Dissemination (CRD) re-analysis was 0.768 (limits for one-way analysis 0.703–0.834)[139] which was derived from Marty et al (2017).[146]

B.3.4.2.1.2 Dialysis utilities

Five studies and one HTA reported utility values for dialysis from the published literature.[34,129-131,136,147] The utility values used by five studies[34,129-131,136] were taken from the TTO studies by Laupacis et al. (1996), Narayan et al. (2007) and Howard et al. (2009),[142,148,149] and ranged from 0.53[34,131] to 0.57.[130,136] The HTA (submitted to CADTH) assessed tolvaptan for autosomal dominant polycystic kidney disease,[147] and used a utility value for end-stage renal disease on dialysis of 0.65 (base-case 0.57), taken from a HRQoL and cost-utility study on haemodialysis using the EQ-5D.[150]

B.3.4.2.1.3 Organ rejection utility values

In the model submitted to NICE comparing letermovir to placebo for the prevention of CMV disease after a stem cell transplant (TA591),[49] a disutility for GvHD of 0.09 was included, based on Pidela et al. (2011) and Brazier and Ara (2011).[151,152] Pidala was a United States (US) observational study that reported SF-36 values in 254 HSCT recipients with chronic GvHD.[151] However, the methodology used to derive the disutility included in the submission was not described.[49] The model submitted to NICE also included a disutility for relapse after stem cell transplant of 0.0114, which was calculated using the difference between the utility reported in Leunis et al.[153] and general population mortality, sourced from Ara et al.[152]

The publication by Blumberg et al. included other utility values listed in the paper by Laupacis et al. (1996)[142] 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.[129] Das et al. (2000) presented utility values (instrument not specified) 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.[138]

A 2015 submission to NICE for everolimus for preventing organ rejection in liver transplantation (TA348) presented 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).[141] The values were found through an SLR which identified seven studies, five of which were studies measuring EQ-5D in a UK population. The HTA submission reported 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.(2004) and Neri et al. (2012) respectively, both UK studies using EQ-5D.[144,154] Utility scores for the health states in the hepatic rejection model and the renal sub-model were based on Ratcliffe et al.(2004) and Neri et al. (2012) respectively, both UK studies using EQ-5D.[144,154]

B.3.4.3 Adverse reactions

Disutility values associated with AEs were excluded from the HRQoL SLR. Mean disutility values for treatment-emergent serious adverse events with an incidence of ≥10% and additional clinically important AEs occurring in patients treated with either IAT or maribavir were estimated from published literature on UK-based disutilities (Table 47). The primary source of information for the disutility values was the Catalogue of EQ-5D Scores for the UK (Sullivan et al. 2011),[155] with other sources for UK disutility values used if there was no suitable condition in Sullivan et al. 2011. If the exact disutility value of the AE was not available, the disutility value of the disorder most closely matching the AE was used. 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 using the following formula: $\frac{Duration\ of\ AE}{365.25}$.

Table 47: Disutility of treatment related adverse events

AE	Mean AE disutility (SE)	Source	Description in source
Acute kidney injury	-0.101 (0.009)	Sullivan et al. 2007[155]	ICD-9 593 Oth Renal & Ureteral Disorders
Anaemia	-0.250[a] (0.025)[b]	Ossa et al. 2007[156]	-
Diarrhoea	-0.073 (0.017)	Sullivan et al. 2007[155]	154 Noninfectious Gastroenteritis
Dysgeusia	0.000 (0.000)	Assumed no care required and therefore zero disutility	-
Fatigue	-0.041[c] (0.004)[b]	Nafees et al. 2017[157]	-
Febrile neutropenia	-0.090 (0.016)	Nafees et al. 2008[158]	-
Headache	-0.027 (0.007)	Sullivan et al. 2007[155]	084 Headaches, Including Migraine
Leukopenia	-0.090[d] (0.015)	Bullement et al. 2019[159]	-
Nausea	-0.025[c] (0.003)	Nafees et al. 2017[157]	-
Neutropenia	-0.090 (0.015)	Nafees et al. 2008[158]	-
Pyrexia	-0.110[e] (0.011)	Beusterien et al. 2010[160]	-
Renal impairment	-0.101 (0.012)	Sullivan et al. 2007[155]	ICD-9 593 Oth Renal & Ureteral Disorders
Thrombocytopenia	-0.108[f] (0.024)	Tolley et al. 2012[161]	-
Vomiting	-0.025[c] (0.003)	Nafees et al. 2017[157]	-

AE=Adverse event; CI=Confidence interval; ICD=International Statistical Classification of Diseases and Related Health Problems; PFS=Progression-free survival; SE=Standard error; TTO=Time trade-off

[a] Difference between no anaemia and moderate anaemia

[b] SE is assumed to be 10% of the mean value

[c] TTO between remaining in health state for 10 years w/o improvement and giving up x number of years for full health. Adjustment from 10 year to 1 year disutility value

[d] Lower 95% CI: −0.062; Upper 95% CI: − 0.122

[e] Based on no change in lymphocytic leukaemia with pyrexia

[f] PFS response with thrombocytopenia - TTO values; PFS responder mean: 0.671

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

B.3.4.4.1 Health state quality of life

The economic model includes health-state utility values for patients with csCMV and n-csCMV who are refractory or resistant to CMV treatment post SOT or HSCT.

The HRQoL SLR did not identify utility values for csCMV or n-csCMV; the utility values identified related either to earlier CMV stage (e.g. 1L pre-emptive treatment) or SOT/HSCT recipients without CMV (e.g. prophylaxis). Therefore, health state utility values from SOLSTICE were applied in the model base-case. Due to the lack of HRQoL data for patients with refractory or resistant CMV, Takeda also carried out a vignette study in to derive additional appropriate health-related utility data, to further support the utility estimates from SOLSTICE and reduce any uncertainty surrounding utility estimates. Utility values sourced from the vignette study are not included within

the base-case; however, they are included within a scenario analysis (Section B.3.8,Table 67).[63]

The vignette study provides alternative utility values to SOLSTICE, which followed patients for 20 weeks, and therefore may not be sufficiently long to adequately capture HRQoL improvements in those with severe disease. In addition, 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 then enter into the rescue arm of SOLSTICE.[107] Crossover potentially introduces bias to utility estimates, as the most severe patients, or patients who experience TRAEs, may be more likely to cross over to the rescue arm and be excluded from the utility analysis; maribavir demonstrated a lower incidence of TEAEs leading to discontinuations compared with IAT (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%).[109]

B.3.4.4.1.1 Week 0 to 52

Outputs from the mixed modelling conducted as part of the IPD analysis indicated that transplant type and response status had a significant effect on utilities and that treatment arm did not have a significant impact.[110] For this reason, in the base case analysis, transplant and health-state specific utility values at week 8 were selected (Table 48).

Table 48: Summary of transplant and health state specific utility values from week 0 to 52

State	Utility value: Mean (SE)	
	SOT	HSCT
csCMV	[redacted]	[redacted]
n-csCMV	[redacted]	[redacted]

csCMV=Clinically significant cytomegalovirus; n-csCMV=Non-clinically significant cytomegalovirus; HSCT=Haematopoietic stem cell transplant; SE=Standard error; SOT=Solid organ transplant
Source: Takeda 2021.[110]

B.3.4.4.1.2 Week 52 onwards

SOLSTICE collected utility values up to 20 weeks. To estimate utility values for SOT and HSCT patients from 52 week onwards, a two-step approach was applied. First, the difference between the mean UK general population utility score at age 53 (starting age of model cohort) [162] and the week 20 SOT and HSCT utilities from the SOLSTICE IPD analysis[110] (Table 49) was calculated. Secondly, this disutility value was applied to the mean UK population utility values in every model cycle. The approach is in line with the ERG's suggested, and the NICE committee's accepted, approach in TA591, where the long-term disutility associated with HSCT 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.[49]

Table 49: Transplant specific utility values from week 52

State	Utility value: Mean (SE)
SOT	0.81 (0.081)
HSCT	0.71 (0.071)

CMV=Cytomegalovirus; HSCT=Haematopoietic stem cell transplant; SE=Standard error; SOT=Solid organ transplant
Source: Szende A, et al. 2014; Takeda 2021.[110,162]

B.3.4.4.1.3 Vignette study

Health state descriptions were developed in conjunction with UK clinicians before valuation by a sample of the UK public (N=[redacted]).[63] Overall, the sample acknowledged the substantial impact of CMV on utility in both SOT and allogeneic HCST patients with CMV infection (Table 50).

Table 50: Vignette study utilities across health states

	Utility value: Mean[a]
Clinically significant - Symptomatic	[redacted]
+ GvHD	[redacted]
+ Graft loss, kidney transplant	[redacted]
+ Graft loss, lung transplant	[redacted]
Clinically significant - Asymptomatic	[redacted]
+ GvHD	[redacted]
+ Graft loss, kidney transplant	[redacted]
+ Graft loss, lung transplant	[redacted]
Non-clinically significant	[redacted]
+ GvHD	[redacted]
+ Graft loss, kidney transplant	[redacted]
+ Graft loss, lung transplant	[redacted]

GvHD=Graft-versus-host disease
[a] Any respondent who was classified as a speeder and assigned the same utility value for each health state, and assigned non-clinically significant CMV a lower utility value than both clinically significant and symptomatic CMV and clinically significant and asymptomatic CMV was excluded from the analysis
Source: Takeda 2021.[63]

B.3.4.4.2 Disease complications

B.3.4.4.2.1 Graft loss

As there was no observed graft loss in SOLSTICE, utility decrements associated with graft loss were estimated from an alternative source. Despite availability of pre- and post-transplant renal and liver transplant utility values from the HRQoL SLR described in Section B.3.4.2, these studies do not reflect the HRQoL impact in a cohort who have had CMV. Therefore, a vignette study was completed to derive QoL scores for CMV patients who have had a graft loss. The utility decrement used in the model to capture the impact of graft loss takes the difference between patients with asymptomatic csCMV and patients with asymptomatic csCMV with kidney graft loss (used for utility

decrement for kidney graft loss) or lung graft loss (used for utility decrement for all graft loss events other than kidney graft loss). (Table 51).

Table 51: Graft loss disutility

Baseline transplant type	Asymptomatic csCMV	Symptomatic csCMV with graft loss	Utility decrement Mean (SE)[a]
Heart transplant	[redacted]	[redacted]	[redacted]
Kidney transplant	[redacted]	[redacted]	[redacted]
Lung transplant	[redacted]	[redacted]	[redacted]
Liver transplant	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

SE=Standard error
[a] SE is assumed to be 10% of the mean value
Source: Takeda 2021.[63]

B.3.4.4.2.2 GvHD

GvHD events are not included in the base case analysis. For the scenario analysis that includes GvHD, the utility decrement applied to each event in the model is 0.09, as identified in the HRQoL SLR (see Section B.3.4.2.1.3).[49]

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Resource identification, measurement and valuation studies

A healthcare resource utilisation (HRU) SLR was conducted to identify published studies reporting HRU for:

i. CMV in SOT or HSCT recipients that is refractory or resistant to pre-emptive treatments
ii. CMV in SOT or HSCT recipients on pre-emptive treatment

The HRU SLR is a compilation of one original SLR and two sets of updates conducted across multiple timeframes from 2017–2021, with the most recent conducted in September 2021. A summary of the timeframes covered for each HRU SLR and update is presented in Table 52. As per the economic evaluation SLR, prophylaxis to prevent CMV disease was excluded from the scope. A summary of key findings is provided below with more study-by-study details provided in Appendix I.

Table 52: Summary of the SLRs conducted for HRU review

Year of search	2017	2020	2021
Version	Original SLR	Update 1	Update 2
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

SLR=Systematic literature review; HRU=Healthcare resource utilisation

B.3.5.1.1 CMV refractory or resistant *to pre-emptive therapy*

Three retrospective observational studies (five publications) were identified for CMV in HSCT recipients that is refractory or resistant to treatments. None of the studies were conducted in the UK; one study was conducted in the US,[163] one study in

Germany[164] and the country was unclear in one study.[165] A summary of key findings is provided in Appendix I.4.1.

B.3.5.1.2 CMV on pre-emptive treatment

In total, 14 studies (16 publications) were identified that reported HRU data for CMV in SOT or HSCT recipients (nine observational studies [eight retrospective and one prospective],[20,21,166-172] three economic evaluations[173-175] and two RCTs).[176,177] Of the 14 studies, 12 reported the economic burden for SOT recipients[20,166-171,173-177], one reported the economic burden for HSCT recipients,[21] and one study reported the economic burden for both SOT and HSCT recipients.[172] Of these 12 studies, four were conducted in the UK.[166,168,169,173] Among the UK studies, one was a modelling study comparing valaciclovir prophylaxis with current practice in renal transplant recipients,[173] one was a case series including renal transplant recipients, and two were retrospective cross-sectional studies in liver transplant recipients.[166,168,169] A summary of key findings is provided in Appendix I.4.2.

Mauskopf et al. (2000) reported the cost of managing CMV with a wait & treat strategy. Disaggregated costs from the cost-effectiveness model were reported without any detail on the costing and resource assumption inputs.[173] Therefore, the results are less relevant for the NICE decision problem. Further detail on this study is provided in Appendix I.4.2.1.

Geddes et al. (2003) analysed the effectiveness and cost of a deferred treatment strategy using weekly CMV polymerase chain reaction (PCR) surveillance in high-risk renal transplant recipients from January 1998 to December 2000 in a UK renal unit. The cost of weekly PCR surveillance in deferred and pre-emptive strategies was estimated, and compared with the cost of 3 months oral ganciclovir prophylaxis. All patients received 14 days of IV ganciclovir 250 mg twice-daily. Some patients received the deferred strategy, where it was assumed that all patients who developed evidence of CMV received, while other patients received treatment when they became CMV PCR positive or developed features of the disease (whichever occurred earlier). In the prophylaxis strategy, all patients received oral ganciclovir 1,500 mg daily for 12 weeks. During the first 3 months post-transplant, 48.8% patients (n=20/41) had CMV. The deferred strategy cost £1,159 per patient (excluding the cost of hospitalisation), compared with £1,381 per patient for pre-emptive strategy and £1,500–£2,213 per patient for prophylaxis strategy.[166]

Singhal et al. (2003) conducted a retrospective cross-sectional study of adult liver transplant recipients in the UK who developed CMV in 1997, and estimated the morbidity and costs associated with disease. Among 116 transplant recipients, 11 patients developed CMV. Treatment consisted of IV ganciclovir in all 11 patients, reduction of immunosuppression in nine patients and IV immunoglobulin in two patients. The median additional LOS was 10 days (range 1–16), with 103 additional hospital days in total (of which 11 were on the intensive care unit [ICU]) compared with patients without CMV disease. In 1997, the total cost associated with these 11 patients was £59,782 (£5,435 per patient [range: £2603–£19,843]).[169]

Shah et al. (2005) reported that, from August 2001 to August 2002, 120 patients underwent liver transplantation in the UK. No cases of symptomatic CMV infection occurred in the donor negative/recipient negative or donor negative/recipient positive patients. Of 49 long-term donor positive survivors, seven patients developed CMV. Costs of managing CMV for the seven patients was £42,860 (£6,123 per patient [range: £1,615–£11,513]) which comprised of drug costs, cost of inpatient care and costs of investigation. The mean additional LOS required by these patients was 14 days (range 1–16) compared to patients without CMV disease.[168]

B.3.5.2 Intervention and comparators' costs and resource use

B.3.5.2.1 Treatment costs

Treatment costs in the model are a combination of acquisition, administration and monitoring costs. A list price of £[redacted] and a patient access scheme (PAS) price of £[redacted] per 8-week treatment cycle for maribavir has been proposed to NHS England. Costs for the individual IAT drugs were sourced from the BNF. In the case of cidofovir, a published UK price was not identified, therefore, the cost of cidofovir in the US was converted into UK currency and used as a proxy. The cost of IAT 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 SOLSTICE. For detail on the approach taken in the model see Section B.3.2.3.

In SOLSTICE, the total exposure time to maribavir and IAT was reported (Table 53).[108] Time on treatment durations are used to adjust the treatment costs per cycle from week 0 to 52 by multiplying by the relevant 4-week acquisition costs (Table 55) divided by 8. An 8-week period was chosen as that is the duration of the study treatment phase, with patients not completing the entire 8-week phase assumed to discontinue from treatment.

Table 53: Time on treatment from SOLSTICE

	Maribavir Mean (SE)[a]	IAT Mean (SE)[a]
Time on treatment, weeks	[redacted]	[redacted]

IAT=Investigator-assigned anti-CMV treatment; SE=Standard error
[a] The SE is assumed to be 10% of the mean value;
Source: Takeda. 2021.[108]

From week 0 to 8, it is assumed that all patients remain on their respective ITT treatment (maribavir or IAT), with costs adjusted by a time-on-treatment parameter to account for treatment discontinuation (Table 53). From week 8 onwards, all patients who have clinically significant CMV are treated with IAT, and therefore, IAT-specific time-on-treatment data are used to adjust relevant costs for patients receiving retreatment.

B.3.5.2.2 Drug acquisition costs

The cost per pack (or solution for infusion) (Table 55) and cost per 4-week cycle for the indicated dose are derived using drug monographs from the British National Formulary (BNF) (Table 54). Although the BNF indicates there is an induction dose

and maintenance dose for all drugs, in practice, clinical expert advice indicated that patients receive a single dosing regimen until CMV has been cleared (i.e. there is no maintenance dose).

Table 54: Drug monographs

Drug	Indication dose[a]	Assumed indicated dose for a 4-week period[b]	IV days per 4-week period
Maribavir	N/A (assumes fixed price for an 8-week dose, irrespective of weight or dose frequency)		N/A (oral drug)
Ganciclovir	Initially 5 mg/kg every 12 hours for 14–21 days, then maintenance 6 mg/kg OD, on 5 days of the week, alternatively maintenance 5 mg/kg OD, maintenance only for patients at risk of relapse; if disease progresses initial induction treatment may be repeated.	5 mg/kg every 12 hours for 28 days	28 days
Valganciclovir	Initially 900 mg BID for 21 days, then maintenance 900 mg OD, induction regimen may be repeated if retinitis progresses.	900 mg BID for 28 days	N/A (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 OD, then increased if tolerated to 90–120 mg/kg OD, 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

N/A=Not applicable; mg=milligrams; kg=kilograms; IV=Intravenous; BID=Twice daily; OD=Once daily
[a] Indicated dose is provided in the BNF.
[b] The assumed doses is from the advisory board which stated that in the UK the induction dose issued to treat CMV until clearance.
Source: NICE (BNF) 2021.[178-181]

Table 55: NHS list price

Drug	Cost per pack	Cost per 4-week cycle
Maribavir	[redacted]	[redacted]
Ganciclovir	£115.00	£963.42
Valganciclovir	£865.17	£1,614.98
Foscarnet	£119.85	£7,530.42
Cidofovir[a]	£562.00	£2,242.01

[a] In the case of cidofovir, a published UK price was not identified, therefore, the cost of cidofovir in the US has been converted into UK currency and used as a proxy
Source: NICE (BNF) 2021; Wolters Kluwer Health Inc. 2021.[178-180,182]

Drug acquisition costs are adjusted for time on treatment, as described below.

B.3.5.2.2.1 Week 0 to 8

The cost of maribavir with a PAS discount for an 8-week treatment cycle is £[redacted]. This cost is incurred by all patients in cycle 0, then adjusted to account for the time on treatment observed in SOLSTICE (costs multiplied by [redacted]% to account for a [redacted]week treatment duration, see Table 53). 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. This cost is multiplied by the time on treatment observed in SOLSTICE in the IAT arm (costs multiplied by [redacted] % to account for a [redacted] -week treatment duration). As the treatment costs are incurred by all patients in cycle 0, no further acquisition costs are incurred by patients in cycle 1 (week 4) or cycle 2 (week 8) of the model.

B.3.5.2.2.2 Week 8 to 52

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 for week 0 to 8 (costs multiplied by [redacted] per cycle [IAT time on treatment is [redacted] weeks]).

B.3.5.2.2.3 Week 52 onwards

The model transitions to Stage 2 from week 52 onwards, where no costs are applied to any patients.

B.3.5.2.3 Monitoring costs

The respective SmPCs were used to estimate the 4-week monitoring frequencies (Table 56 and Table 57) for each anti-CMV agent considered in this economic model. In the case of maribavir, the relevant monitoring frequencies were assumed to be equal to the monitoring requirements of valganciclovir, as this is the only oral IAT drug. The frequencies reported in Table 57 were multiplied by the relevant unit cost for each monitoring type, to derive a 4-week monitoring cost (Table 58). For week 0 to 52, the monitoring costs were adjusted for time on treatment. From week 52 onwards, it was assumed no patients were on treatment, so monitoring costs were not included.

Table 56: Monitoring requirements extracted from SmPC of each product

Drug	SmPC summary
Maribavir	Assumed same as valganciclovir – the only other oral therapy
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. 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. Neutropenia may occur during cidofovir therapy. Neutrophil count should be monitored while receiving cidofovir therapy

SmPC=Summary of product characteristics
Source: Cymevene SmPC 2021; Valcyte SmPC 2018; Foscavir SmPC 2020; Cidofovir SmPC 2020; Aciclovir SmPC 2021.[72-76]

Table 57: Weekly monitoring frequency

Drug	Complete blood count	Renal function (SCr)	Electrolytes	Neutrophils
Maribavir	1	0	0	0
Ganciclovir	3.5	0	0	0
Valganciclovir	1	0	0	0
Foscarnet	0	3.5	3.5	0
Cidofovir[a]	0	3.5	0	3.5

[a] In the case of cidofovir, monitoring frequency is not reported in the SmPC; therefore the US monitoring frequency used in the US has been used as a proxy
SCr=Serum creatinine
Source: Gilead Sciences Inc. 2010; NHS 2021.[183,184]

Table 58: Monitoring costs

Drug	Unit costs, £ (SE)[a]	HRG code
Complete blood count	1.91 (0.191)	DAPS03
Renal function (SCr)	1.22 (0.122)	DAPS04
Electrolytes	1.22 (0.122)	DAPS04
Neutrophils	2.58 (0.258)	DAPS05

HRG=Healthcare resource group; SCr=Serum creatinine; SE=Standard error
[a] SE is assumed to be 10% of the cost
Source: NICE 2021.[185]

B.3.5.2.4 Administration costs

For oral drugs (maribavir and valganciclovir), a one-off administration cost of £210 is included, based on the National schedule of NHS costs (SB11Z – "Deliver Exclusively Oral Chemotherapy").[71] This approach is in line with the ERG's preferred approach in TA591 (letermovir).[49]

For IV drugs (ganciclovir, foscarnet, cidofovir), the cost of a single complex infusion is applied once per day of treatment, regardless of the setting and number of IV doses required. This aligns with the NICE committee's accepted approach in TA591. For example, though patients on ganciclovir require 5 mg/kg twice per day, this is costed as a single complex IV infusion rather than two separate infusions. The cost of infusion,

£404, is derived from the National schedule of NHS costs (SB14Z – "Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance"). The total number of IV days required has been calculated using the drug monograph from the BNF (Table 54). This is a conservative assumption, as patients require more than one infusion per day when treated with ganciclovir and foscarnet; therefore, the cost may be higher than that in the model. This is also in line with the ERG's preferred, and the NICE committee's accepted, approach in TA591 (letermovir).[49]

B.3.5.3 Health-state unit costs and resource use

The HRU SLR did not provide relevant costs for health-state unit cost and resource use in refractory or resistant CMV population.

In the base case, the frequency of hospitalisation is taken from the HRU data observed in the IPD analysis of SOLSTICE (Table 59).[110] The analysis categorised patients into response and no response groups at week 8, and explored HRU between these groups through to the end of the trial at week 20. The analysis found that patients who achieved a response at week 8 had a lower risk of hospitalisation compared with those who had not achieved a response (Table 59). The hospitalisation risks in the response and no response groups were used as proxies for in the n-csCMV and cs-CMV health states, respectively.

Table 59: Healthcare resource use (4-week probability)

Health resource	4-week probability of HRU (SOT): Mean (SE)[a]	4-week probability of HRU (HSCT): Mean (SE)
Hospitalisation (response/csCMV)	0.259 (0.026)	0.241 (0.024)
Hospitalisation (no response/n-csCMV)	0.153 (0.015)	0.217 (0.022)

csCMV=Clinically significant CMV; HRU=Healthcare resource utilization; SOT=Solid organ transplant; HSCT=Haemopoietic stem cell transplant; ns-csCMV=Non-clinically significant CMV; SE=Standard error

[a] The standard error 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

Source: Takeda 2021; Takeda 2021.[108,110]

Healthcare costs for each health state were sourced from the National Schedule of NHS costs – 2019/2020 (shown in Table 60). In SOLSTICE, patients who were in the csCMV health state were required to have viral load tests twice per week (eight times over a four-week cycle) to monitor the progression of disease, with a cost per test of £33.15. This was in line with that used in TA591 (letermovir).[49]

Table 60: Health resource costs

Health resource	Cost, £ (SE)	HRG Code
Hospitalisation (response/csCMV)	7,019.85 (701.99)	Weighted average of WJ02A-WJ02B[a]
Hospitalisation (no response/n-csCMV)	1,969.53 (196.95)	Weighted average of WJ02C-WJ02E[a]

csCMV=Clinically significant CMV; HRG=Healthcare resource group; ns-csCMV=Non-clinically significant CMV; SE=Standard error
[a] SE was assumed to be 10% of the cost
[b] ICD code B259: Cytomegaloviral disease, unspecified leads to HRG code WJ02. Total unit activity and unit cost has been used.
Source: NHS 2021.[71]

B.3.5.4 Adverse reaction unit costs and resource use

The costs of each AE were sourced from the National Schedule of NHS costs – Year 2019–2020, with a weighted average of multiple HRG codes used to calculate the cost of an individual AE when appropriate, as summarised in Table 61. The costs associated with each AE are multiplied by the proportion of each AE outlined in Table 45 (Section B.3.3.4), and applied for each respective event per cycle.

Table 61*: Cost of treatment related adverse events*

AE	Cost, £ (SE)[a]	HRG Code[b]
Acute kidney injury	1,955.06 (195.50)	Weighted average of LA07H-LA07P
Anaemia	1,159.16 (115.92)	Weighted average of SA03G and SA03H
Diarrhoea	795.58 (79.56)	FD01J
Dysgeusia	0	N/A
Fatigue	761.70 (76.17)	WH17C, Used code grouper to find HRG code, Malaise and fatigue ICD code R53 leads to HRG code WH17
Febrile neutropenia	2,883.68 (288.37)	Weighted average of SA35A-SA35B
Headache	643.36 (64.34)	Weighted average of AA31C-AA31E
Leukopenia	1,080.78 (108.08)	Weighted average of SA08G-SA08J
Nausea	838.22 (83.82)	FD10M
Neutropenia	1,425.12 (142.51)	Weighted average of SA35C-SA35E
Pyrexia	795.43 (79.54)	WJ07D
Renal impairment	1,375.85 (137.58)	Weighted average of LA09J-LA09Q
Thrombocytopenia	771.92 (77.19)	Weighted average of SA12G – SA12K
Vomiting	838.22 (83.82)	FD10M

AE=Adverse event; SE=Standard error; HRG=Healthcare resource group; N/A=Not applicable
[a] SE is assumed to be 10% of the cost
[b] All HRG costs were sourced from the total unit cost column. Where a weighted average is stated across a range of HRG codes the total unit activity and total unit cost column has been used to create a weighted average of cost
Source: NHS 2021.[71]

B.3.5.5 Miscellaneous unit costs and resource use

B.3.5.5.1 Disease complications

B.3.5.5.1.1 Graft loss

As the National Schedule of NHS costs does not provide a breakdown of the costs associated with re-transplantation, it is conservatively assumed that the cost of a second transplant due to graft loss is equal to the particular organ transplant cost from

the National Schedule of NHS costs. The costs associated with re-transplantation due to graft loss are summarised in Table 62 and applied for each graft loss event.

Table 62: Retransplant costs

Transplant type	Retransplant Cost, £ (SE)[a]	HRG Code[b]
Heart	65,038.86 (6,503.89)	ED05Z
Kidney transplant	13,967.54 (1,396.75)	Weighted average LA01A–03B
Lung transplant	57,350.32 (5,735.03)	DZ01Z
Liver transplant	21,629.65 (2,162.97)	GA15A
Other	43,619.60 (4,361.96)	GA14Z

SE=Standard error; HRG=Healthcare resource group
[a] SE is assumed to be 10% of the cost
[b] All HRG costs were sourced from the total unit cost column. Where a weighted average is stated across a range of HRG codes the total unit activity and total unit cost column has been used to create a weighted average of cost
Source: NHS 2021.[71]

B.3.5.5.1.2 GvHD

GvHD events are not included in the base case due to limited clinical evidence that CMV has a causal relationship with GvHD (see Section B.1.3.4 Clinical burden). In the scenario analysis where GvHD is included, the cost applied in the model is £11,448. This cost is sourced from a recent NICE technology appraisal for letermovir (TA591), [49] which was accepted by the NICE committee, and is adjusted for inflation.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

The base case model control settings and assumptions are presented below in Table 63.

Table 63: Base-case settings

Setting	Base-case value/assumption	Source in submission
Cost-effectiveness model settings		
Analysis mode	Deterministic	
Time horizon	47 years	B.3.2.2.3
WTP threshold	£20,000	
Perspective	Payer	B.3.2.2.5
Cost of maribavir	[redacted]	B.3.5.2.1
Cohort size	1,000	
Currency	£	
Discount rate (costs and benefits)	3.5%	B.3.2.2.6
Number of PSA simulations	10,000	
Cycle length	4-week from year 0 to 3 Annual cycles from year 3 to lifetime	B.3.2.2.4
Population		
Age	53 years	B.3.3.1
Weight (kg)	74.80	
Sex (male, %)	61	
Average time since transplant (years) – SOT	1.00	Assumption
Average time since transplant (years) – HSCT	1.00	

Setting	Base-case value/assumption	Source in submission
% of SOT patients	60%	B.3.3.1
% of HSCT patients	40%	
Treatment pathway		
Treatment arm	Maribavir then retreatment with IAT	B.3.2.3
Comparator arm	IAT then retreatment with IAT	
IAT treatment distribution (initial treatment and retreatment)		
Ganciclovir	25.4%	B.3.2.3
Valganciclovir	25.9%	
Foscarnet	43.5%	
Cidofovir	5.2%	
Model structure		
Stage 2 Markov (alive/dead model)	52 weeks onwards	B.3.2.2.2
Cost and utility		
Total time on treatment (weeks) [0 to 52] – Maribavir	[redacted] weeks	B.3.5.1
Total time on treatment (weeks) [0 to 52] – IAT	[redacted] weeks	
Quality of life measure	EQ-5D	B.3.4
Retreatment effectiveness (clearance)	Same as initial treatment	B.3.3.2
Retreatment effectiveness (recurrence)	Same as initial treatment	

CMV=Cytomegalovirus; EQ-5D=EuroQol 5 dimensions; HSCT=Haematopoietic stem cell transplant; IAT=Investigator-assigned anti-CMV treatment; kg=Kilogram; N/A=Not applicable; NICE=The National Institute for Heath and Care Excellence; SOT=Solid organ transplant; WTP=Willingness-to-pay; PSA=Probabilistic sensitivity analysis

B.3.6.2 Assumptions

The assumptions included in the economic model are presented in Table 64.

Table 64: Base-case assumptions

Setting	Base-case input selection/assumption	Source in submission	Justification
Treatment efficacy			
Clearance and recurrence	ITT	B.3.3.2.1, B.3.3.2.2	The ITT population preserves the randomisation for this important input parameter Benefit of maribavir over IAT was observed regardless of treatment type Definition of recurrence includes the requirement of treatment which was validated with clinical experts
AEs			
AE incidence rates – maribavir and IAT	Clinically important AEs in addition to TEAEs occurring ≥10% in either treatment arm	B.3.3.4	Inclusion of clinically relevant AEs from SOLSTICE will capture all AEs that may impact HRQoL or costs
AE costs – maribavir and IAT	Costs for each AE use NHS reference costs	B.3.5.4	Model takes a UK payer perspective and thus uses NHS costs
AE disutility – maribavir and IAT	AE disutility was sourced from the literature, with studies assumed to have presented the disutility of chronic conditions over	B.3.4.3	Utility decrements sourced from UK catalogues to align with NICE reference case and UK base-case

Setting	Base-case input selection/assumption	Source in submission	Justification
	one year unless otherwise specified Utility decrement was adjusted for duration of each AE type		When utility decrement was unavailable for an AE type, a proxy disease area was used
Costs			
Cyclical 4-week acquisition costs – maribavir	PAS price	B.3.5.2.2	
Cyclical 4-week acquisition costs – all IAT drugs	BNF[185] Cost of Cidofovir estimated from US sources	B.3.5.2.2	NICE reference case No cost was reported in the BNF for cidofovir
Administration unit costs	National reference costs[186]	B.3.5.2.4	
Monitoring unit costs	National reference costs[186]	B.3.5.2.3	
Monitoring frequency – ganciclovir, valganciclovir, foscarnet	Ganciclovir SmPC[72] Valganciclovir SmPC[73] Foscarnet SmPC[74]	B.3.5.2.3	NICE reference case
Monitoring frequency – cidofovir	Cidofovir SmPC[75]	B.3.5.2.3	Unavailable in medicines.org and therefore apply the manufacturers recommendations
Monitoring frequency – maribavir	Same as valgancivlovir[73]	B.3.5.2.3	Valganciclovir is the only oral IAT treatment, and as maribavir is also administered orally it is assumed to have the same monitoring requirements
HRU – SOT	ITT (frequency per person)	B.3.5.3	Aligns with SOLSTICE
HRU – HSCT	ITT (frequency per person)	B.3.5.3	Aligns with SOLSTICE
HRU unit costs	NHS reference costs[186]	B.3.5.3	NICE reference case
Disease complications			
Graft loss – baseline transplant distribution	Only included in scenario analysis	B.3.3.2.4	Aligns with SOLSTICE, where no graft loss was observed
4-week probability of graft loss	Hakimi et al. 2017[20]	B.3.3.2.4	While SOLSTICE did not observe any graft loss, clinical experts indicated that it is an important consideration, therefore values from the literature were used
Retransplant costs	NHS Reference Costs 19/20. Retransplant costs are assumed to be the same as initial transplant costs[71]	B.3.5.5.1	Cost for retransplant are not available on the NHS cost schedule
Retransplant disutility	Literature	B.3.4.4.2	

Setting	Base-case input selection/assumption	Source in submission	Justification
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	B.3.3.2.4	There was no graft loss in SOLSTICE and therefore values are sourced from the literature Assumes no increase in mortality in the base-case for patients who have retransplant
4-week probability of GvHD event	Literature (scenario analysis)	B.3.3.2.4	Scenario analysis only, as there is limited evidence for the causal relationship that CMV causes GvHD
GvHD costs	NICE TA591[49] (scenario analysis)	B.3.5.5.1	
GvHD disutility	Literature (scenario analysis)	B.3.4.4.2	
Utility			
EQ-5D utility value – maribavir and IAT (week 0–52)	Transplant and health state specific (at week 8)	B.3.4.4.1	Transplant and health state specific were used as the IPD analysis indicated that transplant type and response status have a significant impact on utility, while the treatment arm did not
Background utility week 52 onwards (at week 20 utility values)	The difference between the UK general population utility and week 20 SOT and HSCT utility from SOLSTICE were used	B.3.4.4.1	Aligns with the ERG recommended approach from NICE TA591
Mortality			
Mortality (weeks 0–8) – maribavir and IAT	Transplant specific	B.3.3.2.3	Treatment did not directly impact mortality in SOLSTICE Clinical experts advised the underlying disease is more important
Mortality (weeks 8 to 52) – csCMV, n-csCMV	Health state specific	B.3.3.2.3	Health state specific mortality was incorporated to better reflect outcomes associated with CMV status
General population mortality – HSCT (week 52 onwards)	HMRN[49]	B.3.3.2.3	In line with the ERG's suggested method to estimate long-term mortality for HSCT For SOT patients one-, two-, five-, and ten-year post-transplant survival estimates for first SOT transplants were converted into their corresponding annual conditional survival probabilities[a]
General population mortality – SOT (week 52 onwards)	NHS Organ Donation Annual Activity Report[116]	B.3.3.2.3	

AE=Adverse event; BNF=British National Formulary; CMV=Cytomegalovirus; csCMV=Clinically significant cytomegalovirus; EQ-5D=EuroQol 5 dimensions; ERG=Evidence Review Group; HMRN=Haematological Malignancy Research Network; GvHD=Graft-versus-host disease; HR=Hazard ratio; HRU=Healthcare resource utilization; HSCT=Haematopoietic stem cell transplant; IAT=Investigator-assigned anti-CMV treatment; IPD=Individual patient data; ITT=Intention-to-treat; NHS=National Health Service; NICE=The National Institute for Heath and Care Excellence; PAS=Patient access scheme; SmPC=Summary of product characteristics; SOT=Solid organ transplant; TEAE=Treatment emergent adverse event; UK=United Kingdom; US=United States

[a] For lung DCD donor types, the survival probabilities were available only for one-, two- and three-year post-transplant, so this organ and donor type was only included in mortality calculations for the first three years post-transplant

B.3.6.3 Probabilistic sensitivity analysis distributions

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 Dirichlet, normal or log-normal distribution as appropriate (shown in Table 65). The mean disutility values were multiplied by -1 to ensure that they were positive, and a beta distribution could be used.

Table 65: Parameter PSA distributions

Parameter group	Parameter name	Distribution	Source in submission
Population characteristics, mean (SE)	Age	Not included in PSA	Section B.3.3.1
	Weight (kg)	Normal	Section B.3.3.1
	Sex (male)	Normal	Section B.3.3.1
	Time since transplant (years)	Log-normal	Assumption
Other parameter groups	Alive dead weeks used	Normal	Section B.3.2.2.5
	Rate of discontinuation	Normal	Section B.3.5.2.2
	IAT drug distribution	Dirichlet	Section 3.2.3
	Time on treatment	Log-normal	Section B.3.5.2
Treatment efficacy	CMV clearance	Beta	Section B.3.3.2.1
	CMV recurrence	Beta	Section B.3.3.2.2
Mortality	SOT/HSCT specific mortality (0 to 8 weeks)	Beta	Section B.3.3.2.3
	csCMV/n-csCMV specific mortality (8 to 52 weeks)	Beta	Section B.3.3.2.3
Number of IV days	Ganciclovir, foscarnet and cidofovir	Normal	Section B.3.5.2.2
Costs	Administration costs	Gamma	Section B.3.5.2.4
	Monitoring costs – by drug	Gamma	Section B.3.5.2.3
	Monitoring costs	Gamma	Section B.3.5.2.3
Monitoring frequency	Maribavir, ganciclovir, valganiclovir, foscarnet and cidofovir	Normal	Section B.3.5.2.3
Health resource utilization	HRU utilization	Log-Normal	Section B.3.5.3
Graft loss	Baseline transplant type	Dirichlet	Section B.3.3.1
	Risk of graft loss	Beta	Section B.3.3.2.4
	Transplant costs	Gamma	Section B.3.5.5.1
	Transplant disutility	Beta	Section B.3.4.4.2
	Transplant mortality - relative risk	Log-normal	Section B.3.3.2.4
Utilities	Health state and transplant specific EQ-5D scores	Beta	Section B.3.4.4.1
	Background utility (week 52 onwards)	Beta	Section B.3.4.4.1
AEs	Costs	Gamma	Section B.3.5.4
	Disutility	Beta	Section B.3.4.3
	Duration	Normal	Section B.3.3.4
	Incidence	Beta	Section B.3.3.4
General population mortality	SOT	Beta	Section B.3.3.2.3
	HSCT	Beta	Section B.3.3.2.3

AE=Adverse event; CMV=Cytomegalovirus; csCMV=Clinically significant CMV; EQ-5D=EuroQol 5 dimensions; HRU=Healthcare resource utilization; HSCT=Haematopoietic stem cell transplant; IAT=Investigator-assigned anti-CMV treatment; kg=Kilogram; IV=Intravenous; N/A=Not applicable; NICE=The National Institute for Heath and Care Excellence; n-csCMV=Non-clinically significant CMV; PSA=Probabilistic sensitivity analysis; SE=Standard error; SOT=Solid organ transplant

B.3.7 Base-case results (ITT)

In patients with CMV infection that is refractory or resistant to treatments after HSCT or SOT, treatment with maribavir results in an increase in QALYs (0.131) and increased costs (£2,004) compared with IAT. This results in an incremental cost per QALY gained of £15,337 (Table 66).

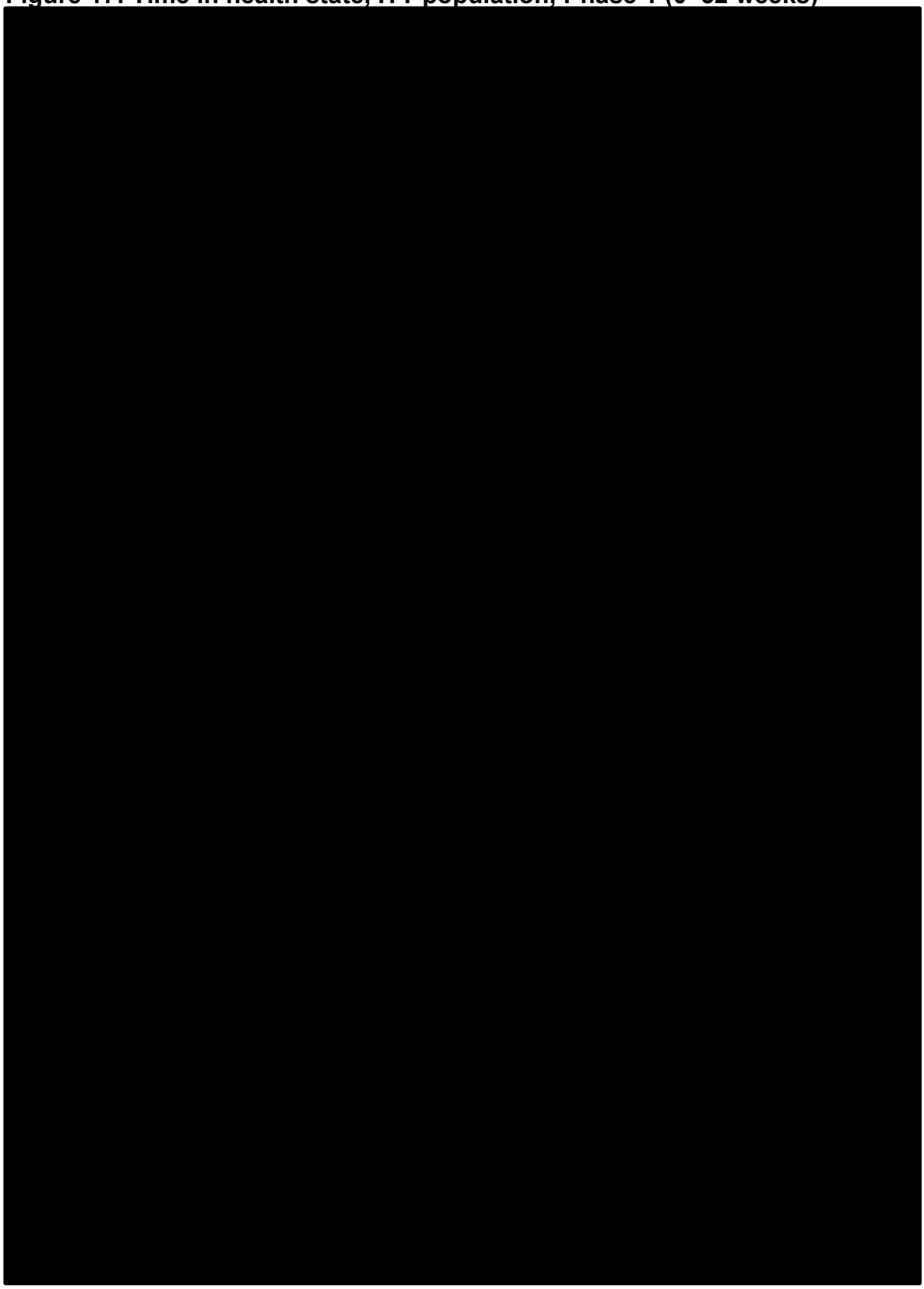
Table 66: Base-case results, ITT population, discounted

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Maribavir	[redacted]	8.39	6.02	2,004	0.160	0.131	15,337
IAT	[redacted]	8.23	5.89				

ICER=Incremental cost-effectiveness ratio; LYG=Life years gained; QALY=Quality-adjusted life year; IAT=Investigator-assigned anti-CMV treatment; ITT=Intention-to-treat

Figure 17 reflects the time spent in each health state (by percentage of the model cohort) over the first 52 weeks of the time horizon for the ITT population. Patients treated with maribavir have improved CMV clearance and reduced recurrence rates compared with patients treated with IAT. Therefore, patients in the IAT arm spend longer in the csCMV health state (0.50 life years in the IAT arm vs. 0.38 life years in maribavir arm; Figure 17).

Figure 17: Time in health state, ITT population, Phase 1 (0–52 weeks)



CMV=Cytomegalovirus; csCMV=Clinically significant CMV; IAT=Investigator-assigned anti-CMV treatment; ITT=Intention-to-treat; ns-csCMV=Non-clinically significant CMV

Figure 18: Lifetime survival – Phase 1 (0–52) and Phase 2 (52 onwards)

IAT=Investigator-assigned anti-CMV treatment

Figure 19: Breakdown of QALYs, ITT discounted

CMV=Cytomegalovirus IAT=Investigator-assigned anti-CMV treatment; ITT=Intention-to-treat; QALY=Quality-adjusted life year

Figure 20 shows the cost breakdown for the discounted base-case results of the ITT population. The key driver of incremental costs is the maribavir acquisition cost, with cost-offsets for reduced treatment administration cost due to the requirement of IV infusion and reduction in hospitalisations.

Figure 20: Cost breakdown, ITT discounted

IAT=Investigator-assigned anti-CMV treatment; ITT=Intention-to-treat; GvHD=Graft-versus-host disease

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was completed to quantify the level of confidence in the output of the base-case analysis, in relation to uncertainty in the model inputs. Model input parameters included in the PSA are specified with mean, SE, and distributions (depending on the type of variable, for example, beta distributions for probabilities). Where possible, the SE values were estimated using trial or published data, however, where this value was not available, the SE value was assumed 10% of the mean.

The mean results for the PSA are presented in Table 67 and the scatterplot is presented in Figure 21. The PSA results are aligned with the deterministic results, with maribavir having greater QALYs and higher costs compared with IAT. This results in an incremental cost per QALY gained of £17,156. The cost-effectiveness acceptability curve (Figure 22) shows the probability that maribavir is cost-effective compared with IAT at a range of WTP thresholds. Maribavir has a 51.83% probability of being cost-effective at a WTP threshold of £20,000 and 61.72% at a WTP threshold of £30,000.

Table 67: PSA Cost effectiveness results – ITT population, discounted

	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER (£/QALY)	Probability cost-effective at £20,000 (%)	Probability cost-effective at £30,000 (%)
Maribavir	[redacted]	6.03	2,176	0.127	17,156	51.83%	61.72%
IAT	[redacted]	5.91				48.17%	38.28%

IAT=Investigator-assigned anti-CMV treatment; ICER=Incremental cost-effectiveness ratio; Incr=Incremental; QALY=Quality-adjusted life year; ITT=Intention-to-treat; PSA=Probabilistic sensitivity analysis

Figure 21: ICER scatterplot

QALY=Quality-adjusted life year; ICER=Incremental cost-effectiveness ratio; WTP=Willingness-to-pay; PSA=Probabilistic sensitivity analysis

Figure 22: Cost-effectiveness acceptability curve

CE=Cost-effectiveness; IAT=Investigator-assigned anti-CMV treatment; WTP=Willingness-to-pay

B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis was conducted by varying key parameters by their SE, 95% CI or +/- 20% of the expected values (base-case) depending on data availability. Certain parameters were varied as a group:

- Transition probabilities
- Mortality
- Drug acquisition costs for all IAT drugs
- Healthcare resource use
- AEs
- Graft loss costs and utility decrements
- Maribavir and IAT utility for all, SOT and HSCT

The top 25 parameters that affected the ICER are shown in the tornado diagram in Figure 23.

Figure 23: Tornado graph

HSCT=Haematopoietic stem cell transplant; IAT=Investigator-assigned anti-CMV treatment; ICER=Incremental cost-effectiveness ratio; IV=Intravenous; kg=Kilogram; SOT=Solid organ transplant

B.3.8.3 Scenario analysis

Scenario analyses were undertaken to investigate the effect of certain model inputs on costs and outcomes. Table 68 summarises the results of the scenario analysis.

Table 68: Scenario analysis results

Scenario; Description		Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY) gained
Base-case		[redacted]	**0.160**	**0.131**	**£15,337**
1	Comparator: Foscarnet only with IAT ToT	[redacted]	0.160	0.131	Dominates
2	Intervention: Retreatment with maribavir in the intervention (maribavir) arm	[redacted]	0.379	0.306	Dominates
3	Costs: No discontinuation after retreatment	[redacted]	0.160	0.131	Dominates
4	Utilities: Transplant and health state utility from week 0–20	[redacted]	0.160	0.128	£15,693
5	Utilities: ITT at week 8	[redacted]	0.160	0.130	£15,400
6	Utilities: ITT at week 0–20	[redacted]	0.160	0.126	£15,844
7	Utilities: Vignette Study and SOLSTICE	[redacted]	0.160	0.143	£13,971
8	Utilities: SF-36 - Transplant and health state specific (at week 8)	[redacted]	0.160	0.124	£16,136
9	Disease complications: Include GvHD	[redacted]	0.160	0.131	£16,314
10	Background mortality only week 8–52	[redacted]	0.008	0.023	£19,774
11	Graft loss - disutility values from literature	[redacted]	0.160	0.131	£15,340
12	Exclude AEs	[redacted]	0.160	0.127	£23,263
13	Exclude duration of AEs	[redacted]	0.160	0.203	£9,890
14	Societal perspective	[redacted]	0.160	0.131	£14,307
15	Retransplant mortality: Off	[redacted]	0.153	0.126	£15,903

AE=Adverse event; GvHD=Graft-versus-host disease; ICER=Incremental cost-effectiveness ratio; ITT=Intention-to-treat; LY=Life year; QALY=Quality-adjusted life year; SF-36=Short form-36; ToT=Time on treatment; IAT=Investigator-assigned anti-CMV treatment

B.3.9 Subgroup analysis (SOT and HSCT)

Each of the ITT discounted results, graphs and figures are also presented for the SOT and HSCT populations in the following sections.

B.3.9.1 SOT

Table 69 provides a summary of the discounted base-case results for SOT patients only, based on the inputs outlined in Section B.3.6.1. Similar to the ITT population results, maribavir results in an increase in QALYs and higher costs compared with IAT. This results in an incremental cost per QALY gained of £9,303.

Table 69: Cost effectiveness results – SOT population, discounted

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Maribavir	[redacted]	9.41	7.05	1,422	0.185	0.153	£9,303
IAT		9.23	6.90				

IAT=Investigator-assigned anti-CMV treatment; ICER=Incremental cost-effectiveness ratio; QALY=Quality-adjusted life year; SOT=Solid organ transplant; LYG=Life-years gained

B.3.9.2 Allogeneic HSCT

Table 70 provides a summary of the discounted base-case results for allogeneic HSCT patients only, based on the inputs outlined in Section B.3.6.1. Similar again to the ITT population results, maribavir has greater QALYs and higher costs compared with IAT. This results in an incremental cost per QALY gained of £29,471.

Table 70: Cost effectiveness results – HSCT population, discounted

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Maribavir	[redacted]	6.85	4.48	2,873	0.123	0.097	29,471
IAT		6.73	4.38				

HSCT=Haematopoietic stem cell transplant; IAT=Investigator-assigned anti-CMV treatment; ICER=Incremental cost-effectiveness ratio; QALY=Quality-adjusted life year; LYG=Life-years gained

B.3.10 Validation

Clinical and health economic experts continually guided the model development from the conceptual stage until the finalisation of the core model.

For the UK adaptation of the Takeda cost-effectiveness model, advice and input was obtained from a UK HTA advisory board of clinicians and health economists, where clinical effectiveness and cost-effectiveness were considered, including the framework for the model-based cost-effectiveness analysis.[14]

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. 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

B.3.11 Interpretation and conclusions of economic evidence

In patients with CMV, maribavir demonstrated a statistically significant and clinically relevant improvement in CMV clearance compared with IAT. The economic model utilised 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. Maribavir is a highly cost-effective treatment option for patients with refractory or resistant CMV post-transplant. In the base-case, for the ITT population (SOT and HSCT combined), the deterministic ICER was £15,337; with higher incremental costs (£2,004), higher incremental QALYs (0.131) and life years (0.160). The ICER in the SOT-only and HSCT-only subgroups were £9,303 and £29,471 respectively; the higher ICER in the HSCT subgroup is

driven by the impact of the underlying disease on mortality, resulting in lower life years and lower overall QALYs.

In the model, due to the impact of clearance and recurrence, patients in the IAT arm spend longer in the csCMV health state (0.50 life years in the IAT arm vs. 0.38 life years in the maribavir arm). As the utility value is lower in the csCMV health state compared with the n-csCMV health state, the impact of treatment on CMV clearance and recurrence are the key drivers for QALYs. In the csCMV health state, as patients are on treatment, the state is associated with higher costs, as well as lower QoL compared with the n-csCMV health state. The key driver of costs in the maribavir arm is the acquisition cost, and in the IAT arm, the key cost driver was the treatment administration cost (due to the requirement of IV infusions).

The economic model does not capture several additional benefits associated with maribavir, potentially demonstrating that the conclusions of the economic analysis are conservative. Firstly, the currently available anti-CMV agents act on one stage within the cell replication pathway: inhibiting DNA polymerase. As a result, resistance to one of the four currently used antivirals confers resistance to the other three reducing efficacy and necessitating a reduction in immunosuppression, thereby putting the graft at risk. Maribavir represents a new anti-CMV class (benzimidazole riboside) that has multi-targeted anti-CMV activity across the CMV lifecycle resulting in maribavir being less susceptible to mutations of the viral DNA polymerase and enabling activity against strains with viral DNA polymerase mutations.[6-9] Due to this, maribavir results in sustained efficacy to allow for patients to build their natural immunity. In addition to this, maribavir can be administered with or without food, resulting in a convenient administration for patients that may improve treatment compliance. In comparison, the only other oral anti-CMV agent, valganciclovir, is recommended to be taken with food, whenever possible.

The eligible patients for maribavir are SOT or allogeneic HSCT recipients. In addition to the substantial clinical burden that these transplants place on patients, the transplants are a large cost for the healthcare system. Given the chronic shortage of organs, tissues, and cells for transplants, patients may be subjected to prolonged waiting times, which may result in death or removal from the transplant list due to deteriorating health.[12,65] Considering the long waiting times, the possibility of transplant failure due to CMV infection thereby results in further complications for patients, including deteriorations in HRQoL (e.g., increased anxiety).[69] Additionally, considering the large investment required from healthcare systems across the patient's transplant journey, there is a need to ensure transplant loss due to CMV does not occur. The availability of maribavir may help ensure that the investments made by patients and healthcare systems in ensuring successful transplants do not go to waste as a result of CMV infection.

CMV infection has a significant impact on the long-term HRQoL. For recipients of allogeneic HSCT who received treatment for CMV infection, fatigue and social functioning are affected.[62] For SOT recipients, patients experience long-term fatigue, lethargy, breathlessness, and an inability to think clearly/process information post-CMV diagnosis.[64] Post-transplant CMV infection has a significant impact on work and

lifestyle, with the need for increased hospital visits/blood tests. Due to chronic health issues and frequent visits and follow-ups to the clinic, patients may be unable to maintain full-time employment. This burden makes it difficult to resume work and maintain lifestyle activities that patients had prior to the transplant.[64,69]

In addition, the longer term impact of CMV viraemia on graft loss, as observed in the retrospective study in renal transplant recipients,[36] is not captured in the economic model, as long-term benefits of CMV in the first year were excluded. This is a conservative assumption, as patients treated with maribavir are more likely to achieve CMV clearance compared with IAT.

A potential limitation of the model is whether the model underestimates time on treatment for the subsequent IAT drugs for patients who do not achieve clearance or have a clinically significant recurrence. Specifically, there could be a case that patients who require retreatment have improved adherence, as clinicians encourage patients to comply with the treatment course to achieve satisfactory clinical outcomes. A scenario analysis, where patients in a retreatment setting have improved adherence (i.e. continue treatment for 8 out of 8 weeks) resulted in maribavir dominating IAT. Other scenario analyses also present instances where maribavir dominates IAT; including in clinical settings where foscarnet is prescribed frequently and retreatment in the maribavir arm is with maribavir. Although certain scenarios (excluding AEs, including background mortality only from week 8–52) do increase the ICER; cumulatively, the evidence illustrates that the base-case adopted in the economic model is potentially a conservative one, with plausible alternative scenarios that could considerably drive the final cost-effectiveness outcome strongly in favour of maribavir (i.e., dominating IAT).

In summary, maribavir represents a highly cost-effective and well tolerated treatment option compared to the current standard of care, for a small patient population with a high unmet need; for patients who are resistant or refractory to treatments for a potentially life-threating CMV infection following an already clinically and economically burdensome SOT or HSCT procedure.

B.4 References

1. Gupta M, Shorman M. *Cytomegalovirus.* Treasure Island, FL: StatPearls Publishing; 2021.
2. Humar A, Snydman D. Cytomegalovirus in solid organ transplant recipients. *American Journal of Transplantation.* 2009;9(s4).
3. Fisher CE, Knudsen JL, Lease ED, et al. Risk factors and outcomes of ganciclovir-resistant cytomegalovirus infection in solid organ transplant recipients. *Clinical Infectious Diseases.* 2017;65(1):57-63.
4. Piret J, Boivin G. Clinical development of letermovir and maribavir: Overview of human cytomegalovirus drug resistance. *Antiviral Res.* 2019;163:91-105.
5. Papanicolaou GA, Silveira FP, Langston AA, 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. *Clinical Infectious Diseases.* 2019;68(8):1255-1264.
6. Marty FM, Alexander B, Brissot E, et al. A Phase 3 Randomized Study of Maribavir (MBV) Versus Investigator-Assigned Antiviral Therapy (IAT) for the Treatment (Tx) of Refractory/Resistant (R/R) Cytomegalovirus (CMV) Infection in Hematopoietic Cell Transplant (HCT) or Solid Organ Transplant (SOT) Recipients. Paper presented at: 2021 TCT| Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR2021.
7. Hamirally S, Kamil JP, Ndassa-Colday YM, et al. Viral mimicry of Cdc2/cyclin-dependent kinase 1 mediates disruption of nuclear lamina during human cytomegalovirus nuclear egress. *PLoS pathogens.* 2009;5(1):e1000275.
8. Krosky PM, Baek M-C, Coen DM. The human cytomegalovirus UL97 protein kinase, an antiviral drug target, is required at the stage of nuclear egress. *Journal of virology.* 2003;77(2):905-914.
9. Prichard MN. Function of human cytomegalovirus UL97 kinase in viral infection and its inhibition by maribavir. *Reviews in medical virology.* 2009;19(4):215-229.
10. Maertens J, Cordonnier C, Jaksch P, et al. Maribavir for Preemptive Treatment of Cytomegalovirus Reactivation. *N Engl J Med.* 2019;381(12):1136-1147.
11. Takeda. New England Journal of Medicine Publishes Results of a Phase 2 Trial Evaluating Takeda's TAK-620 (Maribavir) as a Potential Treatment of Cytomegalovirus (CMV) Infection. 2019; https://www.takeda.com/newsroom/newsreleases/2019/new-england-journal-of-medicine-publishes-results-of-a-phase-2-trial-evaluating-takedas-tak-620-maribavir-as-a-potential-treatment-of-cytomegalovirus-cmv-infection2/. Accessed December, 2021.
12. NHS Blood and Transplant. Organ Donation and Transplantation: Activity Report 2019/20. 2020; https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/19220/activity-report-2019-2020.pdf. Accessed December, 2021.
13. BSBMTCT Registry. BSBMTCT Registry: 2019 Annual Activity. *British Society of Blood and Marrow Transplantation and Cellular Therapies* 2019; https://bsbmtct.org/activity/2019/ Accessed December, 2021.
14. Takeda. Data on file. Market access (HTA) ad board report. 2021.

15. Dropulic LK. The impact of cytomegalovirus infection on solid organ transplantation. *ADVANCED STUDIES IN MEDICINE.* 2006;6(7):319.
16. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. *Clinical infectious diseases.* 2002;34(8):1094-1097.
17. Cho SY, Lee DG, Kim HJ. Cytomegalovirus Infections after Hematopoietic Stem Cell Transplantation: Current Status and Future Immunotherapy. *Int J Mol Sci.* 2019;20(11).
18. Teira P, Battiwalla M, Ramanathan M, et al. Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: a CIBMTR analysis. *Blood.* 2016;127(20):2427-2438.
19. Liu J, Kong J, Chang Y, 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. *Clinical Microbiology and Infection.* 2015;21(12):1121. e1129-1121. e1115.
20. Hakimi Z, Aballéa S, Ferchichi S, et al. Burden of cytomegalovirus disease in solid organ transplant recipients: a national matched cohort study in an inpatient setting. *Transplant Infectious Disease.* 2017;19(5):e12732.
21. Hakimi Z, Ferchichi S, Aballea S, 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;66(4):95-101.
22. British Transplantation Society. The prevention and management of CMV disease after solid organ transplantation. 2015.
23. Emery V, Zuckerman M, Jackson G, et al. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. *British journal of haematology.* 2013;162(1):25-39.
24. Crough T, Khanna R. Immunobiology of human cytomegalovirus: from bench to bedside. *Clinical microbiology reviews.* 2009;22(1):76-98.
25. De la Hoz RE, Stephens G, Sherlock C. Diagnosis and treatment approaches of CMV infections in adult patients. *Journal of clinical virology.* 2002;25:1-12.
26. Razonable RR, Emery VC. Management of CMV infection and disease in transplant patients. 27-29 February 2004. *Herpes: the journal of the IHMF.* 2004;11(3):77-86.
27. Danziger-Isakov LA ST. *Pediatric Transplant and Oncology Infectious Diseases.* 2021.
28. Ramanan P, Razonable RR. Cytomegalovirus infections in solid organ transplantation: a review. *Infect Chemother.* 2013;45(3):260-271.
29. Beltran PMJ, Cristea IM. The life cycle and pathogenesis of human cytomegalovirus infection: lessons from proteomics. *Expert review of proteomics.* 2014;11(6):697.
30. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clinical Infectious Diseases.* 2016:ciw668.
31. Lumbreras C, Manuel O, Len O, ten Berge IJ, Sgarabotto D, Hirsch HH. Cytomegalovirus infection in solid organ transplant recipients. *Clin Microbiol Infect.* 2014;20 Suppl 7:19-26.

32. Styczynski J. Who is the patient at risk of CMV recurrence: a review of the current scientific evidence with a focus on hematopoietic cell transplantation. *Infectious diseases and therapy.* 2018;7(1):1-16.
33. Dykewicz CA, Centers for Disease C, Prevention, Infectious Diseases Society of A, American Society of B, Marrow T. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. *Clin Infect Dis.* 2001;33(2):139-144.
34. 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;20(11):2449-2458.
35. Bergamasco A GC, Arredondo-Bisono T, Sen R, Hirji I, Moride Y. Epidemiology of resistant and refractory cytomegalovirus infection following solid organ or haematopoietic stem cell transplant: a systematic review. *Virtual Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT).* 2021.
36. Dobrer S ea. Precision Medicine in Transplantation: Magnitude, Duration, and Impact of CMV Viremia on Graft and Mortality Outcomes. European Society for Organ Transplantation (ESOT) 20th Congress 2021 2021; Milan, IT.
37. Khurana MP, Lodding IP, Mocroft A, et al. Risk factors for failure of primary (Val) ganciclovir prophylaxis against cytomegalovirus infection and disease in solid organ transplant recipients. Paper presented at: Open forum infectious diseases2019.
38. Molina-Ortega A, Martín-Gandul C, Mena-Romo J, 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;25(6):753-758.
39. Navarro D, Ferreira A, Caeiro F, et al. PREVENTIVE CMV STRATEGIES: A CENTER's EXPERIENCE: P681. *Transplant International.* 2015;28.
40. Reekie J, Khurana MP, Lodding IP, et al. 1079. The Risk of Cytomegalovirus (CMV) Infection and Recurrence Among Solid Organ Transplant Recipients. Paper presented at: Open Forum Infectious Diseases2020.
41. Serrano M, Guillen-Grima F, Martin-Moreno P, et al. 4CPS-097 Extended versus standard cytomegalovirus prophylaxis in solid organ transplantation. British Medical Journal Publishing Group; 2018.
42. Serrano-Alonso M, Guillen-Grima F, Martin-Moreno P, et al. Reduction in mortality associated with secondary cytomegalovirus prophylaxis after solid organ transplantation. *Transplant Infectious Disease.* 2018;20(3):e12873.
43. Gracia-Ahufinger I, Ferrando-Martinez S, Montejo M, et al. Pre-transplant thymic function is associated with the risk of cytomegalovirus disease after solid organ transplantation. *Clin Microbiol Infect.* 2015;21(5):511 e511-517.
44. Navarro D, Fernández-Ruiz M, Aguado JM, Sandonís V, Pérez-Romero P. Going beyond serology for stratifying the risk of CMV infection in transplant recipients. *Reviews in Medical Virology.* 2019;29(1):e2017.
45. Mengelle C, Rostaing L, Weclawiak H, Rossignol C, Kamar N, Izopet J. Prophylaxis versus pre-emptive treatment for prevention of cytomegalovirus infection in CMV-seropositive orthotopic liver-transplant recipients. *J Med Virol.* 2015;87(5):836-844.

46. Lollinga WT, Rurenga-Gard L, van Doesum W, et al. High human cytomegalovirus DNAemia early post-transplantation associates with irreversible and progressive loss of renal function - a retrospective study. *Transpl Int.* 2017;30(8):817-826.
47. Servais S, Dumontier N, Biard L, 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 and Infection.* 2016;22(3):289. e281-289. e287.
48. Sola Aparicio E, Cardenoso L, Lopez Pereira P, et al. Impact of cmv replication in overall survival in allogeneic HSCT recipients. Paper presented at: BONE MARROW TRANSPLANTATION2019.
49. NICE. Letermovir for preventing cytomegalovirus disease after a stem cell transplant: Appraisal consultation committee papers (TA591). 2019; https://www.nice.org.uk/guidance/ta591/chapter/1-Recommendations. Accessed December, 2021.
50. Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2020. 2021; https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2020. Accessed December, 2021.
51. Aziz F, Jorgenson MR, Parajuli S, et al. Polyomavirus and cytomegalovirus infections are risk factors for grafts loss in simultaneous pancreas and kidney transplant. *Transplant Infectious Disease.* 2020;22(3):e13272.
52. López-Oliva MO, Flores J, Madero R, et al. Cytomegalovirus infection after kidney transplantation and long-term graft loss. *Nefrología (English Edition).* 2017;37(5):515-525.
53. Singh R, Peters-Sengers H, Remmerswaal EB, et al. Clinical consequences of primary CMV infection after renal transplantation: a case–control study. *Transplant International.* 2020;33(9):1116-1127.
54. Ljungman P, Perez-Bercoff L, Jonsson J, et al. Risk factors for the development of cytomegalovirus disease after allogeneic stem cell transplantation. *haematologica.* 2006;91(1):78-83.
55. Ghimire S, Weber D, Mavin E, Wang XN, Dickinson AM, Holler E. Pathophysiology of GvHD and Other HSCT-Related Major Complications. *Front Immunol.* 2017;8:79.
56. Cantoni N, Hirsch HH, Khanna N, et al. Evidence for a bidirectional relationship between cytomegalovirus replication and acute graft-versus-host disease. *Biol Blood Marrow Transplant.* 2010;16(9):1309-1314.
57. ISRCTN registry. Cytomegalovirus (CMV) in allogeneic hematopoietic stem cell transplant patients. 2021; https://www.isrctn.com/ISRCTN78128786. Accessed December, 2021.
58. ISRCTN registry. Cytomegalovirus (CMV) in solid organ transplant patients. 2021; https://www.isrctn.com/ISRCTN78128786. Accessed December, 2021.
59. Takeda. Data on file. OTUS SOT Interim analysis study results. 2021.
60. Takeda. Data on file. OTUS HSCT Interim analysis study results. 2021.
61. Hakimi N, Dorey J, Hakimi Z, Aballea S, Odeyemi I, Toumi M. PIN77 Elicitation of Health-Related Quality of Life Concepts Associated With Cytomegalovirus in Transplant Recipients. *Value in Health.* 2012;15(7):A399.

62. Yong M SR, Yeon ZH, et al. The Long Term Impact of Cytomegalovirus (CMV) Viremia on Quality of Life in Allogeneic Haematopoietic Cell Transplant Recipients (HCT). *Biology of Blood and Marrow Transplantation.* 2020;26(3):S359-S360.
63. Takeda. Data on file, Vignette results 2021
64. Takeda. Data on file. Patient group ad board report. 2021.
65. NHS Blood and Transplant. Statistics about organ donation. 2021; https://www.organdonation.nhs.uk/helping-you-to-decide/about-organ-donation/statistics-about-organ-donation/. Accessed 16 December, 2021.
66. Ravanan R, Callaghan CJ, Mumford L, et al. SARS-CoV-2 infection and early mortality of waitlisted and solid organ transplant recipients in England: A national cohort study. *Am J Transplant.* 2020;20(11):3008-3018.
67. NHS Blood and Transplant. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 2017; https://www.england.nhs.uk/wp-content/uploads/2017/02/clin-comms-policy-16068p.pdf. Accessed December, 2021.
68. NHS Blood and Transplant. How long is the wait for a kidney? 2021; nhsbt.nhs.uk/organ-transplantation/kidney/receiving-a-kidney/how-long-is-the-wait-for-a-kidney/. Accessed December, 2021.
69. Takeda. Data on file. CMV Patient Journey (EXA/GB/MARI/0014). 2021.
70. Hakimi Z, Hakimi-Hawken N, Dorey J, Aballea S, Odeyemi I, Toumi M. Impact of Cytomegalovirus Infection and Treatment on Patient Reported Outcomes In Haematopoietic Cell Transplant Recipients. *Value in Health.* 2017;20(9):A793.
71. NHS. 2019/20 National Cost Collection data. 2021; https://www.england.nhs.uk/wp-content/uploads/2021/06/2_National_schedule_of_NHS_costs_FY19_20_V2.xlsx. Accessed December, 2021.
72. Cymevene SmPC. Cymevene 500mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc). 2021; https://www.medicines.org.uk/emc/product/10242/smpc Accessed 16 December, 2021.
73. Valcyte SmPC. Valcyte 450 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC). 2018; https://www.medicines.org.uk/emc/product/1641/smpc. Accessed 16 December, 2021.
74. Foscavir SmPC. Foscavir 24 mg/ml Solution for Infusion - Summary of Product Characteristics (SmPC). 2020; https://www.medicines.org.uk/emc/product/874. Accessed 16 December, 2021.
75. Cidofovir SmPC. Cidofovir 75 mg/ml Concentrate for Solution for Infusion - Summary of Product Characteristics (SmPC). 2020; https://www.medicines.org.uk/emc/product/11151. Accessed 16 December, 2021.
76. Aciclovir SmPC. Aciclovir 25 mg/ml Concentrate for Solution for Infusion - Summary of Product Characteristics (SmPC). 2021; https://www.medicines.org.uk/emc/product/377/smpc#CLINICAL_PRECAUTIONS. Accessed 16 December, 2021.

77. De Miguel C, Royuela A, Azorin MFP, et al. P0706 Cytomegalovirus (CMV) impact on clinical outcomes and resource use after allogeneic hematopoietic cell transplantation: the influence of recurrent episodes of CMV infection. Paper presented at: European Society of Clinical Microbiology and Infectious Diseases; 21-24 April 2018, 2018; Madrid, Spain.
78. Robin C, Hémery F, Dindorf 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;17(1):1-8.
79. Prevymis SmPC. Prevymis 240 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC). 2021; https://www.medicines.org.uk/emc/product/11943/smpc#gref. Accessed 16 December, 2021.
80. Takeda. Data on file. Medical ad board report. 2021.
81. Cymevene SmPC. Cymevene 500mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc). 2020; https://www.medicines.org.uk/emc/product/10242/smpc Accessed 29 January 2021.
82. Ljungman P, Styczynski J, Einsele H. *Viral Infections. In: The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies [Internet].* Vol 7th edition. Cham (CH): Springer; 2019.
83. Musick W ea. Multi-center Observational Characterization of Cytomegalovirus Antiviral Use in Allogenic Hematopoietic Stem-cell Transplantation (HCT) Recipients. *Open Forum Infectious Diseases.* 2017;4(S1):S715.
84. Zavras P, Su Y, 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. *Biology of Blood and Marrow Transplantation.* 2020;26(8):1482-1491.
85. Galetaki D ea. Retrospective Cohort Analysis to Determine the Incidence of CMV Infection and Disease in Allogeneic Hematopoietic Cell Transplant Recipients at an Academic Children's Hospital. *Open Forum Infectious Disease.* 2019;V(S2):639-640.
86. Yang Y, Yu B, Chen Y. Blood disorders typically associated with renal transplantation. *Frontiers in cell and developmental biology.* 2015;3:18.
87. Lurain NS, Chou S. Antiviral drug resistance of human cytomegalovirus. *Clinical microbiology reviews.* 2010;23(4):689-712.
88. El Chaer F, Shah DP, Chemaly RF. How I treat resistant cytomegalovirus infection in hematopoietic cell transplantation recipients. *Blood.* 2016;128(23):2624-2636.
89. Vejrazkova E, Pliskova L, Hubacek P, et al. Clinical and genotypic CMV drug resistance in HSCT recipients: a single center epidemiological and clinical data. *Bone marrow transplantation.* 2019;54(1):146-149.
90. Hakki M, Chou S. The biology of cytomegalovirus drug resistance. *Curr Opin Infect Dis.* 2011;24(6):605-611.
91. NHS Blood and Transplant. More black, Asian and minority ethnic people are becoming organ donors, but shortage remains critical. 2019; https://www.nhsbt.nhs.uk/news/more-black-asian-and-minority-ethnic-people-

are-becoming-organ-donors-but-shortage-remains-critical/. Accessed December, 2021.
92. NHS Blood and Transplant. Key stats from the BAME supplementary report 2017-18. 2018; https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/12164/bame-transplant-activity-report-stats.pdf. Accessed December, 2021.
93. Office for National Statistics. 2011 census - KS201UK - Ethnic group 2014; https://www.nomisweb.co.uk/query/construct/summary.asp?mode=construct&version=0&dataset=1504. Accessed December, 2021.
94. NHS Blood and Transplant. Organ Donation and Transplantation data for Black, Asian and Minority Ethnic (BAME) communities. 2020; https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/19753/bame-report-201920.pdf. Accessed December, 2021.
95. Zachary AA, Leffell MS. HLA Mismatching Strategies for Solid Organ Transplantation - A Balancing Act. *Front Immunol.* 2016;7:575.
96. Heldal K ea. Should patients older than 65 years be offered a second kidney transplat? *BMC Nephrol.* 2017;18(13).
97. NHS Blood and Transplant. Annual report on kidney transplantation. Report for 2018/19. 2019; https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/17289/kidney-annual-report-2018-19-november19.pdf. Accessed December, 2021.
98. Duarte RF, S. A, R.F. C, et al. Maribavir vs. investigator-assigned therapy (IAT) for the treatment of transplant recipients with refractory/resistant (R/R) cytomegalovirus infection: Efficacy data from a randomized phase 3 open-label study. Paper presented at: 47th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT)2021.
99. Hantz S, Garnier-Geoffroy F, Mazeron MC, et al. Drug-resistant cytomegalovirus in transplant recipients: a French cohort study. *J Antimicrob Chemother.* 2010;65(12):2628-2640.
100. Yin Z, Xu N., Jiang L., Shi P., Fan Z., Huang F., Liu Q., Sun J., Yu G. Cidofovir, a Choice for Salvage Treatment of CMV Infection in the Patients with Haploidentical Hematopoitic Stem Cell Transplantation. *Blood.* 2020;136:40-41.
101. Veit T, Munker, D.,Barton, J.,Milger, K.,Kauke, T.,Meiser, B.,Michel, S.,Zoller, M.,Nitschko, H.,Keppler, O. T.,Behr, J.,Kneidinger, N. Letermovir in lung transplant recipients with cytomegalovirus infection: A retrospective observational study. *Am J Transplant.* 2021;21(10):3449-3455.
102. Pierce B, Richardson, C. L.,Lacloche, L.,Allen, A.,Ison, M. G. Safety and efficacy of foscarnet for the management of ganciclovir-resistant or refractory cytomegalovirus infections: A single-center study. *Transpl Infect Dis.* 2018;20(2):e12852.
103. Avery RK, Arav-Boger, R., Marr, K. A., Kraus, E., Shoham, S., Lees, L., Trollinger, B.,Shah, P., Ambinder, R.,Neofytos, D.,Ostrander, D.,Forman, M.,Valsamakis, A. Outcomes in Transplant Recipients Treated With Foscarnet for Ganciclovir-Resistant or Refractory Cytomegalovirus Infection. *Transplantation.* 2016;100(10):e74-80.
104. Myhre HA, Haug Dorenberg, D.,Kristiansen, K. I.,Rollag, H.,Leivestad, T.,Asberg, A.,Hartmann, A. Incidence and outcomes of ganciclovir-resistant

cytomegalovirus infections in 1244 kidney transplant recipients. *Transplantation.* 2011;92(2):217-223.
105. Foresto RD, Hazin M.A., Zapata A., Santos D.W.C. Safety and efficacy of management of refractory cytomegalovirus infection in kidney transplant recipients treated with foscarnet and conversion from antimetabolite to mtor inhibitor. *Journal of the American Society of Nephrology.* 2018;29.
106. Kohlschmidt M, Christopeit M., Wolschke C., Ayuk F., Kröger N., Langebrake C. Efficacy and toxicity of ganciclovir and foscarnet combination therapy for refractory Cytomegalovirus reactivation in adult allogeneic stem cell transplant recipients. *Bone Marrow Transplantation.* 2019;53:555-556.
107. Avery RK, Alain S, Alexander BD, et al. Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial. *Clin Infect Dis.* 2021.
108. Takeda. SHP620-303 Clinical Study Report. 2021.
109. Avery RK, et al. Supplement - Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial. *Clin Infect Dis.* 2021.
110. Takeda. Data on File. SHP620-303 Individual Patient Data Analysis. 2021.
111. 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.
112. Nuijten M, Kielar C., Peggs K. Cost-effectiveness analysis of a directly selected CMV-specific t cell therapy for management of CMV disease in patients post allogeneic stem cell transplantation: A UK analysis. *Haematologica.* 2016;101:594-595.
113. Takeda. Data on File. Expert Health Economist Interviews Summary 2021.
114. NICE Decision Support Unit. Guide to the methods of technology appraisal 2013. 2013; https://www.nice.org.uk/process/pmg9/chapter/the-reference-case. Accessed December, 2021.
115. Office for National Statistics. National life tables: UK. 2020; https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. Accessed December, 2021.
116. NHS Blood and Transplant. Organ and Tissue Donation and Transplantation Annual Activity Report 2020/2021. 2021; https://www.odt.nhs.uk/statistics-and-reports/annual-activity-report/. Accessed December, 2021.
117. 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.* 2019;38(10):1067-1074.
118. Kim HJ, Larson JJ, Lim YS, et al. Impact of MELD on waitlist outcome of retransplant candidates. *Am J Transplant.* 2010;10(12):2652-2657.
119. 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.* 2015;28(8):990-999.

120. Kawut SM, Lederer DJ, Keshavjee S, et al. Outcomes after lung retransplantation in the modern era. *Am J Respir Crit Care Med.* 2008;177(1):114-120.
121. The British Transplant Society. *Management of the Failing Kidney Transplant.* 2014.
122. NICE (NG107). RRT and conservative management: Cost-effectiveness analysis: HDF versus high flux HD. *NICE Guidelines*2018.
123. Rayner HC, Pisoni RL, Bommer J, 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.* 2004;19(1):108-120.
124. Liem YS, Bosch JL, Hunink MG. Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta-analysis. *Value Health.* 2008;11(4):733-741.
125. Hahn T, McCarthy PL, Jr., Zhang MJ, 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;26(35):5728-5734.
126. Van Hout B, Janssen M, Feng Y-S, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in health.* 2012;15(5):708-715.
127. 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 in Health.* 2018;21:S451-S452.
128. Muduma G, Odeyemi, I.,Pollock, R. F. 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;19(10):995-1002.
129. Blumberg EA, Hauser I.A., Stanisic S., Mueller E., Berenson K., Gahlemann C.G., Humar A., Jardine A.G. Prolonged prophylaxis with valganciclovir is cost effective in reducing posttransplant cytomegalovirus disease within the United States. *Transplantation.* 2010;90(12):1420-1426.
130. Luan FL, Kommareddi M, Ojo AO. Universal prophylaxis is cost effective in cytomegalovirus serology-positive kidney transplant patients. *Transplantation.* 2011;91(2):237-244.
131. Puttarajappa CM, Hariharan S., Smith K.J. 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):290-298.
132. 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. *Biology of Blood and Marrow Transplantation.* 2018;24(3).
133. Alsumali A, Chemaly R.F., Graham J., Jiang Y., Merchant S., Miles L., Schelfhout J., Yang J., Tang Y. Cost-effectiveness analysis of cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplant recipients from a US payer perspective. *J Med Virol.* 2021;93(6):3786-3794.

134. Babigumira JB, Lubinga, S. J., Castro, E., & Custer, B. Cost-utility and budget impact of methylene blue-treated plasma compared to quarantine plasma. *Blood Transfus.* 2018;16(2):154-162.
135. 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;12:1127-1138.
136. Tilden DP, Chapman J., Davey P.J., Solly M.L., Crowley S. A decision-analytic economic evaluation of valaciclovir prophylaxis for the prevention of cytomegalovirus infection and disease in renal transplantation. *Clinical Transplantation.* 2004;18(3):312-320.
137. Chan TS-Y, Cheng S.S.-Y., Chen W.-T., Hsu D.C., Chau R.W.-Y., Kang S.H., Alsumali A., Kwong Y.-L. Cost-effectiveness of letermovir as cytomegalovirus prophylaxis in adult recipients of allogeneic hematopoietic stem cell transplantation in Hong Kong. *J Med Econ.* 2020;23(12):1485-1492.
138. Das A. Cost-effectiveness of different strategies of cytomegalovirus prophylaxis in orthotopic liver transplant recipients. *Hepatology.* 2000;31(2):311-317.
139. CADTH. Pharmacoeconomic Review Report: Letermovir. 2018 Letermovir.
140. CADTH. CDR Pharmacoeconomic Review Report For Tolvaptan (Jinarc). 2016 Tolvaptan.
141. NICE. Everolimus for preventing organ rejection in liver transplantation-Technology appraisal guidance (TA348). 2015.
142. Laupacis A, Keown, P.,Pus, N.,Krueger, H.,Ferguson, B.,Wong, C.,Muirhead, N. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int.* 1996;50(1):235-242.
143. Buti M, Casado MA, Fosbrook L, Wong JB, Esteban R. . Cost-effectiveness of combination therapy for naive patients with chronic hepatitis C. *Journal of Hepatology* 2000;33.
144. Ratcliffe J, Longworth L, Young T, Bryan S, Burroughs A, Buxton M. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. *Liver Transpl.* 2002;8(3):263-270.
145. Van Agthoven M, Segeren, C. M.,Buijt, I.,Uyl-de Groot, C. A.,van der Holt, B.,Lokhorst, H. M.,Sonneveld, P. 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;40(8):1159-1169.
146. Marty FM, Ljungman, P.,Chemaly, R. F.,Maertens, J.,Dadwal, S. S.,Duarte, R. F.Haider, S.,Ullmann, A. J.,Katayama, Y.,Brown, J.,Mullane, K. M.,Boeckh, M.,Blumberg, E. A.,Einsele, H.,Snydman, D. R.,Kanda, Y.,DiNubile, M. J.,Teal, V. L.,Wan, H.,Murata, Y.,Kartsonis, N. A.,Leavitt, R. Y.,Badshah, C. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. *N Engl J Med.* 2017;377(25):2433-2444.
147. CADTH. CDR Pharmacoeconomic Review Report For Tolvaptan (Jinarc). 2018 Tolvaptan.

148. Howard K, Salkeld, G.,White, S.,McDonald, S.,Chadban, S.,Craig, J. C.,Cass, A. The cost-effectiveness of increasing kidney transplantation and home-based dialysis. *Nephrology (Carlton).* 2009;14(1):123-132.
149. Narayan R, Perkins, R. M.,Berbano, E. P.,Yuan, C. M.,Neff, R. T.,Sawyers, E. S.,Yeo, F. E.,Vidal-Trecan, G. M.,Abbott, K. C. Parathyroidectomy versus cinacalcet hydrochloride-based medical therapy in the management of hyperparathyroidism in ESRD: a cost utility analysis. *Am J Kidney Dis.* 2007;49(6):801-813.
150. McFarlane PA, Bayoumi, A. M.,Pierratos, A.,Redelmeier, D. A. The quality of life and cost utility of home nocturnal and conventional in-center hemodialysis. *Kidney Int.* 2003;64(3):1004-1011.
151. Pidala J, Kurland, B.,Chai, X.,Majhail, N.,Weisdorf, D. J.,Pavletic, S.,Cutler, C.,Jacobsohn, D.,Palmer, J.,Arai, S.,Jagasia, M.Lee, S. J. 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;117(17):4651-4657.
152. Ara R, Brazier, J. E. 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;14(4):539-545.
153. Leunis A, Redekop, W. K., Uyl-de Groot, C. A., Lowenberg, B. Impaired health-related quality of life in acute myeloid leukemia survivors: a single-center study. *Eur J Haematol.* 2014;93(3):198-206.
154. Neri L, McEwan, Phil, Sennfält, Karin, Baboolal, Kesh. 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;10:139-139.
155. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making.* 2011;31(6):800-804.
156. Ossa DF, Briggs A, McIntosh E, Cowell W, Littlewood T, Sculpher M. Recombinant erythropoietin for chemotherapy-related anaemia. *Pharmacoeconomics.* 2007;25(3):223-237.
157. 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;13(5):e195-e203.
158. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes.* 2008;6(1):1-15.
159. Bullement A, Nathan P, Willis A, et al. Cost effectiveness of avelumab for metastatic Merkel cell carcinoma. *PharmacoEconomics-open.* 2019;3(3):377-390.
160. Beusterien KM, Davies J, Leach M, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. *Health Qual Life Outcomes.* 2010;8:50.
161. 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. *The European Journal of Health Economics.* 2013;14(5):749-759.
162. Szende A, Janssen B, Cabases J. In: Szende A, Janssen B, Cabases J, eds. *Self-Reported Population Health: An International Perspective based on EQ-5D*. Dordrecht (NL)2014.

163. Chen J, Abella Ross J., Tegtmeier B., Yang D., Ito J.I., Zaia J.A., Dickter J.K., Nakamura R., Mokhtari S., Kriengkauykiat J., Al Malki M.M., Dadwal S.S. Cost analysis of ganciclovir and foscarnet in recipients of allogeneic hematopoietic cell transplant with cytomegalovirus viremia. *Transpl Infect Dis.* 2020;22(2):e13233.
164. Derigs P, A. Radujkovic, M. L. Schubert, P. Schnitzler, T. Schöning, C. Müller-Tidow, U. Hegenbart, S. O. Schönland, T. Luft, P. Dreger and M. Schmitt. Letermovir prophylaxis is effective in preventing cytomegalovirus reactivation after allogeneic hematopoietic cell transplantation: single-center real-world data. *Ann Hematol.* 2021;100(8):2087-2093.
165. De Miguel C, Royuela A., Portero M.F., Cruz J.L., Martínez-Muñoz M.E., Sánchez M.I., Bautista G., Cabrera R., Duarte R.F. Cytomegalovirus (CMV) impact on clinical outcomes and resource use after allogeneic hematopoietic cell transplantation: The influence of recurrent episodes of cmv infection. *Bone Marrow Transplantation.* 2020;55:462-463.
166. Geddes CC, Church C.C., Collidge T., McCruden E.A.B., Gillespie G., Matthews E., Hainmueller A., Briggs J.D. Management of cytomegalovirus infection by weekly surveillance after renal transplant: analysis of cost, rejection and renal function. *Nephrol Dial Transplant.* 2003;18(9):1891-1898.
167. McCarthy JM, Karim M.A., Krueger H., Keown P.A. The cost impact of cytomegalovirus disease in renal transplant recipients. *Transplantation.* 1993;55(6).
168. Shah T, Lai W.K., Mutimer D. Impact of targeted oral ganciclovir prophylaxis for transplant recipients of livers from cytomegalovirus-seropositive donors. *Transplant Infectious Disease.* 2005;7(2):57-62.
169. Singhal S, Khan O.A., Bramble R.A., Mutimer D.J.V. Cytomegalovirus disease following liver transplantation: an analysis of prophylaxis strategies. *Journal of Infection.* 2003;47(2):104-109.
170. Seehofer D, Meisel H., Rayes N., Stein A., Langrehr J.M., Settmacher U., Neuhaus P. Prospective evaluation of the clinical utility of different methods for the detection of human cytomegalovirus disease after liver transplantation. *Am J Transplant.* 2004;4(8):1331-1337.
171. Leong RWL, Smith D.W., Garas G., Beaman J.M., Mitchell A.W., Heath D.I., House A.K., Jeffrey G.P. Aciclovir or ganciclovir universal prophylaxis of cytomegalovirus infection in liver transplantation: An economic analysis. 2004;34(7):410-415.
172. Ferchichi S, Aballea S., Goryakin Y., Hakimi Z., Odeyemi I., Toumi M. A Retrospective Study On The Burden Of Cytomegalovirus Disease In Immunosuppressed Persons Following Transplantation Between 2007 And 2011 In France. *Value in Health.* 2013;16(3).
173. Mauskopf JA, Richter A., Annemans L., Maclaine G. Cost-effectiveness model of cytomegalovirus management strategies in renal transplantation: Comparing valaciclovir prophylaxis with current practice. *PharmacoEconomics.* 2000;18(3):239-251.
174. Legendre C, Beard, S. M.,Crochard, A.,Lebranchu, Y.,Pouteil-Noble, C.,Richter, A.,Durand-Zaleski, I. The cost-effectiveness of prophylaxis with valaciclovir in the management of cytomegalovirus after renal transplantation. *Eur J Health Econ.* 2005;6(2):172-182.

175. Annemans L, Moeremans K., Mutimer D., Schneeberger H., Milligan D., Kubin M. Modeling costs and cost-effectiveness of different CMV management strategies in liver transplant recipients as a support for current and future decision making. *Value Health.* 2002;5(4):347-358.
176. Reischig T, Opatrny Jr. K., Bouda M., Treska V., Jindra P., Svecova M. A randomized prospective controlled trial of oral ganciclovir versus oral valacyclovir for prophylaxis of cytomegalovirus disease after renal transplantation. *Transplant International.* 2002;15(12).
177. Kielberger L, Bouda M., Jindra P., Reischig T. Pharmacoeconomic impact of different regimens to prevent cytomegalovirus infection in renal transplant recipients. *Kidney Blood Press Res.* 2012;35(6):407-416.
178. NICE (BNF). British National Formulary (BNF): Ganciclovir (as Ganciclovir sodium) 500mg (Reig Jofre UK Ltd). 2021; https://bnf.nice.org.uk/drug/ganciclovir.html. Accessed 10 December, 2021.
179. NICE (BNF). British National Formulary (BNF): Valganciclovir (as Valganciclovir hydrochloride) 450mg (Mylan). 2021; https://bnf.nice.org.uk/drug/valganciclovir.html. Accessed 10 December, 2021.
180. NICE (BNF). British National Formulary (BNF): Foscarnet sodium 24mg per 1ml (Clinigen Healthcare Ltd). 2021; https://bnf.nice.org.uk/drug/foscarnet-sodium.html. Accessed 10 December, 2021.
181. NICE (BNF). British National Formulary (BNF): Cidofovir. 2021; https://bnf.nice.org.uk/drug/cidofovir.html. Accessed 10 December, 2021.
182. Wolters Kluwer Health Inc. Medi-Span Price Rx. Cidofovir Intravenous Solution 75 MG/ML. 2021; https://pricerx.medispan.com. Accessed 15 December, 2021.
183. Medicines.org. Electronic Medicines Compendium (emc). 2020; https://www.medicines.org.uk/emc/. Accessed 2021.
184. Gilead Sciences Inc. Vistide®(cidofovir injection). 2010; http://www.gilead.com/-/media/files/pdfs/medicines/other/vistide/vistide.pdf. Accessed December, 2021.
185. NICE (BNF). British National Formulary (BNF). 2021; https://bnf.nice.org.uk/. Accessed 2021.
186. National Health Service. 2019-20 Reference Costs 2021; https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/reference-costs. Accessed December, 2021.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

Clarification questions

January 2022

File name	Version	Contains confidential information	Date
ID3900 maribavir clarification questions to PM for company_Takeda response [REDACTED]	1.0	No	16 February 2022

Notes for company

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Section A: Clarification on effectiveness data

A1. Priority question. Please clarify if the marketing authorisation for maribavir is expected to state that maribavir is to be used only when a patient is resistant or refractory to their last anti-CMV treatment. That is, patients who achieve clearance on maribavir will not be re-treated with maribavir if they have recurrence after clearance on maribavir.

Maribavir is proposed to be indicated for the treatment of adults with post transplant cytomegalovirus (CMV) infection and/or disease who are resistant and/or refractory to one or more prior therapy including ganciclovir, valganciclovir, cidofovir or foscarnet. We do not expect patients will be retreated with maribavir following recurrence after clearance on maribavir. Prior therapy on maribavir was an exclusion criteria within the SOLSTICE trial so data on maribavir retreatment is not available.

A2. Priority question. Please provide information on mean and median time since transplant surgery at baseline for each treatment arm and based on transplant type.

Time since transplant was not captured in the SOLSTICE trial. As these patients are refractory / resistant to previous CMV therapy the time since transplant is not a

useful measure as the population could have had multiple CMV infections and various number of anti CMV therapies over time.

A3. Priority question. Please confirm what treatment was used for CMV prophylaxis for each treatment arm. Please also provide the breakdown of the number of patients who received CMV prophylaxis based on transplant type.

Data on prior therapy was captured in SOLSTICE. However, it is not reported if the specific treatment was used for prophylaxis or previous therapy in the RR population (who may have received multiple prior treatments).

Overall, 41.2% of subjects had used CMV prophylaxis (unspecified) prior to the first episode of CMV infection that was refractory to treatment at entry to this study (maribavir: 100 [42.6%] subjects; IAT: 45 [38.5%] subjects). Prophylaxis for CMV occurred [redacted] recipients: [redacted] SOT recipients versus [redacted] HSCT recipients.

Given the prophylactic-only indication for letermovir, we are able to confirm that letermovir was given to [redacted] of patients [redacted] IAT and [redacted] maribavir), however availability of letermovir across the various trial sites was variable as marketing authorisation was granted in 2018 and the SOLSTICE clinical trial started in 2016.

A4. Priority question. Please complete table 1 (see below) by providing results by treatment arm based on time since surgery. Please provide the number of patients and results separately for patients with a time from surgery to randomisation of

- **A) ≤ 3 months**
- **B) > 3 months to ≤ 6 months**
- **C) > 6 months to ≤ 12 months**
- **D) > 12 months**

Based on the results provided in Table 1, please discuss if the relative treatment effect of maribavir is expected to differ by time since surgery.

Time since surgery was not captured in SOLSTICE (please see response to question A2) and unfortunately it is not possible to perform this analysis to complete Table 1. Given the mechanism of action of maribavir there is no known reason why the treatment effect of maribavir would differ according to time since surgery. Time since surgery may be associated with other variables such as level of immunosuppression and overall frailty score, so if there is significant variance between arms it could confound the overall results.

Table 1.

	≤3 months since surgery						>3 months to ≤6 months since surgery						>6 months to ≤12 months since surgery						>12 months since surgery					
	IAT		Mar				IAT		Mar				IAT		Mar				IAT		Mar			
Number at baseline																								
	n/N	%	n/N	%	Dif.	p	n/N	%	n/N	%	Dif.	p	n/N	%	n/N	%	Dif.	p	n/N	%	n/N	%	Dif.	p
Clearance at 4 wks																								
Clearance at 8 wks																								
Clinically relevant recurrence at wk 8 for patients with clearance at 4 wks																								
Clinically relevant recurrence at wk 20 for patients with clearance at 8 wks																								
Mortality																								

Type of transplant																								
HSCT: GvHD																								
HSCT: Total																								
SOT: Kidney																								
SOT: Lung																								
SOT: Heart																								
SOT: Total																								
Number of patients hospitalised																								
p - please provide the p-value and the respective 95% CI																								

A5. Priority question. Please complete table 2 (see below) by providing results for the ITT population (with the respective statistical significance of the difference between arms) and the subgroup of patients in the IAT arm receiving foscarnet (with the statistical significance of the difference between the maribavir and foscarnet arms).

Please see Table 2 completed below. Data on clearance at week 20 for foscarnet alone are not available, and clearance at week 4 is taken from a *post-hoc* individual patient data (IPD) analysis conducted to inform the CEM model, as the timepoint for the primary efficacy analysis in SOLSTICE was week 8. Two sample proportionality test p-values have been calculated.

Table 2. Clearance and clinically relecant recurrence by treatment arm, transplant type and resistance status

	IAT (total)				IAT (foscarnet)				Mar	
Number at baseline	117				47				235	
	n/N	%	Dif.	p	n/N	%	Dif.	p	n/N	%
Clearance at 4 wks	[redacted]									
Clearance at 8 wks	[redacted]									
Clearance at 20 wks	[redacted]									
Clinically relevant recurrence at wk 8 for patients with clearance at 4 wks	[redacted]									
Clinically relevant recurrence at wk 20 for patients with clearance at 8 wks	[redacted]									
Mortality at week 8	[redacted]									
Mortality at week 20	[redacted]									
Type of transplant										
HSCT: GvHD	[redacted]									

HSCT: Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOT: Kidney	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOT: Lung	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOT: Heart	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOT: Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients hospitalised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resistance diagnosis:										
Resistant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not resistant (refractory)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p - please provide the p-value and the respective 95% CI Dif. – please provide % difference versus maribavir NR, not reported *Deaths only reported for safety set										

A6. Priority question. Please complete table 3 (see below) by providing results by treatment arm based on the current CMV infection being either the first or a later episode post-transplant. Please provide the number of patients and results separately for patients for whom the current CMV episode is

A. the first episode post-transplant

B. a second or later episode post-transplant

Avery (2021) states that 162/235 (68.9%) maribavir and 78/116 (66.7%) IAT patients have their current CMV infection as the first episode post transplant. However, this may not be the first episode in their lifetime, since [redacted] ([redacted]%) maribavir and [redacted] ([redacted]%) were R+ at entry to the trial. Because of this we do not have the data to complete Table 3. Furthermore, all patients had to have an infection resistant and/or refractory to their previous therapy and thus all infections treated, whether by maribavir or IAT were more complex than a straightforward initial first episode. Numerous sensitivity analyses were performed including baseline viral load, which may be predictive of whether the episode is first or later post-transplant, since earlier episodes tend to be characterised by higher viral loads. No difference was seen between results for either low or higher viral loads.

Table 3.

	First CMV episode post-transplant						Second or later CMV episode post-transplant					
	IAT		Mar				IAT		Mar			
Number at baseline												
	n/N	%	n/N	%	Dif.	p	n/N	%	n/N	%	Dif.	p
Clearance at 4 wks												
Clearance at 8 wks												
Clinically relevant recurrence at wk 8 for patients with clearance at 4 wks												
Clinically relevant recurrence at wk 20 for patients with clearance at 8 wks												
p - please provide the p-value and the respective 95% CI												

A7. Priority question. Please complete table 4 (see below) by providing results based on the baseline resistance status being either resistant or not resistant (refractory). Please provide the number of patients and results separately for patients for whom the baseline resistance status is

C. resistant

D. not resistant (refractory)

Of the 350 patients who received at least one dose of IAT (n=116) or maribavir (n=234), [redacted] ([redacted]%) patients in the IAT arm and [redacted] ([redacted]%) patients in the maribavir arm had evaluable CMV genotypic data at baseline.

Of the patients with evaluable CMV genotypic data at baseline, [redacted] ([redacted]%) and [redacted] ([redacted]%) had at least one confirmed and previously reported GCV/VGCV, FOS or CDV resistance-associated mutation in pUL97 and/or pUL54 at baseline, in the IAT- and maribavir arms, respectively.

Treatment response at Week 8 by IAT resistance status is shown in Table 4, however, response rates at Week 4 are not available as the only analysed timepoints in SOLSTICE were Week 8 and Week 20 (Week 4 data, where available, are taken from a *post-hoc* IPD analysis conducted to inform the CEM model). Data on clinically relevant recurrence by resistance status are also not available. Results should be interpreted with caution as it is not known whether resistance status or mutation type influenced investigator choice of IAT in SOLSTICE, and some confirmed pUL97 and pUL54 mutations are known to confer low grade or variable resistance (or only modest resistance when present alone). In addition, as genotyping is not performed in routine clinical practice, data to support the effect of resistance mutations on treatment outcomes are lacking.

Table 4. Treatment response by resistance status

	Baseline resistance status: Resistant						Baseline resistance status: Not resistant					
	IAT (N=103)		Mar (N=217)				IAT (N=103)		Mar (N=217)			
Number at baseline	[redacted]		[redacted]				[redacted]		[redacted]			
	n/N	% (95% CI)	n/N	%	Adjusted Dif. (95% CI)	p	n/N	% (95% CI)	n/N	%	Adjusted Dif. (95% CI)	p
Clearance at 4 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Clearance at 8 wks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinically relevant recurrence at wk 8 for patients with clearance at 4 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Clinically relevant recurrence at wk 20 for patients with clearance at 8 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

p - please provide the p-value and the respective 95% CI
NR, not reported

A8. Priority question. Please provide unadjusted results for

E) the primary outcome (confirmed CMV viraemia clearance at Week 8)

F) confirmed CMV viraemia clearance and CMV infection symptom control at Week 8, 12, and 20.

The unadjusted results for the primary outcome are presented in Table B:

Table B: Unadjusted results for the primary outcome

CMV Vireamia clearance response at week 8	**IAT (N=117) n (%)**	**Maribavir (N=235) n (%)**
Responders	[redacted]	[redacted]
Non responders	[redacted]	[redacted]
Unadjusted difference in proportion of responders (95% CI)	[redacted]	

Note: Unadjusted difference in proportion (Maribavir – IAT) and the corresponding 95% CI is computed by the normal approximation method.

Results at Week 8 for the proportion of responders who achieved CMV viremia clearance and CMV infection symptom control are identical to the results of the primary efficacy endpoint analysis, indicating that all responders for the primary endpoint also had CMV infection symptom control at Week 8.

The proportion of responders who achieved CMV viremia clearance and CMV infection symptom control at Week 8 and maintained the effect through Week 12 and Week 20 off treatment was approximately [redacted] for maribavir-treated subjects than for the IAT group, regardless of the duration of follow-up (see Table C).

Table C: Confirmed CMV viraemia clearance and CMV infection symptom control at Week 8, 12, and 20

CMV Vireamia clearance and CMV infection symptom control	**IAT (N=117) n (%)**	**Maribavir (N=235) n (%)**
At Study week 8		
Responders	[redacted]	[redacted]
Non responders	[redacted]	[redacted]
Unadjusted difference (95% CI)		[redacted]
At Study week 12		
Responders	[redacted]	[redacted]
Non responders	[redacted]	[redacted]
Unadjusted difference (95% CI)		[redacted]
At Study week 20		
Responders	[redacted]	[redacted]
Non responders	[redacted]	[redacted]
Unadjusted difference (95% CI)		[redacted]

Note: Unadjusted difference in proportion (Maribavir – IAT) and the corresponding 95% CI is computed by the normal approximation method.

A9. Priority question. Please provide data on the number of patients hospitalised at week 4, 8, and 20. Please provide the data by treatment arm, type of transplant, and response (clearance [CMV/nCMV]) at each timepoint. Please also provide a breakdown of the reason for hospitalisations due to drug administration, AE, severe CMV disease or other reasons.

Hospitalisation rates by treatment arm at Weeks 8 and 20 are shown in Table D. There was a significant [redacted]% reduction (p=0.021) in hospitalisations observed in the maribavir arm during the on- treatment phase (Week 8) compared with IAT. Data at Week 4, and subgroup data by transplant type and response, are not available.

Table D: Hospitalisations

	Week 8		Week 20	
	IAT (N=117)	**Maribavir (N=235)**	**IAT (N=117)**	**Maribavir (N=235)**
Admissions	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted difference, maribavir vs IAT	[redacted]		[redacted]	
Patients with ≥1 admission, n (%)				
Any admission	[redacted]	[redacted]	[redacted]	[redacted]
General ward admission	[redacted]	[redacted]	[redacted]	[redacted]
ICU admission	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted annual rate, 95% CI				
Any admission	[redacted]	[redacted]	[redacted]	[redacted]
General ward admission	[redacted]	[redacted]	[redacted]	[redacted]
ICU admission	[redacted]	[redacted]	[redacted]	[redacted]
Week 8 rates are adjusted for duration of time on treatment (52 days for maribavir, 35.7 days for IAT) Week 20 rates are adjusted for duration of time in study (132.1 days for maribavir, 92.9 days for IAT)				

Reasons for hospitalisation by treatment arm are shown in Table E. Reasons were captured as free text in the CRF and categorised by specified categories of interest and Medical Dictionary for Regulatory Activities (MedDRA) codes. CMV-related events (CMV infection/disease and treatment) were the most frequently reported reasons for hospitalisation.

Table E: Reason for hospitaliation by treatment arm

Reason for hospitalisation	**IAT (N=117)**	**Maribavir (N=235)**	**Overall (N=352)**
CMV infection/disease	[redacted]	[redacted]	[redacted]
CMV treatment	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Transplant or graft complications	[redacted]	[redacted]	[redacted]
GVHD	[redacted]	[redacted]	[redacted]
AE (unspecified)	[redacted]	[redacted]	[redacted]
Multiple reasons listed	[redacted]	[redacted]	[redacted]
MedDRA category			
01. Blood and lymphatic system disorder	[redacted]	[redacted]	[redacted]
02. Cardiac disorders	[redacted]	[redacted]	[redacted]
03. Congenital, familial and genetic disorders	[redacted]	[redacted]	[redacted]
04. Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]
05. Endocrine disorders	[redacted]	[redacted]	[redacted]
06. Eye disorders	[redacted]	[redacted]	[redacted]
07. Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
08. General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
09. Hepatobiliary disorders	[redacted]	[redacted]	[redacted]
10. Immune system disorders	[redacted]	[redacted]	[redacted]
11. Infections and infestations	[redacted]	[redacted]	[redacted]
12. Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
13. Investigations	[redacted]	[redacted]	[redacted]

14. Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
15. Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
16. Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]	[redacted]
17. Nervous system disorders	[redacted]	[redacted]	[redacted]
18. Pregnancy, puerperium and perinatal conditions	[redacted]	[redacted]	[redacted]
19. Psychiatric disorders	[redacted]	[redacted]	[redacted]
20. Renal and urinary disorders	[redacted]	[redacted]	[redacted]
21. Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]
22. Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
23. Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
24. Social circumstances	[redacted]	[redacted]	[redacted]
25. Surgical and medical procedures	[redacted]	[redacted]	[redacted]
26. Vascular disorders	[redacted]	[redacted]	[redacted]
27. Product issues	[redacted]	[redacted]	[redacted]

A10. Priority question. Please clarify the criteria for recurrence requiring treatment in SOLSTICE. If any of the criteria are subjective and so subject to potential bias in an open-label trial, how was potential bias minimised for the assessment of clinically relevant recurrence?

No specific additional definition was supplied regarding definition of a recurrent infection requiring treatment beyond the definition of initial infection requiring treatment. We would therefore expect the requirement for recurrence requiring treatment to be the same i.e. *The participant must have a documented CMV infection in whole blood or plasma, with a screening value of greater than or equal to (>=) 2730 international units per milliliter (IU/mL) in whole blood or >= 910 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. 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.* This threshold was selected following discussions with regulatory authorities and in careful consideration towards including patients with clinically significant CMV viremia. The description of recurrence was in similar terms as “clinically significant.”

A11. Priority question. Please provide Kaplan-Meier data on the Cumulative Probability of First CMV Viremia Clearance at Week 4 to CMV Viremia Recurrence Requiring Alternative Treatment by Treatment Group up to Week 8.

The proportion of patients that had recurrence requiring treatment between week 4 and week 8 is included in Table 12. Given the sample size of patients who have recurrence requiring treatment between week 4 and week 8 is limited and the time frame of conducting the survival analysis (a 4-week period) is short, generating Kaplan-Meier data is not appropriate as the results would not generate interpretable outcomes.

A12. Priority question. Please provide mortality data at 20 weeks for the safety population by treatment arm and separately for the rescue arm and for those randomised to IAT who did not cross over to the rescue arm.

[redacted] ([redacted]%) IAT and [redacted] ([redacted]%) maribavir patients died within the first 20 weeks after the first dose.

Of the 22 subjects who received rescue therapy, 1 death was reported during rescue treatment with maribavir in a subject that originally was given foscarnet. The Investigator assessed that the death was not related to the subject's investigator assigned study treatment (foscarnet) or to rescue treatment with maribavir.

A13. Please provide data on TEAEs leading to discontinuation for patients treated with cidofovir (safety set, CS Table 28)?

[redacted] of the six ([redacted]%) cidofovir patients discontinued study-assigned treatment due to TEAEs. [redacted]

A14. In the CS it is stated that, "Any patient who could not reasonably be assumed to have had a recurrence requiring treatment between weeks 4 and 8 (i.e., due to death or lack of data on CMV viral load) was excluded from the efficacy analysis". Please provide information on how many patients were assumed not to have had a recurrence and excluded from the analysis.

Please find a response to this question detailed in Table F below:

Table F:Calculation of the number of patients who had a recurrence requiring treatment

	IAT	Maribavir	Included in calculations	Source
	Response at Week 4	Response at Week 4		
Response status at Week 8				
CMV measurements through week 8 but did not meet response criteria	[redacted]	[redacted]	Included	[redacted]
Number of subjects from response at week 4 to recurrence requiring treatment at week 8	[redacted]	[redacted]	Included	[redacted]
Alternative anti-CMV treatment	[redacted]	[redacted]	Included	[redacted]
Discontinuation due to adverse events	[redacted]	[redacted]	Included	[redacted]
Total included (n)	[redacted]	[redacted]		[redacted]
Discontinuation due to non-compliance with study schedule	[redacted]	[redacted]	Excluded	[redacted]
Due to other reason but remained in the study	[redacted]	[redacted]	Excluded	[redacted]
Withdrawal by subjects	[redacted]	[redacted]	Excluded	[redacted]
Dead (between week 4 to week 8)	[redacted]	[redacted]	Excluded	[redacted]
Total (n/N)	[redacted]	[redacted]		

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user-selectable options in the economic model so that these can be combined.

For all KM data requested and used by the company, please provide the KM data in Excel, together with the number of patients at risk.

Furthermore, if the company chooses to update its base case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

B1. Priority question. Given the length of the Excel equations informing the model traces, model validation in the available time for this STA will be difficult. In the interest of transparency, please provide a model specification document which mathematically describes the transitions between states in the model (in differential or iterative form but absent of any IF/OR/AND statements included in the Excel model which merely enable scenarios).

In Table G the transitions between each of the five different health state traces shown in the Markov engines of the model are explained.

Table G: Health state transition matrix

From → To	**csCMV treatment 1**	**n-csCMV (1)**	**csCMV retreatment**	**n-csCMV (2)**	**Dead**
csCMV treatment 1	Possible to stay in this state up to week 8. After week 8, those still with csCMV are moved onto retreatment and move to the csCMV retreatment trace	Patients can only move from csCMV treatment 1 to n-csCMV(1) from week 0 to 8	After week 8, those still with csCMV are moved onto retreatment and move to the csCMV retreatment trace	N/A – patients can only move in to this trace from csCMV retreatment	Transition defined by mortality rate for those with csCMV
n-csCMV(1)	This transition is only possible up to week 8. The transition is defined by the rate of recurrence from week 0 to 4 and then week 4 to 8	This transition is defined by the number of patients who do not have a recurrence in each respective cycle. You can only stay in the n-csCMV(1) trace if you clear between	Defined by the number of patients who have a recurrence in each respective cycle	N/A – patients can only move into this trace from csCMV retreatment	Transition defined by mortality rate for those with n-csCMV

From → To	csCMV treatment 1	n-csCMV (1)	csCMV retreatment	n-csCMV (2)	Dead
		week 0 -8 and never have a recurrence.			
csCMV retreatment	N/A - patients cannot move from the csCMV retreatment trace to the csCMV treatment 1 health state	N/A – patients cannot move from the csCMV retreatment trace to the n-csCMV (1) because this trace can only be entered into between weeks 0-8 from the csCMV treatment 1 trace	Defined by the number of patients who do not clear in each respective cycle	Defined by the number of patients who have a clearance in each respective cycle	Transition defined by mortality rate for those with csCMV
n-csCMV (2)	N/A - patients cannot move from the csCMV retreatment trace to the n-csCMV (2) health state as all patients who clear up to week 9 are moved into the n-csCMV(1) trace or at week 8 those who are still in this trace are moved to the csCMV retreatment trace	N/A patients can only enter the n-csCMV (1) trace between weeks 0-8 from the csCMV treatment 1 trace	Defined by the number of patients who have a recurrence in each respective cycle	Defined by the number of patients who do not have a recurrence in each respective cycle	Transition defined by mortality rate for those with n-csCMV

Table H provides an example of how the different lines in the formulas in the engine represent the transition calculations. There are five different formulas taken from the Markov engine (Maribavir) cells AH18, AI20, AJ20,AK20 and AL20. Each of the formulas represents a cell calculation from one of the five states in the engine (csCMV treatment 1, n-csCMV (1), csCMV retreatment, n-csCMV (2) and Dead).

Formula reference 1: Markov engine (Maribavir) – AH18

```
1  =AH17*(1-$O18)*(1-dblDataGraftLossRiskClinicallySignificantCMVUsed)*(1-dblDataTrtEfficacyMaribavirClearanceSOT4to8Used)
2  +AI17*(1-$P18)*(1-dblDataGraftLossRiskNonClinicallySignificantCMVUsed)*IF(dblControlScenarioRecurrenceFrequency="On",$AD18,1)*dblDataTrtEfficacyMaribavirRecurrenceSOT4to8Used
```

Formula reference 2: Markov engine (Maribavir) – AI20

```
1  =AI19*(1-$P20)*(1-dblDataGraftLossRiskNonClinicallySignificantCMVUsed)*(1-IF(dblControlScenarioRecurrenceFrequency="On",$AD20,1)*dblDataTrtEfficacyMaribavirRecurrenceSOT8to20Used)
```

Formula reference 3: Markov engine (Maribavir) – AJ20

```
1  =AH19*(1-$O20)*(1-dblDataGraftLossRiskClinicallySignificantCMVUsed)*(1-IF(dblControlRetreatment="On",$AE20,1)*IFS($AI$12="Maribavir",dblDataTrtEfficacyMaribavirClearanceSOT8to20Used,$AI$12="IAT",dblDataTrtEfficacyIATClearanceSOT8to20Used))
2  +AI19*(1-$P20)*(1-dblDataGraftLossRiskNonClinicallySignificantCMVUsed)*IF(dblControlScenarioRecurrenceFrequency="On",$AD20,1)*dblDataTrtEfficacyMaribavirRecurrenceSOT8to20Used
3  +AJ19*(1-$O20)*(1-dblDataGraftLossRiskClinicallySignificantCMVUsed)*(1-IF(dblControlRetreatment="On",$AE20,1)*IFS($AI$12="Maribavir",dblDataTrtEfficacyMaribavirClearanceSOT8to20Used,$AI$12="IAT",dblDataTrtEfficacyIATClearanceSOT8to20Used))
4  +AK19*(1-$P20)*(1-dblDataGraftLossRiskNonClinicallySignificantCMVUsed)*IF(dblControlScenarioRecurrenceFrequency="On",$AF20,1)*IFS($AI$12="Maribavir",dblDataTrtEfficacyMaribavirRecurrenceSOT8to20Used,$AI$12="IAT",dblDataTrtEfficacyIATRecurrenceSOT8to20Used)
```

Formula reference 4: Markov engine (Maribavir) – AK20

1 =(AH18*(1-$O19)*(1-dblDataGraftLossRiskClinicallySignificantCMVUsed)*
IF(dblControlRetreatment="On",$AE19,1)*IFS($AI$12="Maribavir",dblDataTrtEfficacyMaribavirClearanceSOT8to20Used,AI12="IAT",
dblDataTrtEfficacyIATClearanceSOT8to20Used))

2 +
AJ18*(1-$O19)*(1-dblDataGraftLossRiskClinicallySignificantCMVUsed)*
IF(dblControlRetreatment="On",$AE19,1)*IFS($AI$12="Maribavir",dblDataTrtEfficacyMaribavirClearanceSOT8to20Used,AI12="IAT",
dblDataTrtEfficacyIATClearanceSOT8to20Used)

3 +AK18*(1-$P19)*(1-dblDataGraftLossRiskNonClinicallySignificantCMVUsed)*
(1-IF(dblControlScenarioRecurrenceFrequency="On",$AF19,1)*IFS($AI$12="Maribavir",dblDataTrtEfficacyMaribavirRecurrenceSOT8to20Used,AI12="IAT",
dblDataTrtEfficacyIATRecurrenceSOT8to20Used))

Formula reference 5: Markov engine (maribavir) – AL20

1 2 3
=(AH19+AJ19)*$O20+(AI19+AK19)*$P20+AL19

Table H: Example transition matrix

	Formula reference 1	Formula reference 2	Formula reference 3	Formula reference 4	Formula reference 5
From → To	csCMV treatment 1	n-csCMV (1)	csCMV retreatment	n-csCMV (2)	Dead
csCMV treatment 1	[1]	N/A	[1]	[1]	[1]
n-csCMV(1)	[2]	[1]	[2]	N/A	[2]
csCMV retreatment	N/A	N/A	[3]	[2]	[1]
n-csCMV (2)	N/A	N/A	[4]	[3]	[2]
Dead	N/A	N/A	N/A	N/A	[3]

B2. Priority question. Given that most of the parameters used in the economic model were sourced from the company's IPD analysis, and the lack of detail provided for the latter, please provide the statistical plan for the IPD analysis (and subsequent report), together with the definition of outcomes used and any additional detail relevant for the analysis conducted.

The IPD analysis was conducted *post-hoc*. We have provided a report in response to these questions

B3. Priority question. Given that lack of detail provided in the CS around hospitalisations in the model, please provide a detailed description of:

- what assumptions were made to model hospitalisations in each treatment arm and what were the assumed reasons for patients in the model needing hospitalisation;

As the underlying disease type (SOT or HSCT) is very different, and there is a difference in the severity of csCMV and n-csCMV patients, the hospitalisation rate used in the model is transplant- and health-state specific. Hospitalisation rates in the IAT and maribavir treatment arms are assumed to be the same, with patients assumed to require hospitalisation due to recurrence of CMV and complications relating to a patient's transplant.

- how the assumptions made in the model relate to the hospitalisations observed in SOLSTICE;

The hospitalisation rate used in the model is taken directly from SOLSTICE and converted into a 4-week probability (see Table N in response to Question B5).

- what input parameters were used to estimate the proportion and the cost of hospitalisations and justify the choice of source for the parameters.

The cost of a hospitalisation for n-csCMV and csCMV has been sourced from the NHS Reference Costs 2019/20 with an HRG code of WJ02 (major infectious disease). This code was used as the ICD-10 codes that relates to "Other cytomegaloviral disease" (B25.8) and "Cytomegaloviral disease, unspecified" (B25.9) correspond to the HRG code WJ02 using the HRG4+ 2020/21 National Costs Grouper. csCMV uses a weighted average of the total cost and activity of HRG codes WJ02A and WJ02B (major infectious diseases with multiple interventions and major infectious diseases with single intervention respectively), while n-csCMV uses a weighted average of WJ02C and WJ02D (major infectious diseases without interventions, with CC score 6+ and 3-5 respectively). Patients hospitalised with n-csCMV have lower severity and therefore and not expected to require additional interventions when hospitalised, while patients hospitalised with csCMV are assumed to require additional interventions due to the increased severity of disease. Takeda have taken a conservative assumption around hospitalisation events in the model by assuming a high cost for the n-csCMV state, a lower cost estimate would favour maribavir (see response to B29).

B4. Priority question. In TA591, the ERG noted that, "*A significant proportion of people with haematological cancers will experience relapse in their underlying disease following a SCT. These people will incur additional resource use and experience lower quality of life*". The ERG added that, "*This* [the omission of relapse from the model] *is problematic as the costs and QALY decrements associated with relapse will not impact evenly on the two groups due differences in the number of patients at risk in the two groups (different mortality rates)*". Therefore, please justify why relapse post-HSCT was not included in the company's base case and include a scenario analysis where

this is included in the model. The ERG suggests using the 47% from the HMRN data from TA591, if deemed appropriate by the company.

Scenario settings: In the Disease Complications sheet, functionality has been added to include the impact of a HSCT relapse for patients. Specific details of the scenario are outlined below in Table I.

Table I: Scenario B4 – inclusion of HSCT relapse

	Total costs	Total LYs	Total QALYs	ICER incremental (£/QALY)
Scenario				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	
Base case				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	

The utility decrement associated with a relapse is -0.01 which was derived by taking the difference in reported utility score for patients with AML from Leunis et al. (2014) and the general population utility reported by Ara et. al. (2011).

In this scenario the probability of relapse was assumed to be 47% and a one-off impact was assumed at week 52. Whilst the disutility impact is assumed to only effect a patient for 3-months, the costs of a relapse is assumed to be incurred for two years. The cost of a relapse (£55,529) was derived by taking the three-month cost of £6,375 for a HSCT relapse reported in TA451 (ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia) and inflating it to 2021 values. This 2021 value was then adjusted further to account for two years of treatment.

Treatment effectiveness

B5. Priority question. Please provide a comparison of the model and SOLSTICE outcomes (survival; number of CMV recurrences; number of CMV clearances; hospitalisations) for all the available time points in SOLSTICE (please see table A as an example).

Table A. Percentage of patients dead in the model and in SOLSTICE

	% death weighted by SOT and HSCT in the model		Difference in mortality	Trial		
Time (Weeks)	maribavir	IAT		maribavir	IAT	Difference in mortality
0	0.0%	0.0%	0.00%	0.0%	0.0%	0.0%
4	3.2%	3.2%	0.00%	3.4%	2.6%	-0.8%
8	5.4%	5.4%	0.00%	6.0%	4.3%	-1.7%
12	7.1%	7.5%	0.33%	-	-	
16	8.8%	9.4%	0.59%	-	-	
20	10.5%	11.2%	0.79%	10.7%	9.5%	-1.2%

Comparison of SOLSTICE and model outcomes are provided in Tables J-P below:

Table J: Mortality trace from the model versus mortality in SOLSTICE

	Mortality % in the model-weighted by SOT and HSCT		SOLSTICE trial mortality		Model trace vs SOLSTICE trial	
Time (weeks)	Maribavir	IAT	Maribavir	IAT	Maribavir	IAT
0	[redacted]					
4						
8						
12						
16						
20						

Table K: Clearance trace from the model versus clearance in SOLSTICE

Clearance	Clearance % in the model-weighted by SOT and HSCT		SOLSTICE trial clearance		Model trace vs SOLSTICE trial	
Time (weeks)	Maribavir	IAT	Maribavir	IAT	Maribavir	IAT
0	[redacted]		[redacted]		[redacted]	
4						
8						
12						
16						
20						

Table L: Clearance inputs used in the model vs clearance in SOLSTICE

Clearance	Clearance input used in the model		SOLSTICE trial clearance	
Time (weeks)	Maribavir	IAT	Maribavir	IAT
0	[redacted]	[redacted]	[redacted]	[redacted]
4				
8				
12				
16	[redacted]	[redacted]		
20				

^The values used in the model were converted into 4-week probabilities using the week 0-8 IAT clearance values from SOLSTICE

It is not possible to calculate the model trace for recurrence as some patients in the csCMV health state will not clear; as these patients are not tracked, the number of patients who recur cannot be calculated.

Table M: Recurrence requiring treatment inputs used in the model versus recurrence requiring treatment in SOLSTICE

Recurrence	Recurrence requiring treatment input used in the model		SOLSTICE trial recurrence requiring treatment	
Time (weeks)	Maribavir	IAT	Maribavir	IAT
0	[redacted]	[redacted]	[redacted]	[redacted]
4				
8				
12				
16	[redacted]	[redacted]	[redacted]	[redacted]
20				

^These values were converted into 4-week probabilities using the recurrence values for maribavir (26.0%) and IAT (35.7%) from the SOLSTICE trial.

Table N: Probability of hospitalisation used in the model versus the hospitalisation rate in SOLSTICE

Hospitalisations	4-week probability of hospitalisation in the model ^		Difference in hospitalisation	Rate of hospitalisation in SOLSTICE		Difference in hospitalisation
Health state – transplant type	SOT	HSCT		SOT	HSCT	
csCMV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n-csCMV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

^The 4-week probability of hospitalisation used in the model is the rate of hospitalisation from SOLSTICE converted into a 4-week probability.

Table O: Hospitalisation trace in the model (calculated using the total cohort of 1000 patients)

Hospitalisations	Maribavir		IAT	
Cycle	SOT	HSCT	SOT	HSCT
0	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]

Table P: Hospitalisation trace in the model (calculated using the number of patients alive in each cycle)

Hospitalisations	Maribavir		IAT	
Cycle	SOT	HSCT	SOT	HSCT
0	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]

B6.Priority question. Please conduct a scenario analysis where the primary outcome data from SOLSTICE (i.e. confirmed CMV viremia clearance at week 8) is used to estimate the first clearance events in the model. In other words, please remove 4 week outcomes from the model, and assume that the first cycle in the model after week 0 is week 8.

The scenario analysis is presented in Table Q below:

Table Q: Scenario B6 – week 0-8 clearance set to zero, and week 8 clearance set to response observed in each treatment arm at week 9 (maribavir 55.7%, IAT 23.9%)

	Total costs	Total LYs	Total QALYs	ICER incremental (£/QALY)
Base case				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	
Scenario				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	

This scenario results in a decrease in the ICER, compared with the base case in the Company Submission (£[redacted] /QALY). Takeda opted to use a four-week ICER to capture evidence of treatment response occurring before the primary endpoint date as illustrated in Figure 1 below.

Figure 1: Cumulative probability of first CMV viremia clearance within study week 8

Whilst removing the first cycle from the model improves the ICER, by using 4-week cycles, Takeda have ensured that the model better reflects the outcomes observed in the trial. In addition, the use of the 4-week cycles prevents the need to incorporate a half-cycle correction.

B7.Priority question. Please confirm what is the assumption on time elapsed since surgery when patients enter the economic model and discuss:

A. the potential discrepancy between the latter assumption and time since surgery for patients who enrolled in SOLSTICE (as requested in question A4). For example, the ERG is concerned that patients >3 months post-surgery are being exposed in the model to the full 52 weeks of increased risk post-surgery. Similar

issues are expected to be observed for the modelled time in hospitalisation due to surgery;

B. **why 52 weeks was the chosen time point for when patients enter the "dead/alive" model and if the company has a clinical rationale for specifically capturing the first 52 weeks after patients initiated treatment with maribavir in the model.**

A: As time since surgery was not captured in the SOLSTICE trial we sought clinical expert opinion to inform a plausible assumption with regard to the time period over which patients in the R/R CMV population are considered to be at risk of CMV reactivation. We also considered the approach taken in the NICE appraisal of letermovir for CMV (NICE TA591, 2019) and discussed with clinical experts the relevance of this to the R/R CMV population.

Clinicians considered 52 weeks to be a reasonable assumed duration for this period from the inititiation of treatment for those eligible for maribavir. The clinical experts also noted that some patients will continue to have reactivations beyond 52 weeks but as a simplifying assumption, a 52 week cut off was reasonable.

It should be noted that, although the assumption aligns with the NICE appraisal of letermovir for CMV (NICE TA591, 2019), the R/R population are a more severe risk group, and represent only a minority of the population modelled in TA591. This higher risk subgroup are likely to need continued treatment for longer and are more prone to needing hospitalisations, whether it be for intravenous anti-CMV treatment or for the management of complications such as graft rejection.

B: The choice to adopt a 2-state Markov model from 12-months onwards was decided through discussions with clinicians from Takeda and an advisory for maribavir (Takeda UK Ltd, 2021). The clinicians advised that the treatment of patients with CMV was not for an indefinite period and almost all patients would be off treatment at 12 months, this is because patients' immunity recovers overtime which results in natural clearance of CMV without the need for an intervention. For this reason, the model does not track CMV status beyond 12 months, and in the second stage (post 12-months) a 2-state Markov model with alive and dead states are used.

Clinicians (Takeda and advisory board experts) advised that continuing treatment beyond 12 months occurred in only rare cases and that it was a reasonable simplifying assumption to shift to the 2 states alive/dead Markov model post-12 months. Incorporating these rare cases in the model would be challenging for two key reasons: 1) the uncertainty around treatment effectiveness (clearance and recurrence) in the long term; 2) the absence of clinical guidelines for long-term treatment of CMV in an R/R population. Clinicians indicated that there would be considerable variation in practice in the treatment pathway beyond 12-months where physicians would determine treatment on a case-by-case basis. Given the expected variation in practice in these rare cases, predicting outcomes for patients would require more complex modelling methods (i.e., a discrete-event simulation) which is not feasible in the absence of robust clinical data.

It should also be noted that the approach (shifting to an alive dead model after 12 months) is consistent with the methods used in a recent health technology appraisal of a prophylactic anti-CMV agent by the National Institute for Health and Care Excellence (NICE TA591, 2019). In this appraisal, a decision tree was used for the first 12 months, and then a 2-state Markov model (Alive and Dead health states) for the remainder of the model horizon.

B8.Priority question. Please conduct a scenario analysis to reflect the different populations in SOLSTICE with regards to time since surgery. Based on clinical expert opinion, and the Hakimi et al. 2017 paper used by the company, the ERG suggests running the model for patients in SOLSTICE who had surgery: less than 3 months before starting treatment with maribavir; between 3 and 6 months; between 6 months and 1 year (if any); and after 1 year (if any), separately, given the expected change in risk of CMV events, graft loss, hospitalisation, and death associated with these periods. Please estimate the resulting total ICER by weighting each separate ICER by the appropriate proportion of patients in SOLSTICE who had surgery within the different periods of time (i.e. <3 months; 3-6 months; 6-12 months; >12 months; as requested in question A4.) Please ensure that patients entering the model do so according to their time since surgery (for example, patients in their <3 months since surgery would experience the same outcomes as patients

currently experience in the model from cycle 0, whereas patients in their 6-12 months post-surgery period would experience the outcomes associated with the current model at, for example, month 9 (which would become cycle 0 for these patients). Consequently, please ensure that the following outcomes are adjusted accordingly:

A. **post-surgery hospitalisation costs (the ERG has learned from clinical experts that SOT patients stay, on average, 4 to 6 weeks in hospital post surgery while HSCT patients stay in hospital for 3 to 5 weeks after transplantation);**

Time since transplant was not captured in the SOLSTICE trial, therefore this analysis is not possible. However, it should be noted that patients in SOLSTICE and the model are those who are R/R to existing treatments, and thus, it would be reasonable to assume that patients would be at least six weeks post-transplant before a patient is classified as R/R.

B. **survival rates;**

Time since transplant was not captured in the SOLSTICE trial, therefore this analysis is not possible.

C. **probability of graft loss (please see question B23) are adjusted accordingly;**

See response to B23.

D. **depending on the answer to question A4 (regarding the relative treatment effect of maribavir), please also adjust the rates of CMV clearance and/or recurrence according to time since surgery, if appropriate.**

Time since transplant was not captured in the SOLSTICE trial, therefore this analysis is not possible. It should also be noted that Takeda have been advised by clinicians that time since surgery would not be expected to be a factor of treatment efficacy. Rather, the fact that patients are classified as R/R means they have limited treatment options, and therefore, treatment response (clearance) is expected to be lower in this cohort compared with patients who have had their first CMV episode. The same is true for relapse following response (recurrence) which is expected to be higher in an R/R cohort. This is confirmed by the low rates of clearance (18.8% of patients achieved clearance at week 8), and high rates of recurrence (35.7% of patients had

recurrence requiring treatment after achieving clearance at week 8) observed in the IAT arm of the trial which best reflects current practice (Table 14.2.3.2.1 and Table 14.2.3.17 of the CSR respectively).

B9. Priority question. Please run a scenario analysis combining the analyses requested in question B6 and B8, making all the necessary adjustments in outcomes.

No additional scenarios were completed for B8, therefore, combining the scenarios requested for B6 with B8 is not possible.

B10. Priority question. Please conduct a scenario analysis using the KM data on confirmed CMV viremia clearance available from SOLSTICE to fit and extrapolate survival curves (according to NICE TSD 14) in order to estimate the proportion of patients with clearance in the model between week 0 and week 52 for each treatment arm.

The economic model incorporates an assumption that all patients who remain in the csCMV state will require treatment. In the first 8 weeks, the probability of clearance has been extracted directly from the SOLSTICE trial using 4 week cycles. After the first 8 weeks, patients remaining in the csCMV state are assumed to require retreatment where patients are treated with one of the four anti-CMV drugs that make up IAT. The efficacy of the IAT drug is assumed to have the same efficacy (treatment response) as was observed in the first 8 weeks. This is a reasonable assumption in an R/R cohort given that these patients have already been treated with one of the IAT drugs at the start of the SOLSTICE trial, therefore, already reflect a population receiving retreatment.

Using KM data to fit survival curves on clearance would not be an appropriate analysis for several reasons. First, patients can have bidirectional movement between response status i.e., a patient who achieves response can relapse and then achieve response again. Furthermore, given that the event of interest in the survival analysis would be time to clearance which is most prominent in patients during the on-treatment phase of the trial, the first 8 weeks of the data is the most robust estimator for clearance in the economic model (rather than an extrapolation of the first 8 weeks). It should also be noted that patients in the IAT arm have switched to

rescue arm and some patients have started alternative anti-CMV treatment. This means that extrapolating the time to response beyond week 20 will have many confounding effects such as patients switching to other lines of therapy, patients change of health states (response to recurrence). Unless all unmeasured confounders are adjusted in the model, the outcome of the analysis may lead to confounding bias and hence factors which are prognostic to the outcome of interest might not be predicted/estimated accurately.

B11. Priority question. Please conduct a scenario analysis using the KM data on CMV viremia recurrence requiring alternative treatment after first CMV viremia clearance at week 8 available from SOLSTICE to fit and extrapolate survival curves (according to NICE TSD 14) in order to estimate the proportion of patients with recurrence CMV in the model between week 0 and week 52 for each treatment arm.

CMV recurrence requiring alternative treatment data is available in the trial from week 8 onwards and up to week 20. For recurrence, only those patients that achieved clearance are at risk of having a recurrence over this time period. This reduces the patients at risk of recurrence, and extrapolation of this period is an inappropriate methodology.

B12. Priority question. Please explain why patients in the maribavir arm who are on treatment (before 8 weeks) and off maribavir treatment (everyone from week 9 to week 52) are assumed to have the same probability (that associated with maribavir treatment) of remaining in the n-csCMV state and the same probability of recurrence. Please provide the equivalent explanation for patients on IATs.

From week 4 to week 8, the probabilities for recurrence requiring treatment are 0.19 and 0.31 for the maribavir arm and the IAT arm, respectively. These probabilities determine the proportion of patients no longer in the n-csCMV state, and therefore, the proportion who remain.

After week 8, these probabilities are not the same as they are based on the data from week 8 to 20 in SOLSTICE, which are extrapolated up to week 52 to inform the remainder of the first phase of the model. The probabilities applied in the model after

week 8 up to week 52 are 0.10 and 0.14 for the maribavir and IAT arms, respectively.

Treatment-specific probabilities of recurrence requiring treatment were used as this was a key outcome demonstrated in the SOLSTICE trial, showing that maribavir treatment was associated with a lower requirement for subsequent anti-CMV treatment for a recurrent CMV episode.

Patients in the model who have a recurrence requiring treatment transition to the csCMV state and receive a subsequent IAT therapy at which point IAT-specific transition probabilities continue to be applied regardless of the initial treatment.

B13. Priority question. Please conduct a scenario analysis where patients in the maribavir and the IAT arms of the model in the n-csCMV state (off treatment) have the same background probability of experiencing events in the model. Given that the KM data on CMV viremia recurrence requiring alternative treatment after first CMV viremia clearance at week 8 available from SOLSTICE suggests that there is no difference in time to recurrence across treatment arms, the ERG suggests that the company pools the data in the two treatment arms to estimate the probability of recurrence (through fitting and extrapolating the pooled KM data according to NICE TSD 14). Alternatively, the ERG suggests that the company sources these data externally, according to other factors such as, for example, type of transplant; organ transplanted; type of immunosuppression treatment being received, etc.

CMV recurrence requiring treatment was an important outcome of the SOLSTICE trial, which demonstrated that maribavir was associated with a reduction in the proportion of patients requiring subsequent anti-CMV therapy to treat a recurrence following clearance of the initial CMV episode.

The KM plot referred to (see ERG Additional Request at the end of the CQ responses) demonstrates this difference in recurrence requiring treatment between the maribavir and IAT groups. There is some uncertainty in these estimates; however, the uncertainty of the probabilities applied in the economic model has been

captured within the probabilistic sensitivity analysis and, therefore, the data and its uncertainty has been appropriately captured within our analyses.
Furthermore, the use of survival analysis to extrapolate these data is not methodologically appropriate given the bidirectional transitions that apply within the Markov model. See response to B10 for more details.

B14. Priority question. A proportion of patients in the model seems to spend a clinically implausible time in the CMV state for the first 52 weeks of the model. For example, in the maribavir arm, about 5% of HSCT patients spend 52 weeks continuously in the CMV state. Therefore, please:

A) Discuss the clinical plausibility of this assumption;

Takeda received clinical advice that it is difficult to predict the duration of time that patients have CMV. Clinicians confirmed that there is a small proportion of patients who will have CMV for a prolonged period of time, but we note that due to fluctuations between health states these are not the same patients at each time point. Furthermore, it would be difficult to quantify this number. Due to limited evidence, Takeda are of the view that in current practice approximately 10%-12% of patients having CMV for prolonged periods of time is a reasonable reflection of current practice. Table R provides details of the proportion of patients in the cvCMV health state for 12 months.

Table R: Proportion of patients occupying the csCMV health state for 12 months

	SOT	HSCT
Maribavir	[redacted]	[redacted]
IAT	[redacted]	[redacted]

B) Conduct a scenario analysis where patients are not allowed to stay in the CMV state for longer than a clinically plausible period.

A limitation of a standard Markov modelling approach is the lack of memory and ability to track the past experiences of patients in the model. One method of implementing memory into the model is relaxing the Markov assumption and incorporating tunnel states. However, due to there not being a definitive clinical view (or published data) of the length of time a patient with R/R CMV will have CMV, incorporating tunnel states becomes increasingly problematic with no firm evidence for the appropriate number of 4-week tunnel states. In addition, the model would

become more complex, require more computational power with languages such as R becoming more appropriate rather than Excel.

Takeda are of the view enhancing model complexity would not be reasonable in this instance, and the 3-state Markov model developed as part of our submission is a pragmatic reflection of patient experience, and the overall structure was well understood and received by both health economists and clinicians when presented during advisory boards. Furthermore, it should be noted that the model retains the functionality to enter alternative recurrence probabilities to patients who have achieved clearance after their first treatment versus subsequent treatments. Takeda explored this functionality with clinicians but received advice that it would be most appropriate to use the SOSTICE data as the preferred input. For the reasons described above, Takeda have decided not to complete the scenario requested in B14.

B15. Priority question. The clinical experts advising the ERG explained that the number and probability of recurrence of CMV events after surgery (especially 1 year after surgery) are highly dependent on the type of organ transplanted (for SOT patients); the underlying cause of disease leading to surgery; and ultimately, the need for immunosuppressive treatment throughout patients' lives. Therefore, can the company please:

- **for the first 20 weeks after patients initiate treatment in the model: ensure that the number of CMV clearances and recurrences modelled in the first 20 weeks of the model approximately matches the number of CMV recurrences and clearances observed in SOLSTICE;**

Please see response to B5, it is not possible to calculate the model trace for recurrence as some patients in the csCMV health state will not clear; as these patients are not tracked, the number of patients who recur cannot be calculated.

- **between week 20 and week 52 of the model: use the extrapolated survival curves requested in B10 and B11 to estimate the probability of recurrence (and associated retreatment) and clearance;**

Please see response to B10 and B11

- **after year 1 in the model: consider modelling the probability of CMV recurrence separately for patients requiring lifetime intensive immunosuppression (for example, lung transplant patients) and therefore likely to have CMV recurrences, and those not requiring immunosuppression (such as HSCT patients without GvHST) and therefore unlikely to have CMV recurrence after year 1 (as is currently assumed in the model).**

Information on patients requiring immunosuppression and those that did not require immunosuppression are not available, however Takeda agree that it would be reasonable to assume that heart and lung transplant patients would require lifetime immunosuppression. Organ type could be a reasonable surrogate for immunosuppression status, however subgroup analysis of the SOLSTICE data by organ type are not available to allow this scenario to be modelled.

B16. Priority question. Clinical expert opinion provided to the ERG indicated that HSCT patients with chronic GvHST (i.e. unresolved GvHST at 100 days post surgery) have higher probability of CMV recurrence due to intense immunosuppressant treatment and are expected to not survive beyond 2 years after surgery. Therefore, please incorporate this subgroup of HSCT patients in the model assuming an equal proportion of GvHST in both treatment arms at baseline and based on pooled data on GvHST prevalence in SOLSTICE.

The presence of GvHST was not an exclusion criteria in the SOLSTICE trial, and Table 2 (response to A5 above) details the number of GvHST patients in the IAT and maribavir arms. Therefore the subgroup are already incorporated in the mortality data. The numbers are [redacted] with [redacted] ([redacted]%) acute and [redacted] ([redacted]%) chronic GvHD patients reported in the IAT arm and [redacted] ([redacted]%) acute and [redacted] ([redacted]%) chronic GvHD patients reported in the maribavir arm.

Clinical feedback has indicated that whilst there is an association between GvHD and CMV the causal nature of the relationship is unclear, particularly regarding the effect of CMV on the incidence of GvHD.

Furthermore, the causal relationship that CMV causes GvHD is not well evidenced in the literature, and Takeda were only able to identify a single study that supported the relationship (Cantoni 2010 doi: 10.1016/j.bbmt.2010.03.020).

Mortality

B17. Priority question. The company's approach to estimating survival in the model indirectly assumes a survival benefit associated with maribavir from week 8 - week 52 through separating survival rates by csCMV status. Given that survival in SOLSTICE was not statistically significantly different between treatment arms (and showed a numerical advantage in the IAT arm), please conduct a scenario analysis where mortality in the model from week 8 to week 52 is estimated in the same way as for week 4 to week 8 (i.e. differing only by type of surgery and not by CMV status and using data from SOLSTICE).

Takeda have received advice from clinicians that there is an important relationship between CMV outcomes and mortality. The model has been designed to capture this relationship. In fact, the ERG for TA591 noted that one of the key limitations of the model developed by the manufacturers for another CMV indication was the inability of the model to capture health state differences in mortality (TA591 Appraisal Consultation Committee Papers p 345). The model we have developed, which has been actively informed on by clinicians and health economic experts in the UK, includes the relationship between CMV and other important clinical outcomes such as mortality, utility and healthcare resource utilisation.

B18. Priority question. The ERG has consistently received clinical expert advice (which is consistent with the Hakimi et al. 2017 paper) that post-surgery mortality is expected to be higher for the first 6 months post-surgery, to then drop, followed by another considerable drop at the end of year 1 after surgery. However, in the economic model patients have the same risk of death from week 8 to week 52. Therefore, can the company please:

C) **Explore the use the overall survival KM data available from SOLSTICE to fit and extrapolate survival curves (according to DSU TSD 14) in order to estimate survival in the model between week 0 and week 52 for each treatment arm;**

D) **If the extrapolations do not result in a decrease in risk of death between month 6 and month 12, discuss the potential explanation and explore if there is any connection between the mortality rates observed in SOLSTICE and time since surgery for trial participants requested in question A4.**

Time since transplant was not captured in the SOLSTICE trial, therefore the analysis request in part C and D is not possible.

B19. Please conduct a scenario analysis where the sex- and age-specific general population mortality rates which have been summed to the transplant specific mortality probabilities from the trial are removed from the model (given that these are competing risks).

In the first 12 months, general population mortality has been removed, the results are presented below in Table S:

Table S: Scenario B19 - general population mortality in the first 12-months removed

ITT	Total costs	Total LYs	Total QALYs	ICER incremental (£/QALY)
Base case				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	
Scenario				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	

- Under this scenario, the ICER reduces only fractionally compared to the base case (£[redacted] vs £[redacted] in the base case)

Mortality - HSCT population

B20. Priority question. The company's approach to estimating survival in the model currently generates a clinically implausible scenario where patients in the HSCT population in the n-csCMV state have a probability of dying of 1.3% every 4 weeks from week 8 to week 52, but have an increase in mortality after week 52 to 1.5%. Clinical expert opinion provided to the ERG informed that HSCT-related mortality is at its highest during the first year post-surgery, therefore, having a mortality increase in the model after year 1 (particularly for n-csCMV patients) does not seem plausible. Please make the necessary amendments to the model inputs to portray a clinically plausible scenario.

In the scenario, the background HSCT mortality are applied from week 0 rather than week 52. The results are presented in Table T below.

Table T: Scenario B20 – background HSCT and SOT mortality applied from week 52 onwards and used for the background mortality for week 0 to 52

ITT	Total costs	Total LYs	Total QALYs	ICER incremental (£/QALY)
Base case				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	
Scenario				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	

B21. Priority question. Please provide the HMRN study used to inform the estimation of mortality in HSCT patients after week 52 in the model, and the data used by the company to infer that "after year 5, the HMRN data showed high attrition". Please ensure that the data provided reports patients' characteristics so that the comparability between the HMRN and the SOLSTICE populations can be studied.

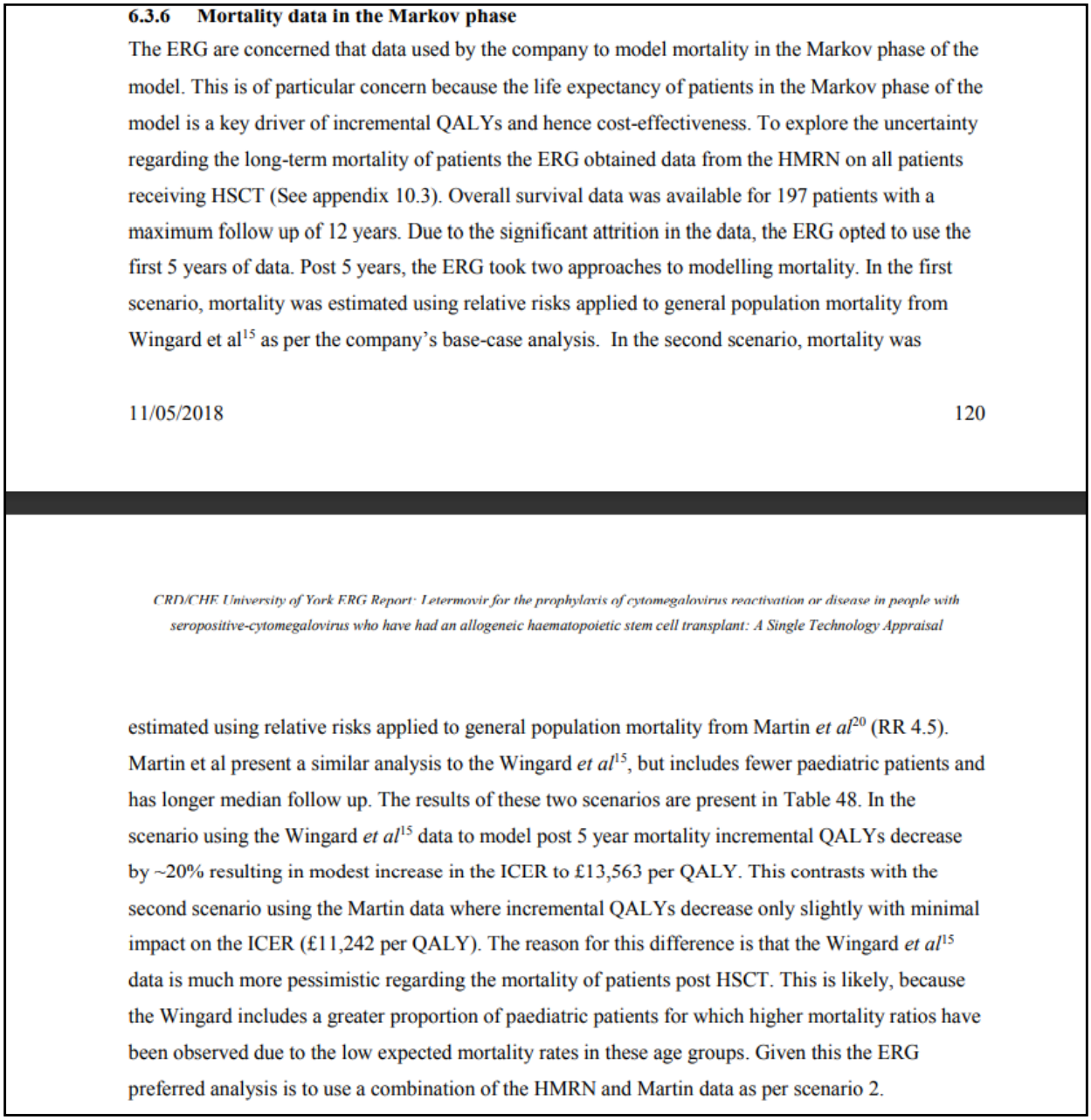
Takeda does not have access of these materials. Rather the materials were derived from the materials available on the NICE website for TA591, within the Appraisal Committee Papers. Below are screenshots of the relevant pages.

Figure 2: HMRN data from TA591

Years post SCT	Mortality rates in company base-case	ERG preferred mortality rates based on HMRN data
2	2.7%	19%
3	2.9%	11%
4	3.1%	5%
5	5.4%	6%
6	5.4%	8%

Source: TA591, Appraisal Consultation Committee Papers, page 36

Figure *3*: ERG comment on high attrition of HMRN data



6.3.6 Mortality data in the Markov phase

The ERG are concerned that data used by the company to model mortality in the Markov phase of the model. This is of particular concern because the life expectancy of patients in the Markov phase of the model is a key driver of incremental QALYs and hence cost-effectiveness. To explore the uncertainty regarding the long-term mortality of patients the ERG obtained data from the HMRN on all patients receiving HSCT (See appendix 10.3). Overall survival data was available for 197 patients with a maximum follow up of 12 years. Due to the significant attrition in the data, the ERG opted to use the first 5 years of data. Post 5 years, the ERG took two approaches to modelling mortality. In the first scenario, mortality was estimated using relative risks applied to general population mortality from Wingard et al[15] as per the company's base-case analysis. In the second scenario, mortality was

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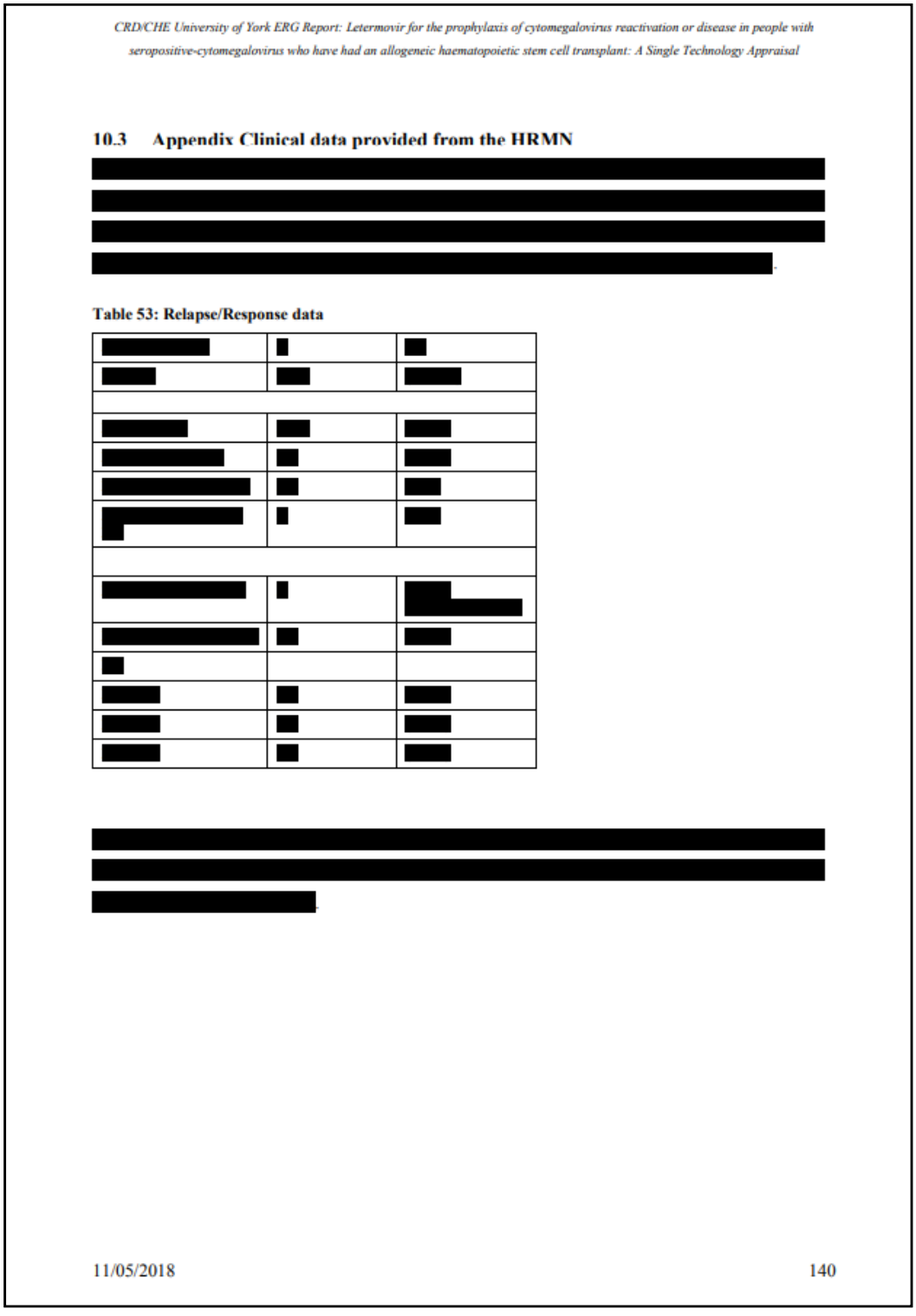
estimated using relative risks applied to general population mortality from Martin *et al*[20] (RR 4.5). Martin et al present a similar analysis to the Wingard *et al*[15], but includes fewer paediatric patients and has longer median follow up. The results of these two scenarios are present in Table 48. In the scenario using the Wingard *et al*[15] data to model post 5 year mortality incremental QALYs decrease by ~20% resulting in modest increase in the ICER to £13,563 per QALY. This contrasts with the second scenario using the Martin data where incremental QALYs decrease only slightly with minimal impact on the ICER (£11,242 per QALY). The reason for this difference is that the Wingard *et al*[15] data is much more pessimistic regarding the mortality of patients post HSCT. This is likely, because the Wingard includes a greater proportion of paediatric patients for which higher mortality ratios have been observed due to the low expected mortality rates in these age groups. Given this the ERG preferred analysis is to use a combination of the HMRN and Martin data as per scenario 2.

Source: TA591 Appraisal Consultation Committee Papers p 445

Figure 4: HMRN data redacted in the Appendix



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10.3 Appendix Clinical data provided from the HRMN

[redacted]

Table 53: Relapse/Response data

[redacted]		

[redacted]

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Source: TA591 Appraisal Consultation Committee Papers pp 465-466

Mortality - SOT population

B22. Please clarify why liver DCD transplants were not considered to estimate mortality in the long-term for liver transplanted patients given the information was

available in the NHS Blood and Transplant report used to inform the other long-term mortality estimates.

Liver DCD has now been included in the SOT mortality calculations with a minimal change in the ICER (Table U).

Table U: Comparison between previous base case and base case with liver DCD included in the mortality calculations

ITT	Total costs	Total LYs	Total QALYs	ICER incremental (£/QALY)
Existing base case				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	
Base case with liver DCD				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	

Transplants

B23. Priority question. The ERG disagrees with the company's interpretation and use of the SOT data from Hakimi et al. 2017. The CS reports a, "*2-year probabilities of graft loss of 9.41% in patients who do not have CMV within 3 months of SOT, and 10.81% in those who have CMV in this period*". Nonetheless the ERG notes that:

A. **the 9.41% and 10.81% estimates seem to be based on 1 year (and thus are not 2-year estimates) - therefore, please adjust these accordingly in the model.**

In the study by Hakimi et al., (2017) the authors state that the 'Transplant recipient were followed up to 24 months after the index date'. Table 3 reports rates of graft loss among patients with CMV who were followed up for at least 12 months. From this table we have estimated the risk of graft loss in a cohort with CMV, it is reported that 61 out of 2146 patients had a graft loss event. Takeda have made an assumption that these patients were followed up for the maximum 24 months,

however, we recognise there is a level uncertainty around this data so we have provided scenario results to reflect the outcome of the model assuming the events occur at 12 months. Using this alternative assumption results in an ICER of £[redacted] per QALY, compared to £[redacted] per QALY in the base case of the Company Submission (Table V).

Table V: Scenario B23A – 4-week probability of graft loss (n-csCMV) is adjusted for one year instead of two years.

ITT	Total costs	Total LYs	Total QALYs	ICER incremental (£/QALY)
Base case				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	
Scenario				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	

B. the paper provides the change in risk of graft loss by time of CMV event within 3 months of surgery; 3 months post-surgery; and 6 months post-surgery; however, the company is using the initial 3 months post surgery estimates (which have shown to be non-statistically significant across CMV and non-CMV patients) for the entire model time horizon. Therefore, please:

-take into account the mean time since surgery upon enrolment of patients in SOLSTICE (requested in question x) to estimate the risk of graft loss in the first 3 months of the model according to Hakimi et al. 2017;

- **make a distinction between the risk of graft loss in the first 3 months; post 3 months and post 6 months of the model where appropriate (and depending on time since surgery at baseline in SOLSTICE).**

Time since transplant was not captured in the SOLSTICE trial, therefore this analysis is not possible. In addition, Takeda have taken the most conservative estimate when incorporating the data from Table 4 of the study by Hakimi et al., (2017) into the economic model. If Takeda were to choose an alternative timepoint from Table 4 of

this study, it would result in the model incorporating an assumption in favour of maribavir.

C. **the paper provides the change in risk of graft loss by type of organ transplant. Given the layout of the model traces already allows for this distinction, please use the probabilities for organ failure for each type of organ in the model.**

The assumptions around graft loss reflects a conservative approach by Takeda. Hakimi et al., (2017) reported that overall, 202 out of 2146 patients had a graft loss event, which was then used to determine the risk of graft loss for patients in the n-csCMV health state.

If Takeda were to incorporate risk of graft loss by transplant type into the model, the results would further favour maribavir. With this assumption, the risk of graft loss would be lower in the n-csCMV state which is the state patients in the maribavir arm of the model spend the longest duration. The lower risk can be quickly assessed by using the data from Hakimi et al., (2017) and generating an updated weighted average 'overall' category which aligns with the transplant distribution in the trial. The weighted average method is illustrated in Table W below:

Table W: Weighted risk of graft loss using transplant specific values and assuming the Hakimi paper reported 12-month data

Transplant	SOLSTICE transplant distribution	Hakimi et al., (2017) Graft loss events in patients without CMV	Weighted risk
Heart*	[redacted]	4.17%	[redacted]
Kidney	[redacted]	11.77%	[redacted]
Lung	[redacted]	8.65%	[redacted]
Liver	[redacted]	3.72%	[redacted]
Other	[redacted]	4.17%	[redacted]
Total weighted risk	**9.29%**		
Company base case	**9.41%**		

*No data available for patients who have had a heart transplant, therefore 'Other' category has been used to assume the risk for heart transplant patients.

To provide further clarification on this point, Takeda have run 5 different scenarios, with an assumption made in each scenario that 100% of patients have either a heart, kidney, lung, liver or other transplant. Each transplant had its own respective risk of graft loss (without CMV) taken from Table 3 of Hakimi et al., (2017) with the assumption that the authors were reporting 12-month data rather than 24-month data. Then, using the SOLSTICE transplant distribution, a weighted average ICER has been calculated which results in an ICER lower than one submitted as part of the company submission (Table X).

Table X: Scenario B23C – applying transplant specific risk of graft loss from Hakimi (assumed to be 12-month data) with each transplant set to 100%

ITT	Total costs	Total LYs	Total QALYs	ICER incremental (£ /QALY)
Base case				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				
100% heart transplant^				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				
100% kidney transplant				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				
100% lung transplant				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				
100% liver transplant				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				
100% other transplant				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				
Weighted average ICER				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				

Note: The risk of graft failure for heart transplant was not reported in Hakimi, so the risk of graft loss from "Other" transplants has been used

B24. Priority question. Given that there were no graft loss events over the 20 weeks of SOLSTICE, can the company please:

A. discuss the potential relationship between the lack of graft loss events in SOLSTICE and time since SOT for patients enrolling in the trial;

Time since transplant was not captured in the SOLSTICE trial, therefore exploring this relationship is not possible.

B. explain why in the model graft loss could occur as early as week 4;

Though graft loss events were not observed in the SOLSTICE trial, the increased occurrence of these events in a post-transplant population who have CMV is well accepted by clinicians. Both clinicians and health economists participating on the advisory board for maribavir indicated that it was important for these events to be included given the important cost and quality of life implications. There are three options to consider:

1) exclusion of graft loss events in the model

2) inclusion of graft loss events in first cycle

3) inclusion of graft loss events from an arbitrary cycle

On the first option, omission of these events could result in the model having a major limitation given there is strong clinical view that CMV can create complications with a patient's graft, and in fact, it is one of the primary reasons for treating CMV with urgency. The second approach, and the approach taken by Takeda, allows the model to accommodate the importance placed on graft loss by clinicians and health economists during the maribavir advisory board. Furthermore, as illustrated by our response to B23 (part c), Takeda have taken a conservative position by not implementing transplant specific risk of graft loss, therefore, taking this information in totality, it would be reasonable to argue we have taken a reasonable and pragmatic approach in the modelling of graft loss events in the model. Finally, the third option would require a robust clinical explanation of why allowing graft loss events in a cycle other than the first would be more appropriate, Takeda has not heard or come across any such evidence.

C. **conduct a scenario analysis where graft loss can only start occurring 3 months after patients surgery.**

Time since transplant was not captured in the SOLSTICE trial and therefore this analysis is not possible. However, it should be noted that as the population reflects an R/R cohort, many patients would be expected to be ≥ 3-months post surgery.

B25. Priority question. Please conduct a scenario analysis where 0% of patients with graft failure do not receive a second transplant and make adjustments where needed for these patients outcomes (i.e. potential changes in mortality risk; need for dialysis, etc.).

Given that there are more graft loss events in the comparator arm, it could be reasonably argued that Takeda have taken a conservative approach when incorporating graft loss into the economic model. In a more complex model, we could have included a unique decision model pathway for each graft loss event type. In this model other important costs could have also been included such as carer related

costs, carer related disutility and other ongoing management costs borne by the healthcare system in both hospital and community settings. However, we decided to simplify our approach in the model by applying the cost of retransplant and the utility decrement associated with a graft loss immediately in a single cycle. This approach allows the model to retain its focus on CMV, reduce computational burden and allows NICE to assess the model's reliability more efficiently rather than conducting an assessment of decision models for heart, kidney, lung, liver and other transplant types.

Below in Table Y we present the scenario requested by the ERG where mortality risk following graft loss, retransplant costs and utility decrements are all set to zero. In this scenario it has been assumed all patients receiving a renal transplant require kidney dialysis. However, we emphasise this scenario to be interpreted with caution given the fact that graft preservation is a primary reason to treat CMV with urgency. Complete omission of the costs, utility and mortality risk associated with these events would be seen as a major limitation in an economic model for CMV.

Scenario settings: Retransplant mortality =0%, Retransplant costs = 0%, Retransplant disutility = 0, Patients on dialysis (with a graft loss) = 100%

Table Y: Scenario B25 – retransplant mortality, costs and disutility set to 0, and 100% of patients who experience a kidney graft loss event receive dialysis

ITT	Total costs	Total LYs	Total QALYs	ICER incremental (£/QALY)
Base case				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				
Scenario				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				

Costs

B26. Priority question. The ERG uncovered an error in the retreatment cost calculation traces which has led to an overestimation of the IAT retreatment cost. A factor of 5.14/8 is included in the retreatment acquisition costs in order

to account for the mean time on IAT treatment from the SOLSTICE trial; however, this factor is not active in the model as the control variable "dblControlScenarioDiscontinuationMethod" is set to "All" rather than "Individual". As such the cost of a full IAT treatment course is applied for each IAT retreatment assuming no early discontinuation. Please ensure that the acquisition costs of each retreatment with IAT reflect the mean time on treatment from the SOLSTICE trial. [see 'Markov engine (Maribavir)'!JA:JA, 'Markov engine (IAT)'!JA:JA, 'Markov engine (Maribavir)'!WG:WG, 'Markov engine (IAT)'!WG:WG]

We have checked the model and we can confirm that it does not have an error. The model makes an adjustment for time on treatment (ToT) between week 0 to 8 and for discontinuation between week 8 and 52.

1. For week 0-8 the ToT estimates are taken directly from SOLSTICE. This adjustment is seen in both the Markov Engines (Maribavir and IAT) and impacts the total costs considered for initial treatment. For SOT the adjustment is made in columns IW, IX and IY. For HSCT, the adjustment is made in columns WD, WE and WF. This adjustment is made as a one-off adjustment at the start of the model i.e., week 0 for the first 8 weeks of the model.

2. For week 8-52, there is an adjustment for discontinuation. This discontinuation rate is derived from the ToT values (i.e. 5.14/8 calculation highlighted above) from the SOLSTICE trial and impacts the total costs include for those receiving retreatment after week 8. A certain percentage of patients (calculated as 1- [5.14/8]) are considered to have discontinued and therefore this percentage of costs are removed from the calculations

B27. Priority question. Please discuss the clinical plausibility of a large proportion of patients remaining in the csCMV retreatment state of the model from week 8 up to week 52 given that the mean duration of IAT treatment in SOLSTICE was 5.14 weeks:

- **For SOT patients: 37.82% of patients, on average, are in the csCMV retreatment state in the maribavir arm between weeks 8**

and 52, while 47.84% of patients, on average, are in the retreatment state of the IAT arm between weeks 8 and 52. This corresponds to an average retreatment duration of 16.64 weeks for the maribavir arm and 21.05 weeks for the IAT arm. [column CF in the "Markov engine (Maribavir)" and "Markov engine (IAT)" sheets]

- **For HSCT patients: 35.83% of patients, on average, are in the csCMV retreatment state in the maribavir arm between weeks 8 and 52 while 45.33% of patients, on average, are in the retreatment state of the IAT arm between weeks 8 and 52. This corresponds to an average retreatment duration of 15.77 weeks for the maribavir arm and 19.95 weeks for the IAT arm. [column RM in the "Markov engine (Maribavir)" and "Markov engine (IAT)" sheets]**

A. Please ensure discontinuation from retreatment is captured by the model correctly (and consistently with time on IAT treatment reported in SOLSTICE).

The treatment of R/R CMV is cyclical and can result in multiple courses of treatment if CMV continues to reactivate. This means there will continue to be patients entering into the csCMV state when further anti-CMV treatment is required. It is therefore clinically plausible for there to be a substantial proportion of patients in the csCMV state for the first 52 weeks of the model. Note this does not mean that the same group of patients are continuously treated for this period. Transitions continue to occur between the health states as patients have recurrences followed by potential subsequent clearances.

The mean duration of 5.14 weeks in the IAT group of the SOLSTICE trial represents the mean duration of treatment within just one 8-week treatment cycle. Although the model does not explicitly model 8-weekly treatment cycles, the adjustment to treatment costs means that two 4-week model cycles represent the equivalent of 5.14 weeks of IAT retreatment.

For the SOT population, the estimated mean periods of retreatment of 16.64 weeks and 21.05 weeks for the maribavir an IAT groups, respectively, represent an average

of 2.08 and 2.63 treatment cycles, respectively. The actual time on treatment assuming 5.14 weeks of treatment within each 8-week cycle gives estimates of 10.69 weeks and 13.52 weeks of retreatment for maribavir and IAT groups, respectively.

For the HSCT population, the estimated mean periods of retreatment of 15.77 weeks and 19.95 weeks for the maribavir an IAT, respectively, represent an average of 1.97 and 2.49 treatment cycles, respectively. The actual time on treatment assuming 5.14 weeks of treatment within each 8-week cycle gives estimates of 10.13 weeks and 12.82 weeks of retreatment for maribavir and IAT groups, respectively.

B28. Priority question. The ERG has concerns that the daily administration costs applied for IV drugs in the IAT arm of the model are overestimated given that the NHS reference cost used pertains to complex chemotherapy at first attendance. This first attendance cost likely includes the costs associated with installation of a catheter among other initial costs associated with hospitalisation. Feedback from the ERG's clinical experts suggested that administration of the IV treatments for CMV (ganciclovir, foscarnet, cidofovir) would utilise an existing central line. The ERG's clinical experts estimated that 4 hours of ICU nurse time would be required per administration during which time a nurse would treat multiple patients. Guidelines for Provision of Intensive Care Services (FICM/ICS) outline a 2:1 patient to nurse ratio for level 2 patients (those which most align with the modelled population).

Therefore, please provide a scenario analysis wherein the administration cost for each IV treatment is calculated based on the PSSRU hourly staff cost of a critical care staff nurse (band 5) assuming that administration for two patients concurrently occupies 4 hours of nurse time.

In our approach for modelling administration costs, Takeda have followed the NICE methods guide used HRG costs from the National Cost Collection for the NHS.

Modelling administration costs based on PSSRU critical care staff nurse hourly cost would not capture the full cost of the administration of current IV anti-CMV therapies; these are complex drugs that are used off-label, therefore in addition to the hourly cost of a nurse, we would also need to consider administration time, supply chain

and pharmacy time (these therapies are weight dependant). Therefore we believe the approach taken is a more accurate reflection of the cost of NHS resource.

In the letermovir submission TA581, IV administration was assumed to incur a unit cost sourced from NHS Reference costs: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (SB14Z). We have used the same approach in our model.

B29. Priority question. The ERG's clinical experts explained that patients would not be re-hospitalised due to CMV disease recurrence alone (but only when an IV treatment is needed or when CMV disease is very severe). Therefore, the application of separate hospitalisation costs to patients in the csCMV and in the n-csCMV health states of the model is likely to overestimate the costs associated with IATs. Please conduct a scenario analysis where:

- **Only patients receiving IV treatment for CMV are hospitalised and incur a cost that relates to hospitalisation to receive an IV treatment only. Please ensure these costs are not double counted through the estimation of administration costs associated with the IV treatments in the model - please see question B28;**
- **If a proportion of patients with severe CMV disease requiring hospitalisation is included in this scenario, please ensure that the proportion of patients matches that of patients in SOLSTICE who required hospitalisation for severe CMV disease (see question A11) and that there is no double counting of costs associated with CMV hospitalisation and CMV treatment.**

Evidence from the SOLSTICE trial indicates that a proportion of patients both in the n-csCMV state and csCMV state are likely to be hospitalised ([redacted] of SOT patients and [redacted] of HSCT patients every 4-week cycle in the csCMV state and [redacted] of SOT patients and [redacted] of HSCT patients in the n-csCMV state). The risk of hospitalisation is greater in the csCMV state. Takeda have taken a conservative assumption around hospitalisation events in the model by assuming a high cost for the n-csCMV state.

We present an alternative scenario in Table Z where we use the average unit cost of a day case (£815.46) from the NHS Cost Schedule.

Scenario setting: cost of hospitalisation for n-csCMV patients set to the unit cost of a Day Case (£815.46)

Table Z: Scenario B29 – cost of hospitalisation for n-csCMV patients set to the average unit cost of a Day Case (£815.46)

ITT	Total costs	Total LYs	Total QALYs	ICER incremental (£/QALY)
Base case				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT	[redacted]	[redacted]	[redacted]	
Scenario				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]

B30. The British National Formulary records for ganciclovir and foscarnet specify the following dosing regimens:

- Ganciclovir treatment of cytomegalovirus disease in adult immunocompromised patients by intravenous infusion:
  "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."
- Valganciclovir for prevention of cytomegalovirus disease in adult patients following solid organ transplantation from a cytomegalovirus positive donor:
  "900 mg daily for 100 days (for 100–200 days following kidney transplantation), to be started within 10 days of transplantation."
- Foscarnet treatment of cytomegalovirus disease in adult patients by intravenous infusion:
  "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."

The 4-week cost of ganciclovir is estimated in the model assuming 5 mg/kg twice daily for 28 days, 900 mg twice daily is assumed for valganciclovir, while 60 mg/kg is assumed three times a day for 28 days.
Therefore, please explain why the loading dose of the ganciclovir and foscarnet regimens has been carried forward for the duration of each treatment and why valganciclovir 900mg is assumed to be taken twice rather than once daily. Please provide a scenario analysis wherein costs (acquisition and administration) of the specified maintenance doses are applied from day 14 of treatment.

The dosing regmens in the BNF indicate there is an induction dose and maintenance dose, however the indications of ganciclovir, valgancicovir in the BNF are not for post-transplant CMV treatment, they are for prophylaxis use. Foscarnet is used off-label and has no indication in CMV prophylaxis or treatment.

In UK clinical practice, (and confirmed at a 2021 Takeda advisory board) patients undergoing treatment for post-transplant CMV do not have a maintenance dose; instead in the UK the induction dose is used to treat CMV until clearance is observed.

The 900mg once a day valganciclovir dose is for the prevention of CMV disease post SOT transplant (e.g. prophylaxis use). In the treatment of CMV infection (which is off-label for post-transplant CMV), the dose is 900mg twice a day (the treatment dose for CMV retinitis as listed on the letermovir SmPC). This treatment dose was confirmed by clinical input at the Takeda 2021 advisory board and local treatment protocols (see http://www.nssg.oxford-haematology.org.uk/bmt/clin-man/B-4-0-cmv-reactivation.pdf for an example).

Quality of life

B31: Priority question. Please provide the details and the results of the mixed effects modelling analysis of SOLSTICE EQ-5D-3L IPD data which

demonstrated that, "*transplant type and response status had a significant effect on utilities and that treatment arm did not have a significant impact*".

Please see Section 3.4 of the IPD analysis report provided in response to question B2. The following summary of the observations from the mixed modelling is given in Section 3.4.2.1:

Observation from mixed modelling of EQ-5D-5L UK crosswalk HSUVs (utilities):

1. *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 27 -Table 31).*
2. *Transplant type as covariate added to response effect came out to be significant (Table 32).*
3. *Hence the mixed modelling analysis did not establish a significant effect of treatment on utilities (Table 33). Response effect and transplant type were significant on utilities from this analysis.*

B32: Priority question. Please provide descriptive statistics for the EQ-5D-3L data collected at each assessment, split by treatment arm and response status:

a) Mean;

b) Standard deviation;

c) Mean change from baseline at all points;

d) p-value and 95% confidence interval for mean change from baseline;

e) Number of responders (to the EQ-5D-3L questionnaire).

Table AA provides the mean and SE for the EQ-5D-3L at each assessment point.

Table AA: EQ-5D-3L by health state and time point

	Maribavir			IAT			Overall		
	m/n	Mean	SE	m/n	Mean	SE	m/n	Mean	SE
Clearance at Week 4									
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Yes	[redacted]								
Clearance at Week 8									
No	[redacted]								
Yes	[redacted]								
Clearance at Week 12									
No	[redacted]								
Yes	[redacted]								
Clearance at Week 16									
No	[redacted]								
Yes	[redacted]								
Clearance at Week 20									
No	[redacted]								
Yes	[redacted]								

B33: Priority question. The ERG noted that, in Tables 17 and 18 of the IPD appendix, the utility estimates were generally higher when response was assessed at week 8 than when assessed between weeks 0 and 20. Please explain:

A. why utility estimates used in the base case model were based on 8-week response rather than response between weeks 0 and 20.

The basecase utility estimates are based on the week 8 response as this aligns with the primary endpoint of the study. A sensitivity analysis was presented in the CS where the utility value from week 20 was provided.

Upon review of the data, it was apparent that the response was unstable in the first 8 weeks as patients were moving between response (clearance) and no response. At week 8 (time point for the primary endpoint), patient response status was deemed adequately stable and therefore the most appropriate time to establish the quality of life associated with response versus no response.

Beyond 8 weeks, there were also concerns regarding the impact of the rescue arm of the trial, which may potentially bias the outcomes if the more severe patients in the IAT group resort to rescue treatment. This could underestimate the difference

between the n-csCMV and csCMV utility estimates, as those who enter the rescue arm of the trial potentially had a more severe quality of life that would not have been captured within the csCMV esitmates when they reverted to maribavir rescue therapy.

B. if analysis was conducted in order to assess if time from baseline does not have a significant effect on the response and no-response utility estimates.

Please see Table AB for this analysis.

Table AB: Time from baseline utility values

	Maribavir N=235	**IAT N=117**
Timepoint		
Baseline		
n	[redacted]	[redacted]
Baseline Mean (SD)	[redacted]	[redacted]
Week 4		
n	[redacted]	[redacted]
Week 4 Mean (SD)	[redacted]	[redacted]
Week 4 responders		
n (responder)	[redacted]	[redacted]
Week 4 Mean (SD)-(responder)	[redacted]	[redacted]
Change from baseline (week 4-baseline)		
n	[redacted]	[redacted]
Mean change from baseline (SE) SD	[redacted]	[redacted]
95% CI of mean change from baseline	[redacted]	[redacted]
p-value difference in change (maribavir-IAT)	[redacted]	
Change from baseline (week 4-baseline) -responders		
n (responders)	[redacted]	[redacted]
Mean change from baseline (SE) SD	[redacted]	[redacted]
95% CI of mean change from baseline	[redacted]	[redacted]
p-value difference in change (maribavir-IAT)	[redacted]	
Week 8		
n	[redacted]	[redacted]
Week 8 Mean (SD)	[redacted]	[redacted]
Week 8 responders		
n (responder)	[redacted]	[redacted]

Week 8 Mean (SD)-(responder)	[redacted]	[redacted]
Change from baseline (week 8-baseline)		
n	[redacted]	[redacted]
Mean change from baseline (SE) SD	[redacted]	[redacted]
95% CI of mean change from baseline	[redacted]	[redacted]
p-value difference in change (maribavir-IAT)	[redacted]	
Change from baseline (week 8-baseline) -responders		
n	[redacted]	[redacted]
Mean change from baseline (SE) SD	[redacted]	[redacted]
95% CI of mean change from baseline	[redacted]	[redacted]
p-value difference in change (maribavir-IAT)	[redacted]	
Week 12		
n	[redacted]	[redacted]
Week 12 Mean (SD)	[redacted]	[redacted]
Week 12 responders		
n (responder)	[redacted]	[redacted]
Week 12 Mean (SD)-(responder)	[redacted]	[redacted]
Change from baseline (week 12-baseline)		
n	[redacted]	[redacted]
Mean change from baseline (SE) SD	[redacted]	[redacted]
95% CI of mean change from baseline	[redacted]	[redacted]
p-value difference in change (maribavir-IAT)	[redacted]	
Change from baseline (week 12-baseline) -responders		
n	[redacted]	[redacted]
Mean change from baseline (SE) SD	[redacted]	[redacted]
95% CI of mean change from baseline	[redacted]	[redacted]
p-value difference in change (maribavir-IAT)	[redacted]	
Week 16		
n	[redacted]	[redacted]
Week 16 Mean (SD)	[redacted]	[redacted]
Week 16 responders		
n (responder)	[redacted]	[redacted]
Week 16 Mean (SD)-(responder)	[redacted]	[redacted]
Change from baseline (week 16-baseline)		
n	[redacted]	[redacted]
Mean change from baseline (SE) SD	[redacted]	[redacted]
95% CI of mean change from baseline	[redacted]	[redacted]

p-value difference in change (maribavir-IAT)	[redacted]	
Change from baseline (week 16-baseline)-responders		
n	[redacted]	[redacted]
Mean change from baseline (SE) SD	[redacted]	[redacted]
95% CI of mean change from baseline	[redacted]	[redacted]
p-value difference in change (maribavir-IAT)	[redacted]	
Week 20		
n	[redacted]	[redacted]
Week 20 Mean (SD)	[redacted]	[redacted]
Week 20 responders		
n (responder)	[redacted]	[redacted]
Week 20 Mean (SD)-(responder)	[redacted]	[redacted]
Change from baseline (week 20-baseline)		
n	[redacted]	[redacted]
Mean change from baseline (SE) SD	[redacted]	[redacted]
95% CI of mean change from baseline	[redacted]	[redacted]
p-value difference in change (maribavir-IAT)	[redacted]	
Change from baseline (week 20-baseline) -responders		
n	[redacted]	[redacted]
Mean change from baseline (SE) SD	[redacted]	[redacted]
95% CI of mean change from baseline	[redacted]	[redacted]
p-value difference in change (maribavir-IAT)	[redacted]	

B34. Priority question. Please conduct a scenario analysis where the utility values used are based on the EQ-5D-3L data available for the entire follow-up period of SOLSTICE. The ERG preferred approach to undertake such request would be to conduct conduct a linear mixed effects regression to estimate the difference in EQ-5D-3L scores by response status and by treatment arm, using multiple imputation to account for any missing observations (and providing an assessment of the underlying missing at random assumption).

The method used to generate health state utility values using data from the mixed modelling analysis involved taking the number of patients records from table C1 of the IPD report (Table) and deriving a weighted average utility score using the EQ-5D values from table C2 of the IPD report (Table). Scenarios are provided in Tables AC - AE.

Table AC: Scenario B34 – utility weights

	Number of records			
Response	**IAT**	**% weight**	**Maribavir**	**% weight**
SOT	[redacted]		[redacted]	
HSCT	[redacted]		[redacted]	
Total	[redacted]	[redacted]	[redacted]	[redacted]
No Response	**IAT**	**% weight**	**Maribavir**	**% weight**
SOT	[redacted]		[redacted]	
HSCT	[redacted]		[redacted]	
Total	[redacted]	[redacted]	[redacted]	[redacted]

Table AD: Scenario B34 – utilities

Original utilities	**IAT**	**Maribavir**
Response	[redacted]	[redacted]
No response		
Weighted utilities (applied to both SOT and HSCT)		
Response	[redacted]	
No response		

Table AE: Scenario B34 – mixed modelling utility results

ITT	Total costs	Total LYs	Total QALYs	ICER incremental (£/QALY)
Base case				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				
Scenario				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				

B35. Priority question. The ERG's clinical experts have advised that the impact of surgery on patients' quality of life is expected to last for the 2 or 3 initial years after surgery. Please conduct a scenario analysis where the disutility value associated with SOT and HSCT applied to the mean UK population utility values in every model cycle after week 52 is only applied to year 2 and year 3 in the model.

Below are the results of the requested scenario with a decrement only applied for 2 years after model week 52. As the starting age of the model is 53 years, this scenario has been implemented by changing the background utility to general population utility from age 56 onwards. This means the transplant-related utility decrement is applied from age 54 (model week 52) to age 56 only. The outputs are presented in Table AF.

Table AF: Scenario B35 – background utility set to general population utility from age 56 onwards

ITT	Total costs	Total LYs	Total QALYs	ICER incremental (£/QALY)
Base case				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				
Scenario				
Maribavir	[redacted]	[redacted]	[redacted]	[redacted]
IAT				

As there is a mortality benefit in the maribavir arm, removing the longer-term utility decrement would be an assumption which favours the final ICER in the direction of maribavir. Takeda have heard from clinical experts that longer-term quality of life decrement would be expected in a patient cohort with CMV. Therefore, in agreement with these clinicians and the ERG for TA591, Takeda have implemented an approach which captures this longer-term utility decrement, with the acknowledgement that this is a conservative assumption.

Advice from clinical experts and patients suggest that the impact on quality of life can last beyond three years post-transplant, particularly in those that suffer chronic GvHD. These can result in patients needing to remain close to a toilet due to gut manifestations, remain away from direct sunlight (due to skin rashes and blisters) and lung problems requiring supplementary oxygen. All of these have a severe impact on daily living, self care and ability to work. Furthermore there are longer-term issues such as an increased risk of secondary malignancies post-HSCT, which can occur in up to 15% of patients 15 years after SCT with myeloablative conditioning (Danlylesko 2018 DOI: 10.1007/s11864-018-0528-y). There can be long-term infertility issues associated with significant psychological distress in HSCT survivors and their respective partner if they wish to conceive a child. (Tichelli 2013 doi: 10.1586/17474086.2013.816507.)

Studies have shown that in SOT patients, long-term (12 year) sustainability of the initial improvement in QoL post-tranplant decreases in time in most areas (physical distress, social/role function and personal function (Ruppert 2010 DOI: 10.1053/j.gastro.2010.06.043).

Additional request for clarifification questions

Figure 5: Kaplan-Meier data on the cumulative probability of first CMV viremia clearance at Week 4 to CMV viremia recurrence requiring alternative treatment by treatment group up to Week 8

The ERG have realised that the Company Submission does not give any detail about half-cycle corrections undertaken in the model, and it seems to us that

no such corrections were applied in the model and would like to ask an additional clarification question, if possible.

Please could you

A. **-confirm if a half cycle correction was used in the model, and if that wasn't the case, to provide a justification of why the adjustment wasn't made**

Takeda have used 4-week cycles in the first 12 months to capture the evidence of early clearance (see B6). The first 12 months captures the important transitions in the model where patients are moving between the csCMV and n-csCMV state. Takeda are of the view that the use of 4-week cycles in the first 12 months is sufficiently granular such that the model does not require a half-cycle correction.

B. apply a half-cycle correction in the model.

See part A response.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	Anthony Nolan and Leukaemia Care

3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Anthony Nolan** saves the lives of people with blood cancer. Founded in 1974 as the world's first stem cell register, we're motivated by a mother's determination to save her son, Anthony. Now saving three lives every day, our charity is a lifesaving legacy. By growing our register of potential stem cell donors, conducting ground-breaking research into improving transplant outcomes, and providing outstanding support and clinical care for patients and their families, Anthony Nolan cures people's blood cancer and blood disorders. The responses in our submission relate specifically to the impact of life-threatening drug-resistant infections on people who require, or who have received, a stem cell transplant. A stem cell transplant is a potentially curative treatment for patients with blood cancers and blood disorders, and usually their last chance of survival. Anthony Nolan's main source of income is the provision of stem cells for transplant to NHS providers, collected from volunteer donors. Voluntary income (and fundraising events through Anthony Nolan Trading Ltd (ANTL) comes from a wide variety of generous supporters, including individual giving, legacies, community and events fundraising, corporate support, and charitable trusts. This helps to fund our ground-breaking scientific research, and growth and diversity of the stem cell donor register. **Leukaemia Care** is a national blood cancer charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 15% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf.

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.	Anthony Nolan: None Leukaemia Care: None
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	Anthony Nolan: None Leukaemia Care: None
5. How did you gather information about the experiences of patients and carers to include in your submission?	The evidence included in this submission has been collected in a collaborative effort between Anthony Nolan and Leukaemia Care. Our submission is based on feedback received from people personally affected by a refractory or resistant post-transplant CMV infection, and expert clinical advice: ● We produced a joint survey for patients and carers who have personal experience of a refractory or resistant post-transplant cytomegalovirus (CMV) infection. Some telephone interviews were also conducted to gather evidence for this submission. ● At the time of submission, there were 12 completed consultation responses by patients who believe themselves to have experienced refractory or resistant post-transplant CMV infections and 4 telephone interviews. Additionally, some of the quotes used in this submission have come from interviews with patients who have experience of a CMV infection that may not have been resistant or refractory. However, these have still been included where appropriate as they represent an important aspect of the patient experience.

	● This was shared with Anthony Nolan's Patients and Families Panel; via the Anthony Nolan Patients and Families Facebook page and social media channels; and to Leukaemia Care's network via direct email and the Leukaemia Care social media channels.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Living with CMV** ● The impact that a refractory or resistant post-transplant cytomegalovirus (CMV) infection has on patients, carers and their loved ones can vary greatly. ● Of the 13 patients who responded to our joint Survey, 70% described living with a refractory or resistant post-transplant CMV infection as difficult or very difficult. 70% of those surveyed also had to stay in hospital for longer or return to hospital as a result of their infection. In some, the CMV infection itself can have few symptoms and it was reported by some to be found during routine blood tests. For others a range of symptoms can be experienced, both as a result of the infection and the side-effects of the treatments of currently available drugs. Common symptoms and side-effects can include fatigue, a fever, issues with airways, Graft Vs Host Disease, and issues with the patient's eyes and bowel. Low blood counts are also common which can result in increased risk of infection and prolonged bleeding, as well as fatigue and breathlessness. **Mental health and wellbeing impact** Often, refractory or resistant post-transplant CMV infections can persist over a prolonged period and references to this were a common theme among survey respondents. Many discussed a *'never ending cycle*' of being unwell, particularly in the context of the infection happening post-transplant. Others described feeling they *'might never leave the hospital'*. Returning to hospital or extending their stay in hospital due to CMV reactivation had a significant effect on the mental health and well-being of patients and their carers. Some discussed being worn down by consistent bad news, focusing so hard on recovering from the transplant that they were 'r*eally knocked back*' by their infection. One commented that they *"had very little quality of life, no social life, unable to work and lost the bit of independence I had built up after leaving hospital after the transplant. I was very depressed and anxious."* A common theme was that many patients described taking a *"massive step backwards"* in their recoveries. They saw the stem cell transplant as a potentially lifesaving treatment, which was hindered by the CMV. Many

	also expressed extreme concern about their immune system, talking about their worries around about their ability to fight off the virus. One family member of someone with a CMV infection described, at times, feeling '*depressed and helpless'*, particularly at the prospect of their loved one running out of options for the treatment and care. The time frames of hospitalisation for those surveyed ranged from none, to over 4 months. Some commented that they felt very unwell as a result of the CMV infection and resultant treatment, with one even commenting that their CMV infection caused them to give up work, leaving them so weak following treatment. They remained very unwell for around 5 months. 70% of survey respondents felt that their CMV infection hindered their post-transplant recovery, this ranged from long-term late effects of their infection and treatment, with some saying it has taken '*5 years to get back to be something like my old self and return to working*' with the CMV contributing to their slow recovery. Other survey respondents noted not showing any symptoms, with the infection picked up during a routine blood test. **Effect on daily life** Patients told us that living with CMV infection had a significant effect on their day-to-day life, including their ability to look after themselves, have a social life, travel, and live independently. ● Some spoke about their inability to work or drive, or the need to repeatedly return to hospital because of their CMV infection. One said, 'h*aving this occur for the last 2 years has been very depressing and due to weekly CMV check-ups has stopped me having holidays and any quality of life as well as disrupting my working life'.* ● Another spoke about their desire to have a '*want a normal life, not tied to a hospital.'* Some also explored having more time off work than anticipated, due to their CMV infection, leading them feeling without a purpose. Some even lost or left their jobs. ● One patient told us that they had to quit their *'dream job'* due to their resistant CMV infection. '*Every time I thought I was almost out the other side I got told I still had high CMV levels…in the end I realised I had no choice but to give up work until I got better, I wasn't prepared for tha*t'. ● Another patient said that their original sick note from their consultant was six months. However, they needed a donor lymphocyte infusion, a procedure which could not happen until the CMV reactivation was under control, which took longer than this period: *"In the end it was so long that I hadn't been at work that they couldn't give any end date for my treatment so they [work] just asked me to leave.*

	They told me I had to come to a disciplinary or agree to resign… The CMV meant the difference between having a job and not having a job." **Carers** The experiences of carers mirrored that of the patients consulted for this survey. Carers described feeling helpless and frustrated by their loved one's constant health complications with one carer saying that they *'feared they would never have their lives back*'.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There has been little accessible clinical data on the use of Maribavir in for treating refractory or resistant cytomegalovirus infection in people who have received a stem cell transplant, it is hoped that maribavir provides an alternative treatment for aggressive infections, where existing comparators have either reduced efficacy or unbearable side effects. The patients that we spoke to had experience with a range of treatments currently available treatments on the NHS. Patients reflected on the need to take multiple drugs for their treatment over a prolonged period as well as the need to go into and remain in hospital for extended stays. Many indicated their preference for drugs that could be taken at home, allowing them to spend less time in hospital. Many of the patients that we have heard from also discussed the side-effects that they experienced from drugs to treat a CMV infection. The hope for many is that if any new drugs are more effective or better tolerated than existing, aggressive treatments, this could have a positive impact on patients. **Foscarnet** Patients who had experienced foscarnet told us that it is '*the real problem'* with their CMV infection and one said that it was '*the most difficult part of their entire treatment, including chemotherapy and the transplant'*. They went on to say that '*I asked the doctor if there was any other option for medication as I didn't want to take it again*'. Patients highlighted the difficulty surrounding the length of the intravenous treatment which takes five hours a day for nine days. Following this, there is a one-to-two hour *'flush'* during which fluid is given to the patient. In the words of a patient: '*It's a really long procedure; you say goodbye to a day every time you go in.'* On the more extreme level, a patient described the feel as *"Burning all the way up my arms and into my heart… I thought my veins were going to disintegrate."* Another said that they *'would initially be sick for a couple of hours, and it would last a couple of hours after that, but you'd feel ill and you'd know you had the next dose coming the next day.'*

	One patient described that treatment with foscarnet meant they *"felt as though I was buzzing like an electric shock. My body felt as though it was vibrating at 50Hz. They realised afterwards that that was a sign of my kidneys failing. They had to stop treatment on that particular occasion. It made me feel really poorly for some time afterwards".* **Valganciclovir** Patients reported that it was mentally beneficial to have a treatment which can be taken orally at home, rather than via a drip at the hospital. However, one said that valganciclovir had a negative impact on blood counts, with a significant drop in neutrophils. The patient then had a small cut that got infected which *'tracked up the vein in my arm… that had me admitted for another week, as it was turning to sepsis*.' Another patient, whose son was just 18 months old when they had their transplant, told us that valganciclovir 'u*sed to just make me really ill. When we were potty training [the patient's son] thought the toilet was just for being sick into, because all he had seen was me being sick into it.'* **Ganciclovir** A carer told us that they perceived ganciclovir as being a key factor in the first stem cell transplant not grafting properly, having a huge effect on their mental health. **Cidofovir** Cidofovir has also been shown to cause significant side-effects in patients, with patients claiming that experiencing cidofovir was worse than foscarnet, despite only being a one-day treatment compared to the nine days required for foscarnet. The cidofovir caused such eye inflammation in one patient that when healthcare professionals tried to give them a second dose, the patient told the HCPs 'you're not taking my vision away as well, it's not happening'. **Letermovir** One patient described letermovir as '*making a significant difference*' to them. Having already contracted a resistant CMV infection during their first transplant they were worried about getting another *'persistent and unpleasant'* CMV infection when they needed a second transplant. However, this patient described letermovir as essential in warding off the CMV during their post-transplant recovery. **Quality of life** Intravenous treatments (ganciclovir, foscarnet, and cidofovir) mean that patients are required to spend time in hospital, either on a day basis or as an in-patient. This had a significant effect on patients' ability to have

	a normal life, including working and having a social life. Patients expressed a preference for oral 'at home' treatments that allowed them to leave the hospital. Many patients described how problems with their well-being were exacerbated by the treatments for CMV infections and their side effects.
8. Is there an unmet need for patients with this condition?	Many patients commented that they would have benefited from being able to be treated at home, outside of a hospital setting. Many respondents referred to the period of time that they were hospitalised, in total amounting to several months for some and showed a strong preference for any treatment options that enable them to get better outside of a hospital setting. More treatments are required therefore that satisfy this criteria, e.g. oral therapies. Patients also highlighted the extremely unpleasant side-effects of many of the currently available medications and noted the importance of any new treatment that is better tolerated or has fewer serious and unpleasant side-effects.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	In Leukaemia Care's 'Living with Leukaemia' survey 50.5% of AML and ALL patients said that oral tablets were their most preferred method of treatment from a list of options. Maribavir, as an oral therapy, is therefore likely to improve patient's experience of treatment and quality of life, due to it's convenience and the option to take it at home. In the Shire clinical trial 55.7% of patients achieved confirmed clearance of CMV DNA at the end of week 8 after taking maribavir. This is compared with 23.9% of patients who achieved the same while on the other comparator anti-CMV treatments. Given the challenges with comparator treatments, patients favour another option for the treatment of drug-resistant CMV infection. Another treatment option is a particularly acute need for those who may have tried all the comparator treatments already or may be unwilling to try them based on their previous experiences with existing treatments.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Maribavir is only being recommended for those over 12, meaning some will not be able to benefit from the availability of this treatment. The main disadvantage of maribavir is that the total number of serious adverse events in the clinical trial is not markedly lower than the comparators. However, as mentioned in the previous section, maribavir does perform better than comparators in terms of its effectiveness at virus clearance and patients often tell us in surveys that they prioritise prolonged life over tolerable side-effects of a treatment. They are typically willing to endure side-effects if it means they have a chance of improved/lengthened survival.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others?	Those who are being treated after multiple lines of other therapies have a significant unmet need, since cytomegalovirus can be extremely debilitating and even life threatening. However, this does not remove the unmet needs of other populations who are resistant to one or two lines of other therapies, since these treatments are known to have significant side effects and quality of life impacts, as previously described.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We have not identified any equality issues.

Other issues	
13. Are there any other issues that you would like the committee to consider?	The costs of treating someone affected by a refractory or resistant post-transplant CMV infection is significant. Often, this requires extended in-patient stays in hospital (some patients told us that they had more than 30 days in hospital over several reactivations of CMV), several rounds of expensive medicines as well as follow up care and support. Use of more efficacious treatments for severe CMV infections could therefore reduce the overall cost of treating a stem cell transplant patient, both as in-patients and within the community.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- All current treatments have toxicity, which are significant in terms of the quality of life impact upon patients.
- Refractory or resistant post-transplant CMV infections have serious effects on a patient's quality of life, can delay their post-transplant recovery and result in extended in-patient stays.
- The experience of refractory or resistant post-transplant CMV infections, and its associated effects, can have a significant psychological impact for both patients' recovery and their families.
- The costs of treating someone affected by a refractory or resistant post-transplant CMV infection can be significant.
- Patients favour a treatment that can be administered orally; there is the potential for this to have both quality of life and cost saving benefits for maribavir over other treatments.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	British Association for the Study of the Liver (BASL) / British Society of Gastroenterology (BSG) / British Liver Transplant Group (BLTG)

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	BASL is the National Association for hepatology. BASL is dedicated to advancing knowledge and understanding of the biology and pathology of the liver for the optimal care of patients. BASL is composed of interested individuals from clinical medicine, clinical and basic research and allied professions. The British Liver Transplant Group (BLTG) sits under the BASL umbrella. BASL is funded through membership and through running its annual scientific meeting and other educational events.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Cytomegalovirus (CMV) is a herpesvirus which can cause infection and tissue-invasive disease in immunocompromised patients after solid-organ transplantation. The aim of treatment would be to prevent CMV disease and improve end organ damage should it have progressed to that extent.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Serial CMV PCR is an objective measure of the degree of viraemia and response. In patients with CMV disease, I would consider titres having fallen below 10% of the initial titre at diagnosis (one Log10 drop) and if end-organ damage is clinically and biochemically improving to be indicators of treatment response.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is an unmet need if there is resistance to ganciclovir, foscarnet and cidofovir but in my view, in liver transplant patients, such a need for Maribavir would be rare.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	The treatment will vary slightly on the solid organ transplant (SOT). For liver transplant recipients, management involves reducing immunosuppression where possible and giving oral (eg valganciclovir) or intravenous antiviral drugs (eg ganciclovir) depending on the severity of illness.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Many liver transplant units in the UK will have local guidance. Other guidance; Razonable R, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019 Kotton CN, Kumar D, Caliendo AM et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation. 2018 Jun;102(6):900-931 British Transplantation Society. The Prevention and Management of CMV Disease after Solid Organ Transplantation. July 2015. Available from https://bts.org.uk/wp-content/uploads/2016/09/14_BTS_CMV_3RDE-1.pdf

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathways of care are not well defined and will vary between centres in the UK and also with the organ transplanted.
• What impact would the technology have on the current pathway of care?	It is proposed that Maribavir would be used to treat refractory or resistant CMV infection after transplant so could be an additional option in this scenario.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is a proposed new anti-CMV agent but could be incorporated in current treatment strategies.
• How does healthcare resource use differ between the technology and current care?	I can't comment fully on this but I would not expect healthcare resource use to differ greatly from current care. I also note that Maribavir is an oral preparation so if patients were well, it could be administered as an outpatient.
• In what clinical setting should the technology be used? (For example,	This would be used in specialist care eg transplant teams.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	I can't comment fully on this but I would think very little and would revolve more about dissemination of product characteristics and when it should be used.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Possibly. I note the recently completed phase III trial on ClinicalTrials.Gov (NCT02931539) and the FDA Briefing Document October 2021. The phase III trial demonstrated that maribavir was statistically superior to Investigator Assigned Treatment (IAT) for the primary endpoint which was clearance of CMV DNA from plasma in a population which had refractory CMV and some who had CMV resistance. In a subgroup analysis in patients who had 'refractory' disease' there was no statistical significance however over IAT.
• Do you expect the technology to increase length of life more than current care?	Unlikely
• Do you expect the technology to increase health-related quality of life more than current care?	Only potentially in the small number of patients who would require its use

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I can't comment fully on this. It would be expected it could be used in patients with resistance/refractory disease to current treatments but I am aware of the subgroup analysis referred to in the FDA briefing report above.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It is an oral preparation which would negate the need for inpatient care if the patient was well yet had resistant/refractory disease. Maribavir targets the UL97 kinase which phosphorylates ganciclovir and aciclovir so these drugs should not be used in combination.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	CMV viral loads (often PCR) are used to guide when to start and stop treatment. This would continue and not be different to current practice.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Unable to comment on this.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Provided Maribavir is proven to be effective in the treatment of patients who have resistant or refractory disease in the context of SOT this could have a significant impact as options are currently limited for this group.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	See previous comment.
• Does the use of the technology address any particular unmet need of the patient population?	Again, please see comment above.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	I can't comment fully on this but from the FDA briefing report there would not appear to be any over and above what could be expected by currently offered treatments.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	I haven't seen the full trial protocol for NCT02931539 but reviewing the information available on clinicaltrials.gov it would seem similar to current UK practice with the choice of antivirals given. Treatment duration was for 8 weeks which is often longer than needed but is the same for both arms.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes should be reduction in viral load and/or improvement in clinical symptoms and biochemistry as relevant. The primary outcome in the trial seems reasonable; 'Confirmed CMV viremia clearance was defined as plasma CMV DNA concentration less than (<) lower limit of quantification (LLOQ) that is, <137 International Units per milliliter (IU/mL) when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive postbaseline samples, separated by at least 5 days. '
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I can't comment fully on this.
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	I haven't seen the full trial analysis so can't comment on this.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No issues any different to current care.
21b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
22 Are ganciclovir with foscarnet and ganciclovir with hyperimmune globulins	Ganciclovir and foscarnet are part of established practice. Hyperimmune globulin has been reported in conjunction with ganciclovir eg to treat pneumonitis (George MJ, Use of ganciclovir plus cytomegalovirus immune globulin to treat CMV pneumonia in orthotopic liver transplant recipients. Transplant Proc.

considered part of established clinical practice in the NHS in England?	1993;25:22). This would not be considered to be standard practice however. It is referred to in the American guidelines referenced earlier by Razonable et al that they may be used as an adjunct to antiviral drugs in transplant recipients with resistant CMV disease but the evidence is weak/low.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Maribavir is an oral preparation and therefore has ease of administration
- There is a need in the small numbers of patients with resistant or refractory disease who have had a solid organ transplant provided Maribavir is demonstrated to be effective
-
-
-

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**UK Renal Pharmacy Group (UK RPG)**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ **X** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **X** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**UK RPG is integrated sub-group within UK Kidney Association (UKKA) and UKKA provide secretariat support to RPG. RPG has a membership elected Executive Committee and is a voluntary, membership organisation for specialist clinical pharmacists working within renal medicine and solid organ transplantation (renal and pancreas). The group receives financial support from corporate pharmaceutical companies which is used to fund educational learning for its members through F2F meetings, virtual meetings, learning tools (online training). UK RPG also writes and maintains UK Renal Drug Database and Renal Drug Handbook.**
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	**No**

manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Main treatment aim is to treat ganciclovir resistant/refractory CMV disease in SOT. (Val)Ganciclovir will remain first line prophylaxis and treatment of post-transplant CMV disease. However, in the rare cases of ganciclovir refractory/resistant CMV disease, maribavir offers an excellent second line treatment over current usual second line agent foscarnet. Drug resistance is suspected if cumulative (Val)Ganciclovir exposure >6 weeks and treatment failure after >2 weeks of ongoing full dose (Val)Ganciclovir
7. What do you consider a clinically significant treatment response? (For example, a	Clinically significant treatment response is control of CMV disease – with continuous reduction in CMV viral load and CMV disease symptom control. In order to stop CMV disease treatment, CMV viral load should be at low level, defined locally in my centre as 2.3 Log(10) copies/ml (less than 200 copies/ml).

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Maribavir offers a significant improvement and advance in currently available treatment options. Also maribavir is an oral agent so would remove need for patient central line access which has additional infection risk in immunocompromised individuals. Most patients require an extended treatment duration >8 weeks to manage CMV resistant disease, and there are associated morbidities with IV access.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	In SOT – usual second line treatment is intravenous foscarnet, which is nephrotoxic and myelotoxic. Cidofovir is also used but has had intermittent supply issues. Maintaining drug availability and supply for a life threatening infection is paramount. High dose IV Ganciclovir can also be used but often myelotoxic. CMV IVIg is rarely used due to significant cost burden and poor evidence in treatment of refractory/resistant disease. Foscarnet is an IV treatment dosed according to renal function. It has an initial induction treatment phase and then reduces to a maintenance phase to control disease. Dose usually requires weekly dose adjustment due to impact on renal function. Average treatment duration is approx. 8-10 weeks adjusted according to CMV viral load response. Furthermore, long term intravenous treatment can result in prolonged in-patient hospital stay. Some patients are able to be trained to self-administer foscarnet

	intravenously and once well enough can be discharged home with IV self-administration devices (e.g. Baxter Intermates®). Oral maribavir treatment will offer significant patient benefit and organisational benefit – staff time saved training/observing patients to self-administer, aseptic services costs to make up and fill IV devices. There is also an environmental benefit from saving on plastic administration lines, plastic infusion bags/devices. British Transplantation Society (BTS) has a national guideline for CMV treatment in solid organ transplantation, this guideline is currently being updated. https://bts.org.uk/wp-content/uploads/2016/09/14_BTS_CMV_3RDE-1.pdf
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – maribavir will be low usage (1% kidney transplant patients) and only for patients with suspected/confirmed ganciclovir resistant CMV disease. It will not be first line treatment for CMV disease in SOT. It will only be prescribed in secondary care under transplant specialist advice and with involvement of infectious disease clinicians.
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Main benefit as an oral agent it will reduce administration burden to NHS staff and patient. It will also reduce patient morbidity from drug induced renal toxicity. As an oral agent it is likely to expedite patient discharge (once patient well enough for discharge) as there is no need for self-administration training/or home IV care package. It is non-nephrotoxic which is a significant benefit. Both foscarnet and cidofovir are contraindicated in poor renal function. Some patients experience disabling side effects with foscarnet (e.g. extremity paraesthesia). Rehabilitation from drug induced paraesthesia can be significant and can result in

	extended inpatient stay and intense physiotherapy/rehabilitation. Use of maribavir would avoid risk of this significant side effect.
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare	Maribavir will be easier to use as it is an oral agent.

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No further additional testing over testing used during conventional treatment.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	

quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes innovative as it is an oral agent and its use will reduce inpatient stay.
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the	Maribavir has a good safety profile with no evidence of myelosuppression or nephrotoxicity. Main reported side effects include dose related taste disturbance and GI related symptoms e,g. diarrhoea and nausea. This side effect profile is different to other available agents which all affect renal function, and hence this is

management of the condition and the patient's quality of life?	a treatment advance especially for renal transplant cohort. In patients with renal dysfunction avoiding use of a known nephrotoxin is always clinically preferable.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials	

but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	
21b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions	
22 Are ganciclovir with foscarnet and ganciclovir with hyperimmune globulins considered part of established clinical practice in the NHS in England?	Ganciclovir with foscarnet can be used, but often in UK foscarnet is used alone as second line treatment. Dual agent therapy may be used if foscarnet alone has adversely impacted on renal function. CMV IVIg (hyperimmune globulin) is rarely used, if at all, in UK practice for treatment of refractory/resistant disease due to high cost and paucity in efficacy data.
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your submission. • Oral agent so will significantly reduce treatment burden for NHS staff and patient • Improved tolerability and reduced patient morbidity over existing treatment agents as non myelotoxic and non-nephrotoxic. • Low usage in renal transplant recipients (approx. 1%) for treatment of ganciclovir resistant/refractory CMV disease • No requirement for indwelling IV catheter for drug administration, which removes risk of associated line-related morbidities and will reduce hospital in-patient stay. •	

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BMJ TAG

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

STA Report

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; drafted the summary and clinical results sections
Ben Mayer	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; drafted the background section and critiqued the company's literature review
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Conor Hickey	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and assisted with drafting the economic sections

All authors read and commented on draft versions of the ERG report.

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List of Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ANC	Absolute neutrophil count
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BSBMT	British Society of Blood and Marrow Transplantation
BSH	British Society for Haematology
BTS	British Transplantation Society
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Conformité Européenne
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
CRD	Centre for Reviews and Dissemination
cCMV	Clinically significant cytomegalovirus
CSR	Clinical study report
cs-recurrence	Clinically significant-recurrence
CUA	Cost-utility analysis
DBD	Donor after brain death
DCD	Donation after circulatory death
DNA	Deoxyribonucleic acid
EAC	Endpoint Adjudication Committee
EBMT	European Society for Blood and Marrow Transplantation
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ER	Endoplasmic reticulum
ERG	Evidence Review Group
FACT-BMT	Functional Assessment of Cancer Therapy - Bone Marrow Transplantation
GORD	Gastro-oesophageal reflux disease
GvHD	Graft-versus-host disease
HCST	Hematopoietic stem cell transplant
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRG	Healthcare resource group
HRU	Healthcare resource utilization

HSCT	Haematopoietic stem cell transplant
HTA	Health technology assessment
IAT	Investigator-assigned anti-CMV treatment
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IPD	Individual patient data
IQR	Interquartile range
IRR	Incidence rate ratio
ITT	Intention-to-treat
IV	Intravenous
LLOQ	Lower limit of quantification
LOS	Length of stay
LYG	Life years gained
MBV	Maribavir
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Multiple myeloma
NHS	National Health Service
NHSBT	National Health Service Blood and Transplant
NICE	National Institute for Health and Care Excellence
NR	Not reported
nCMV	Non-clinically significant Cytomegalovirus
ONS	Office of National Statistics
OTUS	Outcomes, treatment patterns and healthcare resource utilization studies
PAS	Patient access scheme
PCR	Polymerase chain reaction
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Oral
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	Short form-36
SF-36v2	Short form-36 Version 2
SLR	Systematic literature review

SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SOT	Solid organ transplant
TEAE	Treatment emergent adverse events
TTO	Time-trade off
UK	United Kingdom
US	United States
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Impact of time since transplant on the clinical data and economic model	3.2.1.2, 3.3
2	Trial conduct and design leading to uncertainty and potential overestimates of maribavir efficacy	3.2.1, 3.2.2.9, 3.3
3	Assumption of time elapsed since transplant at baseline in the model	4.2.2, 4.2.4, 4.2.6
4	Structural assumptions in the company's model	4.2.4
5	Overestimation of recurrences in the model	4.2.6.1, 4.2.6, 4.2.6.2.1, 4.2.6.2.1.1
6	Modelling of mortality in stage 1 Markov	4.2.6.3
7	Modelling of mortality in stage 2 Markov	4.2.6.3.4
8	Modelling of graft failure	4.2.6.4
9	Modelling of disease complications	4.2.6.5
10	Estimation of utilities	4.2.8
11	Estimation of costs	4.2.9

The ERG-recommended changes to the economic model, together with additional requests for clarification, are described in detail in Section 6 of the report. Given the ERG's conclusion that the company's model is currently unfit for purpose, the ERG does not have a preferred ICER.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the probability of clearance in the first 2 cycles of the model (i.e., 8 weeks), which in turn leads to a lower probability of graft loss and better survival.
- Decreasing the probability of recurrence after week 8 for maribavir patients who achieved clearance at week 8. This also leads to a lower probability of graft loss and better survival.

Overall, the technology is modelled to affect costs by:

- Its higher unit cost compared to IATs.
- Decreasing the probability of recurrence and associated costs of treatment and disease management.
- Decreasing the probability of patients being hospitalised due to CMV.
- Decreasing the probability of graft loss and associated complications.

The modelling assumptions that have the greatest effect on the ICER are:

- The probability of recurrence.
- The duration of the stage 1 Markov model.
- The assumption around time since transplant at baseline in the model.

1.3 The clinical effectiveness evidence: summary of the ERG's key issues

Table 2. Issue 1. Impact of time since transplant on the clinical data and economic model

Report section	3.2.1.2 and 3.3
Description of issue and why the ERG has identified it as important	Time since transplant is an important prognostic factor with a decreasing risk of CMV infection (recurrence), graft loss and mortality with an increasing time since transplant. Mean time since transplant was imbalanced between the treatment arms in SOLSTICE, with a longer time since transplant favouring maribavir, in the overall trial population as well as in the HSCT and SOT subgroups. Importantly, any difference in time since transplant between the trial population, the modelled population and patients in UK clinical practice may affect the generalisability of the clinical and cost effectiveness results.
What alternative approach has the ERG suggested?	The ERG suggests the company re-analyses its clinical data adjusting for the imbalance in time since transplant between the treatment arms and implement these results in an updated economic model. The ERG also suggests that the company clarify its proposed position for maribavir and include that analysis in the economic model as well as providing the cost-effectiveness results from the SOLSTICE trial (with appropriate analyses of the clinical data).
What is the expected effect on the cost-effectiveness estimates?	Correcting the imbalance in mean time since surgery is likely to increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion may confirm the generalisability of the trial data to clinical practice.

Abbreviations: Abbreviations: CMV, cytomegalovirus; ICER, incremental cost-effectiveness ratio.

Table 3. Issue 2. Trial conduct and design leading to uncertainty and potential overestimates of maribavir efficacy

Report section	3.2.1, 3.2.2.9, and 3.3
Description of issue and why the ERG has identified it as important	• A large proportion of patients in the IAT arm were assigned to an anti-CMV treatment for which they had confirmed resistance. This is likely to lead to an underestimate of clearance in the IAT arm and therefore an overestimate of the relative efficacy of maribavir compared to what would be expected in clinical practice. • The outcome data for clearance and clinically relevant recurrence informing the economic model are based on retrospective *post hoc* analyses at a higher risk of bias. • The assessment of clinically relevant recurrence is highly subjective and at a high risk of bias due to the open label trial design and the need for alternative anti-CMV treatment at the discretion of the investigator. • During the trial period there was an increasing amount of missing data for the outcomes of clearance and clinically relevant recurrence. With outcome data captured as response rates, the large amount of missing data is likely to lead to conservative estimates of events in both treatment arms without providing a robust estimate of the uncertainty around the estimates.
What alternative approach has the ERG suggested?	Using KM data (rather than response rates) for the primary outcome in the trial for clearance and the pre-specified analyses for recurrence (rather than *post hoc* analyses of other time points) in the economic model will provide more robust estimates of the clinical efficacy of maribavir.
What is the expected effect on the cost-effectiveness estimates?	The assumptions the company makes in its estimates of clearance and recurrence are like to favour maribavir. As such, using the approach suggested by the ERG is likely to increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	Using KM data for the primary outcome in the trial for clearance and the pre-specified analyses for recurrence in the economic model will provide more robust estimates of the clinical efficacy of maribavir. However, the issues created by the IAT assignment at randomisation and the assessment of clinically relevant recurrence are unlikely to be resolved with additional evidence or analyses.

Abbreviations: CMV, Cytomegalovirus; HSCT, Hematopoietic stem cell transplant; SOT, Solid organ transplant; IAT, investigator-assigned antiviral therapy; GvHD, graft-versus-host-disease; ICER, incremental cost-effectiveness ratio.

1.4 The cost-effectiveness evidence: summary of the ERG's key issues

Table 4. Issue 3. Assumption of time elapsed since transplant at baseline in the model

Report section	4.2.2, 4.2.4, 4.2.6
Description of issue and why the ERG has identified it as important	The ERG remains unclear on the company's assumption of mean time elapsed since transplant at baseline in the model. Currently, the model seems to estimate the cost effectiveness for maribavir in r/r patients when given immediately after surgery, which fails to: - Reflect the mean time since transplant for the overall trial population (mean time since surgery at baseline in SOLSTICE for SOT patients was [redacted] days for maribavir and [redacted] days for IAT patients, respectively. For HSCT patients time since transplant was shorter and the difference between the treatment arms was less pronounced: mean of [redacted] days for maribavir and [redacted] days for IAT). - Reflect the r/r setting, where patients could receive prophylaxis

	after transplant, and would only initiate treatment with maribavir after failing on first line IAT. Furthermore, SOLSTICE data on mean time since transplant for SOT patients are in direct contradiction with the company's main modelling assumption that no CMV events occur 12 months after transplant. The evidence available in literature and clinical expert opinion provided to the ERG consistently reported that patients' clinical outcomes (such as mortality and risk of graft loss) vary as time from transplant elapses. Crucially, the ERG heard from its clinical experts that the probability of recurrence is unlikely to depend on the type of treatment on which patient achieved clearance (i.e., maribavir vs IAT), but instead to be dependent on time since transplant and on the level of lifelong immunosuppression needed by patients. Therefore, the ERG considers that time since surgery is a fundamental aspect of the cost effectiveness of maribavir.
What alternative approach has the ERG suggested?	1. The company should capture the cost-effectiveness of maribavir in the trial population, where the mean time from transplant at baseline in the trial is appropriately modelled. 2. The company should clarify the intended use for maribavir in the treatment pathway. If the company's value proposition is that maribavir should be given as early as possible for r/r patients in the UK, then: - For SOT patients – clinical expert opinion should be used to inform the minimum time when patients, on average, would be eligible to start maribavir. The ERG has heard from its experts that this is likely to vary according to patients receiving prophylaxis (in which case the minimum period could be 4 months) or not (in which case the minimum period could be 1 month). - For HSCT patients – since the approval of letermovir by NICE (TA591), the majority of patients receive at least 100 days of prophylaxis with letermovir before moving on to a first line treatment with IAT. Therefore, similar to SOT patients, the ERG recommends that clinical expert opinion is used by the company to inform the minimum time when patients, on average, would be eligible to start maribavir after HSCT in UK clinical practice. The company should ensure that all model inputs are adjusted to the assumptions made around time since transplant (as detailed in the list of recommendations from the ERG in Section 6 of the report).
What is the expected effect on the cost-effectiveness estimates?	It is difficult to anticipate the effect of the proposed changes on the ICER. It is, however, likely that maribavir becomes less cost effective as time from transplant elapses, given the reduction in risk for some of the clinical outcomes upon which maribavir has an effect. Therefore, the ERG anticipates that the ICER for the trial population will be higher than the ICER for the UK population.
What additional evidence or analyses might help to resolve this key issue?	The analyses suggested by the ERG.

Abbreviations: CMV, Cytomegalovirus; HSCT, Hematopoietic stem cell transplant; SOT, Solid organ transplant; IAT, investigator-assigned antiviral therapy; GvHD, graft-versus-host-disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; r/r, resistant or refractory.

Table 5. Issue 4. Structural assumptions in the company's model

Report section	4.2.4
Description of issue and why the ERG has identified it as important	The stage 1 Markov model (first 52 weeks of the model) allows for multiple clearance and recurrence episodes per patient at various time points, however the outcomes reported in SOLSTICE were clearance (week 8 clearance being the primary outcome in the trial and week 4 clearance being a retrospective *post-hoc* outcome); and recurrence after first clearance (i.e., only one episode of recurrence after one episode of clearance). The company did not present any evidence to substantiate why patients could have multiple recurrences in the model between 8 and 52 weeks. The company is using 20-week data from SOLSTICE on first recurrences to model multiple recurrences outcomes up to week 52 based on the assumption that outcomes observed 4-weekly during the 20-week follow-up of SOLSTICE would be observed until week 52. Currently, having the stage 1 Markov model extended to 52 weeks does not add any methodological or conceptual benefit to the economic analysis, and only introduces a bias in favour of maribavir as the estimates of treatment effectiveness used by the company at week 20 are in favour of maribavir. Even though the company assumed that patients switch to IATs after failing on maribavir, the company also assumed that the probability of a CMV recurrence was that associated with the most recent treatment received, which means that patients who achieved a first clearance with maribavir still experienced the lower probability of recurrence associated with maribavir even when off treatment. The switch from the stage 1 to the stage 2 Markov (dead/alive) model after week 52 results in 35.56% of patients in the maribavir arm and 38.98% of patients the IAT arm having CMV at week 52 and being cured at week 56. The ERG considers that this stark drop lacks face validity and that it is more likely that the proportion of CMV cases decreases more gradually over time, until CMV is resolved. Finally, the company's implicit assumption that no CMV events occur after 12 months in the model is in contradiction of the SOLSTICE data for SOT patients, and of clinical expert opinion.
What alternative approach has the ERG suggested?	Using the SOLSTICE KM trial data, and some of the company's current assumptions it is possible to model patients' pathway through a "full cycle" of events (i.e., first clearance, first recurrence and second clearance) in the model without compromising data integrity (see Issue 5 for more details on this). The company should obtain clinical expert opinion and/or external data to validate the average frequency of subsequent "full cycles" of events in order to capture the likelihood of SOT patients having multiple episodes of CMV recurrences throughout their lives. The duration of the stage 1 Markov model should be determined by the duration of these cycles. The company can then repeat these cycles of events as appropriate in the model.
What is the expected effect on the cost-effectiveness estimates?	The ICER is expected to increase as the probability of further recurrences decreases in the stage 1 Markov model. However, the opposite would be true for the increase in recurrences for the stage 2 Markov for SOT patients.
What additional evidence or analyses might help to	The analyses suggested by the ERG, however, if the company does not use the recommended KM data, and instead uses the point estimates for the

resolve this key issue?	probability of clearance and recurrence at specific times in SOLTICE – the ERG recommends that the company changes the stage 1 Markov to be 20 weeks to effectively model the trial events only.

Abbreviations: Abbreviations: CMV, Cytomegalovirus; HSCT, Hematopoietic stem cell transplant; SOT, Solid organ transplant; IAT, investigator-assigned antiviral therapy; GvHD, graft-versus-host-disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 6. Issue 5. Overestimation of recurrence in the model

Report section	4.2.6.1, 4.2.6, 4.2.6.2.1, 4.2.6.2.1.1
Description of issue and why the ERG has identified it as important	The company's use of recurrence data from SOLSTICE is fundamentally flawed and introduces a bias in favour of maribavir. The company's assumption that the 4-weekly probability of recurrence at the end of the trial period remains the same until week 52 in the model, combined with the assumption that patients who achieved clearance with maribavir have a lower probability of recurrence (regardless of how long they have been off treatment), considerably overestimates recurrences in the model as well as the benefit associated with maribavir. The ERG heard from its clinical experts that the probability of recurrence is unlikely to depend on the type of treatment on which patient achieved clearance, but instead to be dependent on time since transplant and on the level of lifelong immunosuppression needed by the patient. Furthermore, the KM data on time to recurrence after first clearance at week 8 from the SOLSTICE CSR suggests no statistically significant difference between recurrence for maribavir and IAT patients.
What alternative approach has the ERG suggested?	By maintaining its current base case assumption that maribavir and IAT patients receive 8 weeks of treatment, after which they will change to an IAT, or a new IAT dose, respectively, if they do not achieve clearance, the company can model a "full cycle" of events. In order to do this, the ERG recommends that the SOLSTICE KM data are used: ○ The KM data on the primary trial outcome (clearance at week 8) associated with maribavir and IAT would determine the proportion of patients achieving first clearance in the model before or at week 8, in each treatment arm, respectively; ○ The KM data on recurrence after first clearance (at week 8) requiring an alternative treatment would determine the proportion of patients with a first recurrence in the model. If the company wishes to use the KM data for maribavir and IAT arms separately, the ERG recommends running an additional scenario analysis where the data are pooled, therefore assuming the same probability of recurrence across treatment arms; ○ The KM data on clearance at week 8 associated with IAT would determine the proportion of patients with second clearance in both treatment arms. The ERG recommends that the company fits and extrapolates the KM data for at least the second clearance event (but ideally for all clearance and recurrence events in one "full cycle") in order to account for 100% of patients having cleared their second recurrence. This will ensure that patients can leave the second CMV event state at a clinically plausible rate.
What is the expected effect on the cost-effectiveness	The ERG conducted two simplified scenario analyses whereby the probability of recurrence in the model after week 8 (when patients are no

estimates?	longer on treatment with maribavir) is assumed to be the same for the IAT and the maribavir arms. In the first scenario the ERG assumed that the probability of recurrence in both treatment arms was that used in the IAT arm (14%); and in the second scenario the ERG assumed that the probability was that associated with maribavir (10%). Both scenarios increased the company's ICER. The first scenario increased the ICER from £15,337 to £70,964; whereas the second scenario increased the ICER to £47,704.
What additional evidence or analyses might help to resolve this key issue?	The company should report the statistical significance of the difference between the KM curves on time to recurrence after first clearance at week 8 from the SOLSTICE CSR. If the company does not use the recommended KM data, and instead uses the point estimates for the probability of clearance and recurrence at specific times in SOLTICE – the ERG recommends that the company changes the stage 1 Markov to be 20 weeks to effectively model the trial events only. The company should correct the estimates being incorrectly used as detailed by the ERG's critique in Section 4.2.6.2.1. and should allow 100% of patients to clear their recurrence at a clinically plausible rate in the model. Furthermore, the company should also use the available SOLSTICE data on clearance at week 8 (instead of week 4) to model clearance.

Abbreviations: Abbreviations: CMV, Cytomegalovirus; HSCT, Hematopoietic stem cell transplant; SOT, Solid organ transplant; IAT, investigator-assigned antiviral therapy; GvHD, graft-versus-host-disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 7. Issue 6. Modelling of mortality in stage 1 Markov

Report section	4.2.6.3
Description of issue and why the ERG has identified it as important	The ERG disagrees with the company's approach of using SOLSTICE data to model a differential in survival related to CMV status. The trial data (which, by default, incorporates the difference in CMV events across treatment arms) shows no significant difference in overall mortality for maribavir and IAT patients, thus suggesting that the CMV-related mortality in the trial was also not significantly different (and numerically similar) across treatment arms. Nevertheless, the ERG agrees with the company's clinical experts' view that CMV occurrence is a key prognostic factor of mortality; however, the ERG notes that this is likely to be dependent on how long after transplant the CMV event occurs. The Hakimi *et al*. 2017 paper looked at the risk of mortality over 12 months following the index date of a CMV infection for SOT patients. The index dates included patients with a CMV event within the first 3 months after transplant, between 3-12 months; and between 6 -12 months. The results of the study show that the annual probability of death during the first year after transplant depended on: type of organ transplanted; presence or absence of CMV; and time of CMV event. A trend could also be noted where having CMV events later after transplant were associated with a lower risk of death vs having CMV events earlier after transplant (7.12% if CMV occurs within 3 months after surgery vs 4.10% if CMV occurs 6 months after surgery). The same trend was observed for patients without CMV (2.84% vs 0.96%), suggesting that the risk of mortality (when no CMV is present) also decreases over the first-year post-transplant.

	Despite the presence of CMV being a determinant predictor of mortality over the first-year post-transplant in Hakimi *et al.*, the data from SOLSTICE indicated that CMV did not impact mortality. For SOT patients, this could potentially be explained by the mean time since transplant at baseline in SOLSTICE ([redacted], respectively). Furthermore, the company assumed that after week 8, the 4-weekly probability of death was 2.5% for SOT patients with CMV and 1.3% for patients without CMV. This represents an increase in the probability of death from week 4-8 (of 0.97%) for both patients with and without CMV. This increase does not seem clinically plausible in light of the data observed in Hakimi *et al.*; the NHS blood and transplant report and clinical expert opinion and again, overestimates the benefit associated with maribavir on survival in the model. The data on survival post HSCT transplant provided in TA591 shows that the rate in mortality also decreases over the first-year post HSCT, with about 28% of patients having died at the end of year 1. Finally, the ERG disagrees with the company's methodological approach of summing sex- and age-specific general population mortality rates to the mortality rates observed in SOLSTICE given these are competing risks. During clarification, the ERG asked that the company removed the former from the analysis. The impact on the final ICER was small.
What alternative approach has the ERG suggested?	The ERG recommends using SOLSTICE KM data to model survival for the stage 1 Markov model. The KM data should be separated only by type of surgery (i.e., SOT vs HSCT). The company should fit survival curves and extrapolate the KM data in order to estimate survival until the end of the stage 1 Markov model. Subsequently: 1. For the trial population - if the company can substantiate, with existent data available in literature, that approximately over 1 year after SOT, CMV still impacts patients' mortality, then the company should use these data to conduct a scenario analysis to estimate a differential in mortality according to CMV in the SOT population. The same is applicable for HSCT patients, although, for approximately over 100 days since transplant. 2. If the company's proposition is that maribavir should be given as early as possible for r/r patients - the company's KM data on survival for the stage 1 Markov model should be adjusted to reflect mortality earlier after transplant; and by CMV status, sourced from available literature (e.g., for SOT patients, the company could use the HRs estimated in Hakimi *et al.* on the impact of mortality on presence of CMV vs no CMV).
What is the expected effect on the cost-effectiveness estimates?	It is difficult to anticipate the effect of the proposed changes on the ICER. It is, however, likely that maribavir becomes less cost effective as time from transplant elapses, given the reduction in risk of mortality.
What additional evidence or analyses might help to resolve this key issue?	The ERG strongly recommends that the company provides KM data on mortality in SOLSTICE by type of transplant (i.e., HSCT vs SOT) so that the committee can understand the difference in mortality in both populations.

Abbreviations: Abbreviations: CMV, Cytomegalovirus; HSCT, Hematopoietic stem cell transplant; SOT, Solid organ transplant; IAT, investigator-assigned antiviral therapy; GvHD, graft-versus-host-disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 8. Issue 7. Modelling of mortality in stage 2 Markov

Report section	4.2.6.3.4
Description of issue and why the ERG has identified it as important	The ERG disagrees with the long-term assumption made for both the SOT and the HSCT populations. That is, the mortality estimates observed for the last year of data available in the NHS Organ Donation Annual Activity Report and in the HMRN data, respectively, would be observed for the remainder of the model (or until general mortality background rates were higher than the transplant-specific rates). Given that the data available indicates that transplant-specific mortality decreases with time since transplant, the company's approach is likely to overestimate the mortality of transplanted patients. In TA591, the ERG noted that the life expectancy of patients in the long-term Markov phase of the model was a key driver of incremental QALYs and hence cost-effectiveness. The ERG for TA591 used the same HMRN data to estimate mortality in the first 5 years post-HSCT, however, after 5 years the ERG ran two scenario analyses assuming different relative risks (RR) in relation to the general population mortality to estimate mortality. The more relevant scenario for this current STA is the scenario using the RR applied to general population mortality from Martin *et al*. (RR 4.5). The ERG anticipates that the same issue would apply to SOT patients, although possibly to a lesser extent, given that the company assumed that the 10-year mortality rate (as opposed for the 5-year rate for HSCT patients) would be observed for patients' lifetime (or until the general population background mortality rate is higher). During clarification, the ERG also noted to the company that the transition from the mortality in the stage 1 Markov to the stage 2 Markov model for HSCT patients implied an increase in mortality rates from 1.3% to 1.5%, which did not reflect a clinically plausible scenario (given that data suggests the opposite trend). The company replied by undertaking a scenario analysis where, "*the background HSCT mortality from the HMRN data was applied from week 0 rather than week 52*" (therefore, excluding the SOLSTICE mortality data from the model). This scenario increased the company's base case ICER from £15,337 to £18,884. Nonetheless, the ERG is unclear if this means that the company also removed the differential in mortality by CMV status from the model.
What alternative approach has the ERG suggested?	The ERG recommends that the company ensures that: - The mortality in the phase 2 Markov model reflects the appropriate time since surgery. - Overall survival is not overestimated after 5 years for HSCT patients and after 10 years for SOT patients. In order to do this the ERG recommends that the company investigates the possibility of using a RR to adjust background survival for patients in the long term (similar to what has been done by the ERG in TA591). - A clinically plausible transition between mortality rates from the stage 1 to the stage 2 Markov models is used.

What is the expected effect on the cost-effectiveness estimates?	Not predictable.
What additional evidence or analyses might help to resolve this key issue?	The analyses suggested by the ERG.

Abbreviations: Abbreviations: CMV, Cytomegalovirus; HSCT, Hematopoietic stem cell transplant; SOT, Solid organ transplant; IAT, investigator-assigned antiviral therapy; GvHD, graft-versus-host-disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 9. Issue 8. Modelling of graft failure

Report section	4.2.6.4
Description of issue and why the ERG has identified it as important	Given the absence of graft loss events in SOLSTICE and clinical expert opinion provided to the ERG that graft failure is only likely to occur from 3 months after patients' transplant, the ERG disagrees with the company's implicit assumption that patients could have graft failure after 4 weeks in the model. The ERG also considers that the company's approach is biased in favour of maribavir as the probability of graft failure events in the model is higher for patients experiencing CMV. The ERG also disagrees with the company's assumption that the rates of graft loss reported in Hakimi *et al.* (used in the model), are based on 2 years follow-up in the study. In reference to the graft loss estimates used by the company, the Hakimi *et al.* study states, "*Recipients with L-CMV-3M [CMV beyond 3 months post-transplant] and L-CMV-6M [CMV beyond 6 months post-transplant] were more likely than controls to experience graft rejection and graft failure over 12 months following the index date*". Therefore, the ERG considers that the estimates provided in the study are annual (instead of biannual). Importantly, the ERG notes that the estimates from Hakimi *et al*. used by the company in their base case are only applicable to patients within their first-year post-surgery (as the rates chosen by the company are for patients who had a CMV event within 3 months after transplant). Therefore, the Hakimi *et al.* estimates used by the company are not reflective of the risk of graft failure for the SOT SOLSTICE population. The ERG disagrees with the company's assumption that 100% of patients with graft failure get a second transplant in the model. The ERG's clinical experts advised that less than 5% of patients get a re-transplant after first graft failure. Therefore, during clarification, the ERG asked that the company conducted a scenario analysis where 0% of patients (instead of 100%) received a second transplant in the model. The company conduct a scenario analysis where the mortality risk following graft loss; re-transplant costs; and re-transplant utility decrements were all set to zero. The company also assumed all patients receiving a renal transplant required kidney dialysis. The ICER increased from £15,337 to £16,211. Nonetheless, the company's scenario analysis failed to take into account the increase in mortality for patients with graft failure, therefore not appropriately capturing the negative impact that the lack of a second transplant would have in patients' survival. In their base case, the company assumed that patients who have a re-

	transplant have an elevated risk of mortality by applying an organ-specific HR sourced from literature to the annual age- and sex-specific mortality. Nonetheless, the ERG notes that some of these HRs (such as the HR estimated for a kidney re-transplant) were estimated as the relative increase in the risk of mortality of a second transplant vs a first transplant (and not vs no transplant). The ERG also has several concerns regarding the company approach to incorporating the quality-of-life impact of graft loss into the model. Firstly, the disutilities were applied only in the 4-week model cycle in which patients experienced graft failure, implicitly assuming that graft loss impacts quality of life for only 4 weeks. The ERG considers this assumption inappropriate as graft loss is non-reversible and expected to have a long-lasting effect a patient's quality of life. As the ERG's clinical experts indicated that only a small minority of patients would receive a second transplant, the ERG considers that the disutility associated with graft failure should be applied until death (accounting for additional age-related reduction in quality of life). Furthermore, as patients who experience graft loss are unlikely to receive a second transplant, those with kidney graft loss are expected to receive lifelong dialysis and therefore the disutility associated with dialysis is applicable for these patients. Additionally, the ERG is uncertain of why the company estimated graft loss disutilities based on utility estimates (with and without graft loss) for health state vignettes of only asymptomatic clinically significant CMV patients, rather than also including estimates for symptomatic clinically significant CMV patients and patients without clinically significant CMV. The ERG recommends that the company clarifies this assumption at TE.

What alternative approach has the ERG suggested?	For the trial population - the company should use clinical expert advice and the available evidence base to substantiate if graft failure events are still likely to happen over 1 year after transplant.
	
	If the company's value proposition is that maribavir should be given as early as possible for r/r patients – the company should ensure that graft failure events reflect time since surgery in this population. Furthermore, the ERG recommends that the company ensures that graft failures can only occur 3 months after patients' transplant. Additionally, the ERG recommends that the company:
	- Uses the KM data from Hakimi *et al*. to fit and extrapolate survival curves in order to estimate the probability of graft failure in the model (taking time since transplant into consideration).
	- Assumes that the proportion of patients receiving a second transplant in the model is less than 5% (or 0% for simplification purposes), however:
	  ○ All kidney transplant patients with a graft failure should be assumed to receive dialysis;
	  ○ All patients with graft failure should have an increase in mortality. If the company decides to use the same HRs as those used in the base case to estimate the increase in patients' mortality, these HRs should be applied to patients SOT-specific mortality and not to background mortality.
	- Applies utility decrements due to graft loss until death (adjusting for age-related utility). For kidney graft loss, it is recommended that the

	utility decrement associated with dialysis is applied.
What is the expected effect on the cost-effectiveness estimates?	Assuming that patients only experienced graft failures 3 months after cycle 0 in the model will decrease the benefit estimated for maribavir, thus increasing the company's ICER. The different changes proposed by the ERG for assessing the consequences of graft failure (i.e. no re-transplant) will work in opposite directions, therefore, the final impact on the ICER cannot be anticipated.
What additional evidence or analyses might help to resolve this key issue?	The ERG recommends that the company clarifies why the estimated graft loss disutilities were only based on asymptomatic clinically significant CMV patients, rather than also including estimates for symptomatic clinically significant CMV patients and patients without clinically significant CMV.

Abbreviations: Abbreviations: CMV, Cytomegalovirus; HSCT, Hematopoietic stem cell transplant; SOT, Solid organ transplant; IAT, investigator-assigned antiviral therapy; GvHD, graft-versus-host-disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 10. Issue 9. Modelling of disease complications

Report section	4.2.6.5
Description of issue and why the ERG has identified it as important	The company's base case did not originally include graft versus host disease (GvHD) events or any leukaemia recurrences in the base case model. After a request from the ERG during clarification, the company provided a scenario analysis including leukaemia recurrences in the model. The company's scenario analysis used similar to the approach to that taken by the company in TA591 to estimate the long-term impact of HSCT. However, in TA591, a scenario analysis was also provided to estimate the impact of leukaemia recurrence, which is the more relevant scenario for the ERG's request of estimating the impact of disease recurrence after HSCT. In TA591, the company considered the impact of disease recurrence on survival; costs; and utilities. A relapse was assumed to be associated with a 0.0114 disutility and with a per-cycle cost of £6,460 (2015/2016 prices). The ERG-preferred scenario in TA591 included the assumption that 47% of patients have disease relapse; and that during the 6-month survival period of these patients, a per cycle cost of £6,460 is applied, together with a per-cycle disutility of 0.0114. For this submission, the company assumed a probability of relapse of 47%; a utility decrement of 0.01 assumed to last for 3 months; and a £55,529 cost of relapse assumed to last for 2 years. In comparison to the ERG scenario in TA591, the company's current scenario underestimates the impact of disease recurrence on survival and quality of life for HSCT patients. With regards to costs, it is likely that the company's approach is overestimating costs, as the company in TA591 assumed a higher cost of disease relapse, but only for 6 months, whereas in this STA the company assumed a lower cost per cycle, however with a duration of 2 years. Furthermore, the ERG is unclear why the duration of leukaemia recurrence would be different for estimating costs and disutilities. During clarification, the ERG also noted that clinical expert opinion indicated that HSCT patients with chronic GvHD (i.e., unresolved GvHD at 100 days post-surgery) have a higher probability of CMV recurrence due to intense

	immunosuppressant treatment and are expected to not survive beyond 2 years after surgery. Out of the 141 HSCT patients in SOLSTICE, new GvHD was reported during the study for [redacted] maribavir patients and for [redacted] HSCT recipients in the IAT group. Furthermore, [redacted] patients and [redacted] patients had chronic GvHD at baseline, in the maribavir and the IAT arms, respectively, while [redacted] patients and [redacted] patients had acute GvHD at baseline, in the in the maribavir and the IAT arms, respectively. It is not possible for the ERG to know which of the new cases of GvHD occurring during SOLSTICE became chronic cases; or which baseline acute cases also became chronic; however, given that HSCT patients entered the trial, on average, over 100 days after transplant ([redacted]) it would be clinically plausible that most new/acute GvHD cases during the trial became chronic. Even though the company considered that the relationship between CMV and GvHD unclear, in the scenario analysis included in the CS, a different 4-weekly rate of GvHD was assumed for CMV and nCMV patients. The company used a hazard ratio of 2.18 (95% CI 1.30-3.65, p-value < 0.01) reported in Cantoni *et al*. which concluded that during phases of CMV replication, patients were at increased risk of developing acute GvHD. The ERG notes that the hazard ratio reported in the study does not provide any information on the relationship between CMV and chronic GvHD.
What alternative approach has the ERG suggested?	In order to estimate the impact of underlying disease recurrence for HSCT patients, the ERG recommends that the company runs a scenario analysis which: - Assumes that 47% of patients with a recurrence live for 6 months from recurrence of leukaemia; - Assumes that patients with disease recurrence experience a per-cycle disutility of 0.0114; - Updates the per-cycle cost of £6,460 (2015/2016 prices) to the correct price year and applies it in every cycle of the model for 6 months. The ERG also recommends including a scenario analysis where the pooled percentage (i.e., not differentiating by CMV or nCMV) of patients with chronic GvHD at baseline in SOLTICE is used to estimate disease in the model; and another scenario where all acute and new cases in SOLSTICE (in addition to the chronic cases at baseline) are assumed to become chronic during the trial. These scenarios should assume that patients with chronic do not survive beyond 2 years after transplant.
What is the expected effect on the cost-effectiveness estimates?	The increase in mortality associated with leukaemia recurrence (independent of CMV) is likely to increase the ICER as less patients would contribute to the long-term benefits associated with maribavir. Similarly, if an assumption were to be included in the model whereby all patients in SOLSTICE with chronic GvHD (independent of CMV status) were assumed to be dead at 2 years after entering the model, it is likely that the ICER associated with maribavir would increase.
What additional evidence or analyses might help to	Investigating further (if possible) how many cases of chronic GvHD were in SOLSTICE.

resolve this key issue?	

Abbreviations: Abbreviations: CMV, Cytomegalovirus; HSCT, Hematopoietic stem cell transplant; SOT, Solid organ transplant; IAT, investigator-assigned antiviral therapy; GvHD, graft-versus-host-disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 11. Issue 10. Estimation of utilities

Report section	4.2.8
Description of issue and why the ERG has identified it as important	The company's approach of using simple averages of cross-walked EQ-5D-3L data to estimate health state utility values without consideration for the bias introduced by incomplete follow up is considered flawed by the ERG. Averaging utility measurements taken for patients at different points in time results in utility estimates which underweight patients for whom fewer utility measurements were taken before they were lost to follow up. Furthermore, given the company's statement that utilities were estimated based on week 0 to week 20 utilities for responders and non-responders at week 8, the ERG remains unclear if the company assessed response at week 8 and then retrospectively averaged utility measurements for responders and non-responder from week 0; or if the utilities were collected from the point of response until week 20. The ERG also notes that averaging utility values across different time points does not provide any information of patients' change in utility from baseline. During the clarification stage the ERG requested the company to provide data on each EQ-5D-5L assessment so that both the extent of loss to follow up, and changes in utility from baseline could be assessed. The company provided the statistical difference for mean change at baseline at all available time points in SOLSTICE across treatment arms, and these were all non-statistically significant. The data provided by the company also showed a higher loss to follow up in the IAT arm. Although data on reasons for loss to follow up was provided, the ERG notes that the substantial difference observed between the maribavir and IAT arms are likely due to confounding factors and the data is likely missing not at random. The ERG also disagrees with the company's approach to estimating the transplant-specific utility values for the stage 2 Markov model as the estimated utility values included patients with and without CMV during the 20-week follow-up of SOLSTICE and led to an implausible transition from the utilities used in the stage 1 and the stage 2 parts of the model. Patients in the SOT CMV state prior to week 52 suffer a drop in utility when the model switches to an alive/dead model. This is inconsistent with the company's assumption that all patients cease CMV treatment due to patients' immune system recovering at 12 months and patients being free from CMV from that point onwards. The ERG is also concerned that the utility values applied beyond 52 weeks in the company base case underestimate the quality of life experienced by nCMV patients. These patients suffer a considerable drop in their quality of life after week 52 without a plausible explanation, given that their CMV status was considered to not change after that point in time. The company applied age-adjustments to the utility values in the stage 2 Markov, however, the ERG notes that the company used Szende *et al*. 2014 as the source of general population utilities rather than Ara *et al*. 2010. The

	ERG notes that Ara *et al*. 2010 has been used extensively in previous NICE technology appraisals and provides more granular utility estimates (by age rather than age ranges).
What alternative approach has the ERG suggested?	The ERG recommends that the company re-estimates the utilities used in the model and investigates whether multiple imputation and pattern-mixture modelling methodologies can limit or overcome the bias (of unknown magnitude and direction) introduced to the utility estimates by the missing not at random EQ-5D data. The ERG also recommends that the company re-evaluates the transitioning in utilities from week 52 to week 56 in the model so that these are consistent with model assumptions and also clinically plausible. It is also recommended that the company utilises Ara *et al*. to estimate the age-related utility decrements applied in the model.
What is the expected effect on the cost-effectiveness estimates?	Not predictable.
What additional evidence or analyses might help to resolve this key issue?	The analysis requested by the ERG.
Abbreviations: Abbreviations: CMV, Cytomegalovirus; HSCT, Hematopoietic stem cell transplant; SOT, Solid organ transplant; IAT, investigator-assigned antiviral therapy; GvHD, graft-versus-host-disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.	

Table 12. Issue 11. Estimation of costs

Report section	4.2.9
Description of issue and why the ERG has identified it as important	The ERG considers that the costs associated with IAT retreatment are overestimated in the model. The company captured treatment discontinuation by applying a time on treatment (ToT) multiplier to the 4-week IAT acquisition and administration costs. However, no stopping rule was applied to retreatment with IATs, therefore, patients in the CMV state (with a recurrence event) were assumed to be on treatment until they exited the state or reached the end of 52-week stage 1 Markov model. Even though it could be argued that patients with a CMV infection after an 8-week round of treatment with one specific IAT would simply switch to another IAT, recurrences are unlikely to happen with the frequency (and the duration) assumed in the company's model. This is related to the overestimation of recurrence episodes in the model (as discussed in Issue 5). The ERG also has concerns that the administration costs applied for IV drugs in the IAT arm are overestimated as the company has assumed that the daily cost of IV administration is equal to an NHS reference cost for complex chemotherapy at first attendance (SB14Z). The ERG considers the company's use of the SB14Z first attendance cost inappropriate for the following reasons: - The 2020/21 National cost collection guidance document notes that this cost applies to only the first administration of a chemotherapy cycle and that another lower reference cost for subsequent elements of a chemotherapy cycle (SB15Z) should be used for "Delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance".

	- Feedback from the ERG's clinical experts suggested that administration of the IV treatments for CMV (ganciclovir, foscarnet, cidofovir) would utilise an existing central line and that approximately 4 hours of ICU nurse time would be required per administration of these IV drugs. As such, the application of a complex chemotherapy at first attendance cost means that costs associated with inserting catheters to facilitate IV treatment would be applied every day for the duration on treatment – this is inconsistent with the ERG's clinical expert feedback. The ERG also notes that company has applied substantially higher unit hospitalisation costs to patients in the CMV health state compared to the nCMV state. This was based on weighted average NHS reference costs for non-elective long stay for infectious diseases with or without interventions (£7,019.85 versus £1,969.53). The ERG notes that application of the higher cost (with interventions) has resulted in double counting the CMV intervention costs given that acquisition and administration costs for CMV treatment are independently included in the model. As such, the ERG considers the company's approach inappropriate and recommends that the company captures the cost of a CMV-related hospitalisation by weighting average NHS reference costs for non-elective long stay for infectious diseases without interventions (WJ02C to WJ02E) and applies the cost to hospitalisations occurring for both the CMV and nCMV health states.
What alternative approach has the ERG suggested?	The ERG recommends that the company estimates the administration cost for IV treatments based on the PSSRU hourly staff cost for a critical care staff nurse (band 5) and a hospital pharmacist, with 4 hours nurse time costed per administration of treatment to 2 patients; and 15 minutes hospital pharmacist time per administration. The ERG recommends that the company applies the weighted average of NHS reference costs for non-elective long stay for infectious diseases without interventions (WJ02C to WJ02E) for hospitalisations occurring for both the CMV and nCMV health states. Given the ERG's clinical experts' opinion that foscarnet is the most relevant comparator to maribavir, the ERG recommends that a scenario analysis is used where the first line IAT treatment consists of the cost of foscarnet only, with the other IATs being a retreatment option for further lines. As discussed in Section 3.2, there was no strong signal from the company's data that the response to foscarnet is different from the other IATs, therefore a change in the cost of the comparator arm will suffice for this analysis.
What is the expected effect on the cost-effectiveness estimates?	Decreasing the costs associated with IATs and with CMV-related hospitalisations in the model will increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	The analysis requested by the ERG.

Abbreviations: Abbreviations: CMV, Cytomegalovirus; HSCT, Hematopoietic stem cell transplant; SOT, Solid organ transplant; IAT, investigator-assigned antiviral therapy; GvHD, graft-versus-host-disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

1.5 Summary of ERG's preferred assumptions and resulting ICER

The ERG-recommended changes to the economic model, together with additional requests for clarification, are described in detail in Section 6 of the report. Given the ERG's conclusion that the company's model is currently unfit for purpose, the ERG does not have a preferred ICER.

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost effectiveness of maribavir (brand name Livtencity™, Takeda) in the treatment of refractory or resistant cytomegalovirus (CMV) infection after transplant.

2.2 Background

Within Section B.1 of the company submission (CS), the company provides an overview of:

- Maribavir, including its mechanism of action, dose and method of administration (CS, Section B.1.2);
- Human CMV, including epidemiology and disease burden (CS, Section B.1.3).

Based on advice from its clinical experts, the Evidence Review Group (ERG) considers the CS to present an accurate overview of the epidemiology and aetiology of CMV, and the management of the disease.

Human CMV is a highly prevalent viral pathogen of the Herpesviridae family, present in approximately 60% to 70% of the population.[1] While CMV infection is generally asymptomatic or mild, when the host immunity is weakened or suppressed, latent CMV can reactivate causing a greater risk to the patient.[1 2] These more severe manifestations of CMV infection are outlined in Table 13. Immunocompromised patients, such as those who have recently undergone a transplant, may be more susceptible to progression from asymptomatic CMV infection to CMV syndrome and tissue invasive disease.

Solid organ transplant (SOT) and allogeneic haematopoietic stem cell transplant (HSCT) patients require the use of potent immunosuppressive chemotherapy, which reduces the patient's protection to CMV; consequently, CMV is a frequent complication after transplantation.[3 4] Due to the immunosuppression required to prevent organ rejection following SOT and allogeneic HSCT, patients are at increased risk to both reactivation of the patient's own latent CMV infection, and a latent CMV infection transferred from the transplant donor to the recipient.[5] CMV infections that are refractory or resistant to currently available antivirals are a major cause of morbidity and mortality among SOT and allogeneic HSCT recipients.[6] Patients can experience severe outcomes when not treated and when resistant or refractory to treatment. If CMV infects an end-organ in SOT patients, it can cause tissue injury that results in organ dysfunction leading to tissue invasive disease such as

CMV pneumonia, gastrointestinal CMV disease, CMV central nervous system disease, and CMV retinitis.[7 8] CMV infection can also lead to tissue invasive disease in patients after HSCT, with risk of oesophagitis, gastroenteritis, hepatitis, retinitis, pneumonia, and encephalitis.[9] Significantly, recurrence of CMV has been identified as a prognostic factor. Risk of mortality has been found to be increased for patients who had undergone a SOT or an allogeneic HSCT and had at least two recurrent CMV episodes.[10 11]

The occurrence of disease caused by CMV in transplanted patients can also be impacted by the matching of serological status between donor and recipient. In SOT, the greatest risk factor for CMV disease is a serological mismatch between the donor and the recipient (the recipient is CMV seronegative and the donor is seropositive, CMV D+/R-).[12] Furthermore, CMV D+/R+ transplantation and CMV D-/R+ transplantation are considered to be of intermediate risk for the development of disease, and CMV D-/R- transplantation is considered low risk (< 5%).[13]

The incidence of CMV infection can also vary amongst SOT patients depending on the type of organ transplanted. Incidence of CMV infection has been noted to be higher in patients undergoing lung or heart-lung transplantation (an incidence of 50–75%) and in patients undergoing pancreas or kidney-pancreas transplantation (an incidence of approximately 50%), while the incidence of CMV is between 9 and 23% after heart transplantation, between 22 and 29% after liver transplantation and between 8 and 32% after kidney transplantation.[14]

Table 13. Definitions of CMV manifestations (adapted from table 3 of the CS)

Terminology	Definition
CMV infection	Prescence of detectable CMV viral particles. A CMV infection can be asymptomatic
CMV disease	A symptomatic CMV infection. CMV disease can be classified as CMV syndrome or tissue invasive disease
CMV syndrome	For SOT patients, CMV syndrome is defined as fever (>38 ºC) for at least 2 days within a 4-day period, CMV detection in blood and either neutropenia or thrombocytopenia For allogeneic HSCT patients, the definition for CMV syndrome is broader and is defined as a combination of fever and bone marrow suppression
CMV tissue invasive disease	Combination of CMV detection or CMV syndrome, plus an end-organ disease (e.g. CMV pneumonia, CMV gastrointestinal disease, CMV hepatitis, CMV nephritis, CMV cystitis, CMV myocarditis, CMV retinitis)

Patients are most vulnerable to CMV infection progressing to CMV disease during the initial period after transplantation, when high levels of immunosuppression are used. The ERG's clinical experts advised that this risk of CMV progression is greatest during the first 3 months after transplant. As patients move to the next phase 3 to 6 months post-transplant, the dose of immunosuppression is

typically reduced and risk of CMV disease reduced. After the first year post-transplant, the patient's own immune system is more able to combat viral replication in most cases and so the risk of clinically significant CMV is reduced even further. HSCT patients with a continued higher risk of CMV infection (> one year post-transplant) are in general those with major GvHD.

Maribavir is an oral bioavailable benzimidazole riboside anti-CMV agent, with a multi-targeted anti-CMV activity through the inhibition of the UL97 protein kinase and its natural substrates. UL97 kinase is involved in multiple stages of the CMV life cycle including phosphorylation of CMV viral and host proteins which modulate the cell-cycle to support viral deoxyribonucleic acid (DNA) synthesis, the regulation of viral gene expression, and the facilitation of nuclear egress of viral particles.[15] In targeting the UL97 enzyme, maribavir acts to inhibit both replication and encapsulation of CMV DNA as well as preventing the escape of viral capsules from infected cells. The multisite action of maribavir is proposed to make the therapy less susceptible to mutations of the viral DNA polymerase which has been found to cause resistance in other therapies used for the treatment of CMV.

2.2.1 Positioning of maribavir in the UK treatment pathway

The CS provides a reasonable overview of current service provision for the management CMV post-transplant, including detail of where maribavir will fit in the treatment pathway.

Currently there is no NICE clinical guidance for the treatment of patients who are refractory or resistant to treatments after SOT or allogeneic HSCT. The company highlights that TA591 – letermovir for prophylaxis of allogeneic HSCT recipients – does not include refractory/resistant CMV and is therefore not relevant to this population.

The management of CMV post-transplant can be approached as either prophylactic or pre-emptive therapy. The goal of prophylaxis is to maintain low or no CMV viraemia during the early post-transplant stage when there is no evidence of infection, while pre-emptive therapy is administered to patients with detectable CMV viraemia (who may be asymptomatic or symptomatic).

The company proposes that maribavir will be offered as a pre-emptive therapy for patients whose infection is refractory or resistant to the most recent CMV treatment. There are currently no medications with marketing authorisation to pre-emptively treat CMV in patients after SOT or allogeneic HSCT in the UK; although the CS and the ERG's clinical experts highlight that there are common antiviral therapies typically used off-label, such as valganciclovir (Valcyte®), ganciclovir (Cymevene®), foscarnet (Foscavir®), and cidofovir. The ERG's clinical experts added that if a patient

achieves CMV clearance with anti-CMV treatment, the risk of recurrence would not vary between treatment options.

2.2.1.1 Treatment pathway for patients with SOT

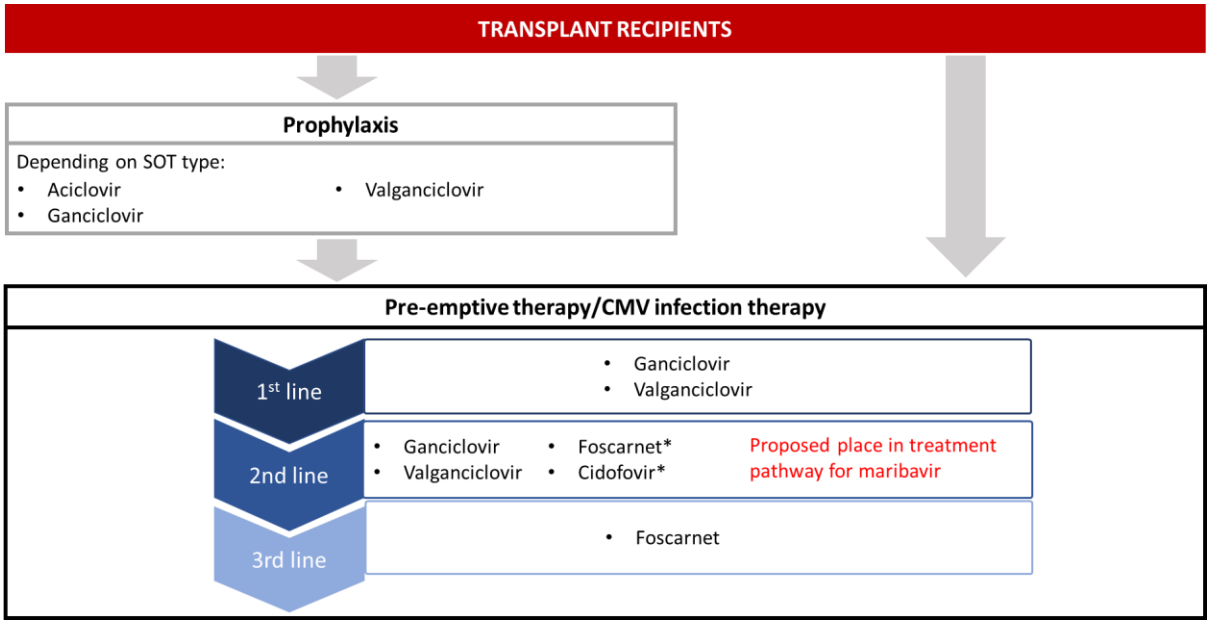
The ERG's clinical experts advised that treatment pathway, risk of CMV and subsequent sequalae for patients who have undergone SOT may depend on the type of organ transplanted and the serological match between donor and recipient. However, typically current treatment pathway for SOT patients would begin with monitoring post-transplant for CMV infection. Assessment for CMV infection may also be carried out if the patient shows evidence of clinically significant disease with indications such as high fever, liver dysfunction, or deterioration in graft function. If clinically significant CMV is found (>30000 µg for SOT) and/or evidence of an exponential rise in virus identified, then pre-emptive therapy would generally be recommended.

The ERG's clinical experts advised that first-line anti-CMV treatment would be administered for ≥14 days before review for effectiveness. Although the CS suggests that genetic testing for resistance to specific anti-CMV treatments is not part of routine UK practice for the management of CMV infection, the ERG's clinical experts advised that if insufficient response to intervention is found after 14 days of therapy, healthcare professionals would usually consider genomic testing to understand if the patient is resistant. The ERG's clinical experts added that if testing shows that patients are not resistant, the next aim would be to optimise the treatment regimen by adjusting dosing and administration before later re-reviewing CMV load. If after treatment optimisation CMV load remains high, patients may be offered an alternative treatment as second-line therapy.

Currently, intravenous (IV) ganciclovir and oral valganciclovir are typically the most common first-line treatments for patients with CMV infection who have undergone an SOT. The company suggests that foscarnet and cidofovir are less frequently used as they are associated with nephrotoxicity. The company adds that patients will typically be retreated with ganciclovir or valganciclovir if recurrence occurs. The company and ERG's clinical experts outline that patients will often receive cidofovir or foscarnet as second-line therapy if they have already failed on or demonstrate resistance to ganciclovir or valganciclovir. The company have proposed that maribavir would be placed within this second-line setting, being offered to SOT patients who are resistant or refractory to their most recent anti-CMV treatment. The company also propose that these second-line treatment options may be given to a patient following failure to clear CMV load beyond the second line of therapy, offering an alternative treatment for those who fail on their most recent anti-CMV intervention. The

company outlines the proposed CMV treatment pathway after SOT and highlight where they believe maribavir would place within this pathway (Figure 1).

Figure 1. Proposed CMV treatment pathway after SOT (adapted from figure 1 of CS summary)



CMV=Cytomegalovirus; SOT=Solid organ transplant
*Requires monitoring of renal function

2.2.1.2 Treatment pathway for patients with HSCT

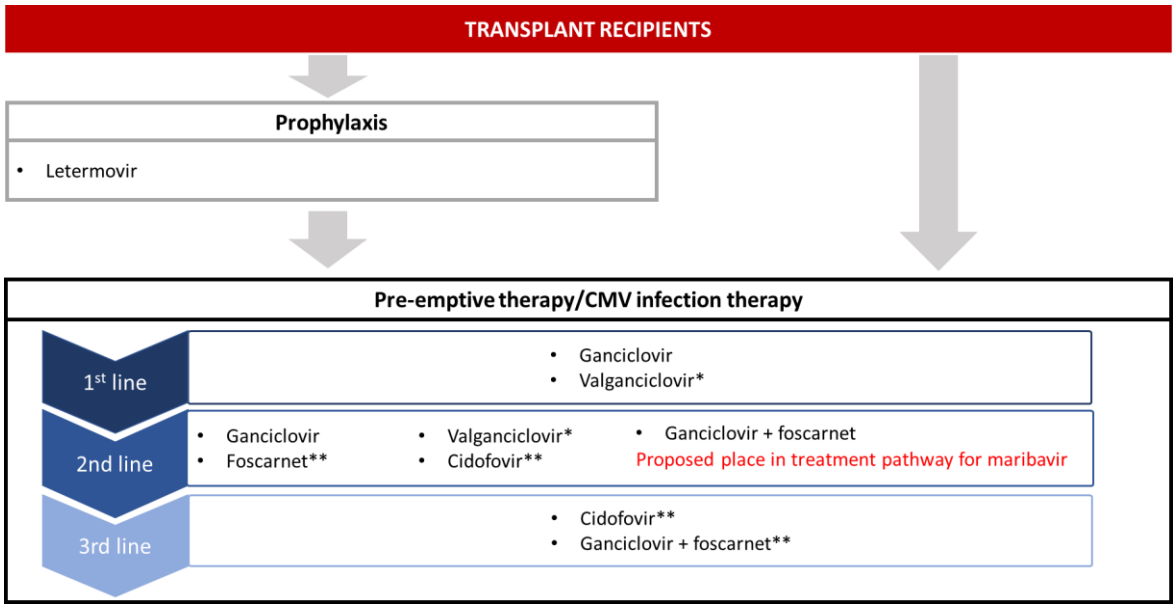
Similar to the treatment pathway for SOT, it is recommended that the treatment pathway for HSCT patients would typically begin with monitoring post-transplant for CMV infection. Letermovir is the only treatment approved for the management of CMV post-HSCT; however, it is used as prophylaxis (rather than pre-emptive treatment) through the first 100 days post-transplant only for patients who are CMV seropositive. The small proportion of patients who are CMV seronegative with a seropositive donor have a lower reactivation risk and do not receive prophylaxis.

If CMV is found (>3000 µg for HSCT) and/or evidence of an exponential rise in virus is identified, then pre-emptive therapy would generally be recommended. As with SOT patients with refractory or resistant CMV post-transplant, the typically available options for first-line treatments include ganciclovir and valganciclovir. The ERG's clinical experts noted that to give ganciclovir or valganciclovir good blood counts are needed and therefore these treatments can't be used until the patient has engrafted (the new bone marrow has grown in and is producing sufficient cells). A minority of patients will not engraft well and for these patients the first line treatment option is foscarnet. However, although the average time to engraftment varies with type of HSCT, for most

patients it is 12 to 21 days, and as letermovir is frequently used in current UK practice, foscarnet is seldom required as a first-line therapy. Following this first-line intervention, assessment of effect would typically take place at 2 to 4 weeks to review viral load, with treatment continuing until clearance or a stable low level of virus is achieved.

Those who fail to clear the CMV load with first-line treatment will be offered foscarnet (either as monotherapy or in addition to ganciclovir) or cidofovir. The company propose that maribavir would be offered as a second-line therapy. As with SOT patients, the company propose that these second-line treatment options may also be given to a patient following failure to clear CMV load beyond the second line of therapy, offering an alternative treatment for those who fail on their most recent anti-CMV intervention. The company outlines the proposed CMV treatment pathway after HSCT (Figure 2).

Figure 2. Proposed CMV treatment pathway after HSCT (adapted from figure 2 of CS summary)



CMV=Cytomegalovirus; HSCT=Haematopoietic stem cell transplant
*For patients without severe gastrointestinal graft-versus-host-disease
**Requires monitoring of renal function

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE together with their rationale for any deviation from the final scope (Table 14). The differences between the decision problem addressed in the CS and the scope are discussed in the sections that follow.

Table 14. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	ERG comment
Intervention(s)	Maribavir	Maribavir	N/A	The intervention specified in the CS is maribavir and this matches the final NICE scope.
Population(s)	People with cytomegalovirus infection that is refractory or resistant to treatments after haematopoietic stem cell transplantation or solid organ transplant	As per the final NICE scope	N/A	The population of the SOLSTICE trial is in line with the scope and included patients are broadly representative of the patient population in UK practice, but patients had a variable time since transplant, which is likely to impact on outcomes including recurrence and mortality. In the economic model it can be inferred that patients are entering the model immediately after transplant. The population in the model is therefore unlikely to be representative of the trial population or the population in clinical practice.
Comparators	•Ganciclovir •Valganciclovir •Foscarnet •Cidofovir •Ganciclovir with foscarnet •Ganciclovir with hyperimmune globulins •Cytotoxic lymphocytes None of the listed comparators currently have a marketing authorisation in the UK for this indication.	•Ganciclovir •Valganciclovir •Foscarnet •Cidofovir None of the listed comparators currently have a marketing authorisation in the UK for this indication.	Cytotoxic lymphocytes and hyperimmune globulins are not included within the decision problem as they are not used in regular clinical practice within the UK. No evidence of their efficacy has been identified by an SLR (Appendix D.1)	The ERG's clinical experts have confirmed that cytotoxic lymphocytes and hyperimmune globulins are not relevant comparators to maribavir. Of the remaining comparators the clinical experts consider foscarnet to be the key comparator for the majority of patients, although for a small proportion of patients ganciclovir, valganciclovir and cidofovir may be relevant alternative treatments for patients in this setting. The company has provided subgroup data patients receiving foscarnet in the comparator arm.
Outcomes	The outcome measures to be considered include:	As per the final NICE scope	N/A	The company has presented data for all outcomes listed in the scope. The primary

	•CMV infection symptom improvement or reduction •Length of hospital stay •Mortality •Tissue invasive disease •Transplant graft function •Viral load •Adverse effects of treatment •Health-related quality of life			outcome in the key trial was viral clearance at week 8. However, in the economic model the company has not directly used the primary outcome but focused on retrospective *post hoc* outcomes of clearance at week 4 and 8 (based on patients without clearance at week 4). Similarly, the economic model is informed by retrospective *post hoc* analyses of clinically relevant recurrence at week 8 (based on clearance at week 4) and at week 20 A low number of patients experienced tissue invasive disease, transplant graft function or died during the study. That is, very limited data were available for these outcomes during the study period.
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: •People who have had HSCT •People who have had SOT The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The NICE submission includes Study 303 data for HSCT and SOT population	N/A	The company has provided subgroup data base on type of transplant for clearance and mortality. The company also provided subgroup results for patients in the IAT group who received foscarnet and for all patients based on time since transplant.

Abbreviations: SmPC, Summary of Product Characteristics; SLR, Systematic literature review; CMV, Cytomegalovirus; HSCT, Hematopoietic stem cell transplant; SOT, Solid organ transplant.

2.3.1 Population

The population in the key trial underpinning the evidence in the CS is in line with the population specified in the NICE final scope; patients enrolled in the trial had a CMV infection that was refractory or resistant to treatments after HSCT or SOT. The clinical experts advising the ERG consider the trial population to be broadly representative of patients who would be eligible for maribavir treatment in UK clinical practice.

The time since transplant is an important prognostic factor which impacts on the risk of CMV infection, mortality and graft loss. In the trial the mean time since transplant was around [redacted] months for SOT patients and [redacted] months for HSCT patients. The ERG's clinical experts consider this to be relatively close to what would be expected in clinical practice for HSCT patients, most of whom will be given 100 days of prophylaxis with letermovir before having a CMV episode, receiving an anti-CMV therapy, and being declared treatment refractory or resistant. The time between transplant and receiving anti-CMV treatment may be closer to 5.5 months for HSCT patients in clinical practice as it usually takes 4 to 6 weeks after prophylactic treatment for the viral load to reach a level requiring treatment. For SOT patients, however, the time between transplant and receiving their first anti-CMV treatment is likely to be much more variable. SOT patients with a mismatched seropositivity between donor and recipient will be given prophylactic treatment for 28 days up to 360 days, depending on the organ transplanted and the anti-CMV treatment used.

However, in the company's economic model, it can be inferred that patients are entering the model immediately after transplant, despite the CS stating that patients enter the model at 1 year post-transplant. The modelled population may therefore not be representative of the trial population or the population treated in clinical practice.

More details about the trial population and its generalisability to patients in UK clinical practice is provided in section 3.2.1. The implications of the difference between the trial population and population in the economic model is discussed in Section 4.2.2.

2.3.2 Intervention

The intervention specified in the CS is maribavir, in line with the NICE final scope. Maribavir does not currently have a marketing authorisation in the UK. European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) approval is expected in November

2022. A draft SmPC was not available at the time of writing but in the SOLSTICE trial maribavir 400 mg (200 mg x 2 tablets) were taken orally twice a day for 8 weeks. The ERG notes that other anti-CMV treatments, such as those offered in the comparator arm, are generally given until clearance or toxicity but are not continued after clearance is achieved in order to maintain it.

The ERG's clinical experts consider that for most CMV treatments, if patients achieve clearance but then have a recurrence, they are likely to be re-treated with the same treatment. However, as the expected marketing authorisation for maribavir is for the treatment of patients who are resistant or refractory to their last anti-CMV treatment, the company has confirmed that maribavir is not expected to be used as re-treatment in those who have achieved clearance and subsequently have a recurrence.

2.3.3 Comparator

The comparators listed in the NICE final scope are:

- Ganciclovir;
- Valganciclovir;
- Foscarnet;
- Cidofovir;
- Ganciclovir with foscarnet;
- Ganciclovir with hyperimmune globulins;
- Cytotoxic lymphocytes.

None of the listed comparators currently have a marketing authorisation in the UK for the treatment of CMV in patients after SOT or HSCT who are refractory or resistant to CMV treatment. Although valganciclovir, ganciclovir, foscarnet, and cidofovir are used off-label for this indication. The ERG's clinical experts have confirmed that cytotoxic lymphocytes and hyperimmune globulins are not used in UK clinical practice for the treatment of CMV infections and are therefore not relevant comparators to maribavir.

In SOLSTICE, the key clinical trial informing this appraisal, patients were randomised to maribavir or investigator assigned anti-CMV treatment (IAT) consisting of ganciclovir, valganciclovir, foscarnet or cidofovir, in line with the comparators listed in the NICE final scope. The choice of specific IAT was at the investigators' discretion and could include mono- or combination therapy (≤2 drugs) with any of the four approved IATs. The ERG's clinical experts advise that of these four anti-CMV treatments,

foscarnet is likely to be the key comparator to maribavir for the majority of patients in the resistant or refractory setting. As described in Section 2.2, and Section B.1.3.8 of the CS, ganciclovir and valganciclovir are recommended first line treatment options both for patients who have had HSCT and those who have had a SOT. For patients who are resistant or refractory to the anti-CMV treatment received, it is recommended to change therapy and the ERG's clinical experts advised that foscarnet is the main treatment given to patients who have failed on ganciclovir or valganciclovir. In SOLSTICE, around 85% of patients received ganciclovir or valganciclovir as the most recent anti-CMV agent prior to randomisation but only 40.5% of patients in the IAT arm were given foscarnet. The assignment of anti-CMV treatment in the trial and its effect on the robustness and generalisability of the trial results are discussed in Section 3.2.1. The company provided subgroup data for patients in the IAT arm who received foscarnet, which are presented in Section 3.2.2.9.

2.3.4 Outcomes

The outcomes listed in the NICE final scope are:

- CMV infection symptom improvement or reduction;
- Length of hospital stay;
- Mortality;
- Tissue invasive disease;
- Transplant graft function;
- Viral load;
- Adverse effects of treatment;
- Health-related quality of life.

The company has presented data for all outcomes listed in the NICE final scope. However, the key outcomes informing the company's economic model are viraemia clearance and clinically relevant recurrence. Neither of these outcomes were specified in the NICE final scope but the ERG agrees with the company that these outcomes provide important measurements of the efficacy of maribavir and the treatment pathway for and progression of CMV infections.

The primary outcome in the SOLSTICE trial was viral clearance at week 8. However, the company has focused on clearance at week 4 as well as clearance at week 8 but for those who did not have clearance at week 4. CMV viral load was assessed weekly throughout the treatment period but both clearance outcomes used in the model were based on retrospective *post hoc* analyses of clearance

data. The robustness of the company's analysis is therefore likely to be lower than if they had used the primary outcome, on which the trial is powered.

In the trial, clinically relevant recurrence was a pre-specified outcome defined as recurrence at the end of the trial period (week 20) that required alternative anti-CMV treatment, based on patients who had clearance at week 8. In the model, the company used the pre-specified outcome of clinically relevant recurrence at week 20, but also a retrospective *post hoc* analysis of clinically relevant recurrence at week 8 based on clearance at week 4.

Data from SOLSTICE on hospitalisations, mortality, adverse events and health-related quality of life did inform the model. However, transplant specific mortality rates (HSCT vs SOT) and mortality rates based on CMV status were used rather than mortality rates based on the treatment received. The mortality data informing the model are discussed in Section 4.2.6.3. Data on the frequency of hospitalisations were taken from the trial but these were also based on CMV status rather than treatment. Data on the length of hospital stay from the trial was not used in the model.

CMV infection symptom improvement or reduction was captured in the key secondary outcome of SOLSTICE: CMV viraemia clearance and symptomatic CMV infection improvement or resolution at the end of week 8, and maintenance of this treatment effect through week 16. As mentioned above, viral load was assessed weekly throughout the treatment period and change in CMV viral load over time was reported in the CS. Results were reported for these outcomes, but they did not inform the economic model. A low number or no patients experienced tissue invasive disease or graft loss during the study. That is, very limited data were available for these outcomes during the study period and trial data for these outcomes did not inform the model.

Further details around outcome assessment in the trial are given in Section 3.2.1.

2.3.5 Subgroups

The NICE final scope specified that people who have had HSCT and SOT should be considered in separate subgroups. The company has provided subgroup data base on type of transplant for some of the relevant outcomes (primary clearance outcome, mortality, graft function) and patients who have had HSCT or SOT are modelled separately in the economic model in terms of mortality and graft loss.

The ERG notes several patient characteristics that are important prognostic factors that may affect the risk of CMV infection, clearance, recurrence and outcomes such as graft loss and mortality. These prognostic factors include time since transplant, the number of prior episodes of CMV infection and confirmed resistance to specific anti-CMV treatments. These are explored in subgroup analyses provided by the company at the clarification stage, which are reported in Section 3.2.2.9.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify, evaluate, and summarise the clinical efficacy and safety of anti-cytomegalovirus (CMV) agents for the treatment of refractory or resistant CMV infection/disease in solid organ transplant (SOT) or haematopoietic stem cell transplant (HSCT) recipients. Full methods and results of the SLR are reported in Appendix D of the company submission (CS). A summary of the methods, together with the Evidence Review Group's (ERG's) critique of the appropriateness of the methods adopted, is presented in Table 15. The SLR presented by the company is a compilation of one original SLR (1 January 2020 to 27 April 2020) and a subsequent update (28 April 2020 to 21 September 2021). Results were compiled for studies identified across both SLRs. Interventions and comparators specified in the inclusion criteria for the SLR encompassed those listed as relevant to the decision problem as set out in the final scope issued by the National Institute for Health and Care Excellence (NICE).[16]

A total of 11 studies (18 citations) reporting relevant data were included in the clinical SLR. From the 11 included, two were RCTs,[17] one a prospective observational study[18 19] and eight were retrospective observational studies.[6 20-26]

Of the two RCTs identified, one study, SOLSTICE (TAK-620-303), was the key trial which forms the main evidence base for the efficacy, safety and tolerability of maribavir in the CS. The other RCT, TAK-620-202, provides dose-comparison data for maribavir and so is presented in Appendix D of the CS as supplementary evidence. Evidence from the observational studies identified in the SLR were not presented by the company as no comparative data was collected and the relevant comparators are included in SOLSTICE. The ERG considers the selection and inclusion of studies by the company to be appropriate.

The included study, SOLSTICE, is a Phase III, multicentre, randomised, open-label, active-controlled study evaluating the efficacy and safety of maribavir compared to investigator-assigned anti-CMV treatment (IAT) in transplant recipients with CMV infections refractory or resistant to ganciclovir, valganciclovir, foscarnet or cidofovir. SOLSTICE was used by the company as the primary source of clinical evidence for maribavir and IAT in the economic model.

Overall, the ERG considers the company's SLR to be of satisfactory quality and likely to have retrieved all studies relevant to maribavir, despite limiting inclusion to English-language publications.

Table 15. Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem.

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Data sources	B.2.1 & Appendix D, Section D1.1	**The ERG considers the sources and dates searched to be appropriate.** Databases searched: • EMBASE • MEDLINE and MEDLINE In-Process • CENTRAL Additional sources: • Clinical Trials • EU Trial registry • Web of science
Search strategies	B.2.1 & Appendix D, Section D1.1	**The ERG is satisfied that searches have identified all evidence relevant to the decision problem.** Search strategies for the literature review combined comprehensive terms for the population, interventions and study designs, using free-text and medical subject headings. Searches were conducted in September 2021 and would be expected to capture contemporary research.
Inclusion criteria	B.2.1 & Appendix D, Section D1.1 (table 4)	**The ERG considers it likely that no relevant evidence was excluded based on the eligibility criteria used.** Literature identified from the SLR was then screened against a refined inclusion criteria in line with the NICE final scope for the purpose of the CS. Full reference details are available in the CS Appendix for the included study and for studies excluded at full-text appraisal. The inclusion of relevant studies was limited to English-language publications.
Screening and data extraction	B.2.1 & Appendix D, Section D1.1 (figure 1)	**The ERG considers the reporting of methods for screening and data extraction to be adequate.** Results of the literature screening processes were summarised in PRISMA diagrams. Details on how the data extraction was carried out are adequately reported.
Tool for quality assessment of included study or studies	B.2.5 & Appendix D, Section D1.3	**The ERG agrees with the company's choice of quality assessment tool.** The company followed an appropriate process of assessing the quality of the key trial and present this in table 15 of the CS. Detailed reasons in support of the judgement of level of bias for each aspect of trial design would improve the validity of the company's quality assessment.

		See Section 3.2.1 for a summary of the ERG's assessment of SOLSTICE.

Abbreviations: CS: company submission; ERG: evidence review group; NICE: National Institute of Health and Care Excellence; SLR: systematic literature review; RoB: risk of bias; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

3.2.1 Critique of the trial

In this section the ERG focuses on aspects of the trial design and conduct, and the impact on the internal and external validity of SOLSTICE. A summary of the trial design is provided in Table 16 followed by a more detailed description and critique of specific aspects of the trial by the ERG. The ERG agrees with the company's assessment of SOLSTICE as being at overall low risk of bias for the analysis of the primary outcome, CMV viraemia clearance at week 8, based on the full trial population (section B.2.5 of the CS). However, the ERG has strong concerns about the robustness of the results for several other outcomes, which are informing the model, and about the generalisability of the trial data to UK clinical practice. In addition, the clinical experts advising the ERG consider it a major weakness of the trial that it includes both SOT and HSCT patients as these are profoundly different populations and that all analyses should therefore have been done separately for the two.

Table 16. Summary of ERG's critique of the design and conduct of PRIMA, the trial evaluating the technology of interest to the decision problem

Aspect of trial design or conduct	Section of CS in which information is reported	Description and ERG's critique
Randomisation	B.2.3.2	Appropriate People randomised 2:1 to maribavir:IAT (ganciclovir [IV], valganciclovir [oral], foscarnet [IV], or cidofovir [IV]) Randomisation was stratified by transplant type (SOT vs HSCT) and baseline plasma CMV DNA viral load (low vs pooled intermediate/high)
Concealment of treatment allocation	CSR, Avery 2021	Appropriate A centralised Interactive Response Technology system was used to allocate patients to the two study arms.
Eligibility criteria	B.2.3.4	The eligibility criteria were in line with the expected marketing authorisation but the definition of resistance and the resulting placement of maribavir in the treatment pathway may differ between the trial and clinical practice.

		Transplant recipients (aged ≥12 years) with a current CMV infection refractory or resistant to the most recently administered of the four anti-CMV treatment agents: ganciclovir, valganciclovir, foscarnet or cidofovir.
Resistance testing	CSR	[redacted]
Baseline characteristics	B.2.3.5, clarification response	Patient characteristics were generally well balanced between the treatment arms in the ITT population and the trial population is generally representative of patients in UK practice. However, some baseline characteristics are likely to have a large impact on the generalisability of the trial results to UK clinical practice. In particular, time since transplant was longer than would be expected for the SOT subgroup and it was unbalanced between the treatment arms for both SOT and HSCT patients.
Treatment assignment	B.2.3.2	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.
Blinding	B.2.3.1	The trial was open-label with patients, investigators, and study centre staff aware of treatment assignment from the start of the study leading to a high risk of bias primarily for the assessment of recurrence.
Difference between groups in treatments given, other than maribavir and IAT	B.2.3.2	Concomitant medications taken during the on-treatment observation period were similar to medications used prior to the trial and was consistent between treatment arms.
Dropouts (high drop out and any unexpected imbalance between groups)	CSR	[redacted]
Outcomes assessed	B.2.3.6	Results of pre-specified outcomes relevant to the decision problem were reported in the CS. However, most outcome data informing the economic model were defined and analysed *post hoc*.
ITT analysis carried out	B.2.4.1	ITT analyses were reported for all efficacy outcomes.
Subgroup analyses	B.2.7	Pre-specified subgroup analyses were performed for the primary and key secondary efficacy outcomes based on stratification factors and clinical characteristics.
Statistical analysis plan		
Sample size and power	B.2.4.3	Appropriate for the primary outcome. It was assumed that at least 60% of maribavir-treated patients (at Visit 9/Week 7) and 40% of IAT-treated patients (Visit 10/Week 8) would have achieved undetectable plasma CMV DNA when calculating the sample

		size for SOLSTICE. A total of 315 patients were required in the ratio of 2:1 (210 patients in maribavir group and 105 patients in the IAT group) to provide 90% power in hypothesis testing at α=0.05 (2-sided test).
Handling of missing data	B.2.4.2.	For clearance, patients who took alternative anti-CMV treatment or maribavir as rescue treatment before Study Week 8 and patients who had missing data due to early discontinuation to confirm viraemia clearance at Study Week 8 were assumed to be non-responders. For recurrence, all CMV DNA measurements after achieving confirmed CMV viraemia clearance regardless of rescue or alternative treatment were included in the assessment.
Analysis for estimate of effect	B.2.4.2	Appropriate. 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 and baseline plasma CMV DNA concentration as two stratification factors. All statistical tests and CIs were 2-sided at α=0.05.

Abbreviations: CS, company submission; CRS, clinical study report; ITT, SOT, solid organ transplant; HCST, hematopoietic stem cell transplant; IAT, investigator-assigned anti-CMV treatment; IV, intravenous; CMH, Cochran-Mantel-Haenszel; DNA, deoxyribonucleic acid.

3.2.1.1 Eligibility criteria

Patients enrolled in the SOLSTICE trial are in line with the expected marketing authorisation and the population specified in the NICE final scope: people with CMV infection that is refractory or resistant to treatments after HSCT or SOT. Refractory to treatment was defined as a documented failure to achieve >1 log10 decrease in CMV DNA level in whole blood or plasma after a 14 day or longer treatment period with intravenous (IV) ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir.

The ERG's clinical experts have advised that it is likely to take longer than 14 days to see a significant reduction in viral DNA. Most patients are therefore likely to be treated for up to 4 weeks before being considered refractory to treatment. If there is a lack of response, the patient would be tested for resistance to the treatment given, and if confirmed the treatment would be changed. However, the results of the genetic testing for resistance may take some time, which means that the decision to switch treatment is a clinical one until resistance is confirmed. That is, in the SOLSTICE trial patients may have been treated for a shorter time before declared refractory than is likely to occur in UK clinical practice. In addition, there are likely to be differences in treatment and assessment of SOT and HSCT patients in clinical practice.

3.2.1.2 *Patient characteristics*

According to the ERG's clinical experts the population of SOLSTICE is largely representative of patients with refractory or resistant CMV after transplant in clinical practice. Baseline characteristics were generally balanced between the treatment arms. However, there were some discrepancies, e.g. the maribavir arm had a higher proportion of patients ≥65 years of age compared with IAT (23.0% and 13.7%, respectively), as well as a higher proportion of male patients (63.0% and 55.6%, respectively). In addition, time since transplant, data for which was provided at clarification, show [redacted]

Around 40% of patients in SOLSTICE had prophylactic anti-CMV treatment. At the clarification stage the company explained that the majority of those who had received prophylaxis were SOT patients ([redacted]) and only a small proportion were HSCT patients [redacted] Prophylaxis is recommended for CMV seronegative recipients who receive a SOT from a donor who is seropositive.[27] This group constituted the majority of SOT patients ([redacted]) in SOLSTICE. The clinical experts advised the ERG that in UK clinical practice this population and therefore the proportion of SOT patients who receive anti-CMV prophylaxis is likely to be substantially lower than in SOLSTICE.

Although data on prior therapy were captured in SOLSTICE, it was not reported if the specific treatment was used for prophylaxis or for how long patients were treated. The recommended management strategy for prophylaxis varies depending on the organ transplanted and the anti-CMV treatment used; prophylactic treatment could be 28 days with ganciclovir or up to 360 days with valganciclovir (for lung transplants).[27] Since the recommendation of letermovir in 2019, the majority of HSCT patients will receive prophylaxis with letermovir for 100 days after transplant. That is, in clinical practice, most HSCT patients are unlikely to have a CMV infection needing alternative treatment in the first 100 days post-transplant. The use or not of prophylactic treatments in the trial provides some information of how long since transplant patients may have entered the SOLSTICE trial, which is an important prognostic factor for which data weren't initially available for this assessment.

Towards the end of the ERG's assessment, the company provided baseline data on the time since transplant for patients in SOLSTICE. The data show that the mean number of days since transplant was [redacted] in the maribavir arm than in the IAT arm (322 vs [redacted] The data

also show that mean time since transplant for SOT patients was [redacted]). For HSCT patients time since transplant was [redacted]). However, the median time since transplant for HSCT patients show [redacted]

The company states that given the mechanism of action of maribavir, there is no known reason why the treatment effect of maribavir would differ according to time since transplant. However, the company acknowledges that time since transplant may be associated with other variables such as level of immunosuppression and overall frailty score, and that any imbalance between the arms in time since transplant may therefore indirectly confound the overall results. The ERG agrees with the company that time since transplant is unlikely to affect the relative treatment efficacy of maribavir and other anti-CMV treatments in terms of clearance, but notes a link between time since transplant and other variables such as level of immunosuppression and, most importantly, the risk of CMV infection, GvHD, mortality, etc. As described in Section 2.2 and in the CS, the risks of CMV infection and adverse events linked to CMV infection are greatly reduced after the initial 6-month period post-transplant and as stated by the company the risk is very small more than 12 months after transplant. The [redacted] in mean time since transplant in SOLSTICE means that the results for all outcomes, with the exception of clearance, are likely to be confounded by this difference with the bias in favour of maribavir.

It is also unclear how long after transplant most patients with refractory or resistant CMV infection are likely to receive maribavir in UK clinical practice, especially for SOT patients for whom there is more variation around who receives prophylactic treatment and for how long. The ERG estimates that the earliest HSCT patients may receive maribavir after transplant is likely to be around 5 months.

3.2.1.3 IAT treatment assignment

For patients randomised to the IAT arm, the investigators chose one of the 4 protocol-defined therapies ganciclovir, valganciclovir, foscarnet, or cidofovir. According to the clinical study report (CSR), the choice was made with knowledge of a patient's past medical history and clinical course with treatment of the current CMV infection and after considering the risk/benefit of potential

treatment options for the patient. The investigator decided whether the patient should continue the prior therapy at the same or increased dose, change to a new anti-CMV drug to which the patient was susceptible/had not been previously exposed, or to select a dual therapy best positioned to benefit the patient.

Changes to the selected IAT(s) at randomisation could not include an addition of, or switch to, another anti-CMV agent not selected at randomisation. Addition of, or switch to, another anti-CMV agent was declared a failure for the purpose of study analysis. However, changes between IV ganciclovir and oral valganciclovir were allowed. It is also noted in the CSR that, "*although refractoriness to at least 1 agent was required for entry into the study, subjects in the IAT arm were not necessarily refractory or resistant to the study treatment that they received as IAT under the study protocol*". As noted in in the baseline characteristics of the patients in SOLSTICE, 52% of patients in the maribavir arm and 60% of patients in the IAT arm had confirmed resistance to ganciclovir, foscarnet, and/or cidofovir at baseline. Out of these patients with confirmed resistance to one or more of the anti-CMV treatments, a large proportion were given an IAT they had confirmed resistance to (Table 17). Based on baseline genotyping results reported in the CSR, 57% of patients given ganciclovir or valganciclovir had a confirmed resistance to these specific treatments.

Table 17. Summary of Baseline Genotyping Results by Anti-CMV Drug and IAT Type Selected (Modified Randomized Set) (reproduced from the CSR Table 18)

Resistant to:	IAT (N=116)	Maribavir (N=234)	IAT Type				
			GCV/VGCV (N=56)	Foscarnet (N=47)	Cidofovir (N=6)	GCV/ Foscarnet (N=3)	VGCV/ Foscarnet (N=4)
GCV/ VGCV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Foscarnet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cidofovir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CMV, cytomegalovirus; IAT, Investigator-assigned anti-CMV treatment; GCV, ganciclovir; VGCV, valganciclovir

According to the ERG's clinical experts, in clinical practice patients will be assessed for resistance if they do not respond adequately to a specific anti-CMV treatment. The results of resistance testing may take some time but if and when resistance is confirmed to the treatment received, the patient will be given an alternative treatment. Continued treatment when resistance has been confirmed is likely to lead to a lower chance of CMV clearance than changing to an alternative anti-CMV treatment. According to the CSR, the reason for the open label trial design and the allowed mix of anti-CMV treatments in the control arm was principally because of the need for the physician to

individualise drug selection for treatment-refractory patients in the IAT arm, choosing the appropriate therapy(ies) based on clinical data and judgment, institutional guidelines, published guidance documents, and other relevant published literature. This was specifically to limit the impact of toxicity on the ability of the patients to complete therapy. The company also highlights that the genetic testing for antiviral resistance in SOLSTICE may have resulted in the identification of the most appropriate treatment for patients in the IAT arm. However, subgroup results based on presence or absence of confirmed resistance indicate that patients in the IAT arm with confirmed resistance did substantially worse, in terms of clearance at week 8, than patient who were refractory but with no confirmed resistance, when compared with maribavir. The subgroup results are presented and discussed in Section 3.2.2.9.

In addition, the ERG's clinical experts advised that maribavir is likely to primarily be used as a second-line therapy after failure on ganciclovir or valganciclovir for both HSCT and SOT patients. In line with this assumption, the most recent anti-CMV agent prior to randomisation was ganciclovir or valganciclovir for the vast majority of patients in the trial (~85%). According to the treatment pathways for HSCT and SOT presented by the company, and supported by the ERG's clinical experts, the most commonly used second-line treatment and therefore the most relevant comparator to maribavir is foscarnet. However, only around 40% of patients in the IAT arm were given foscarnet monotherapy in the trial.

The low proportion of patients given foscarnet and the high proportion of patients re-treated with a ganciclovir and valganciclovir despite confirmed resistance indicates that the choice of treatment in the IAT arm may not have been as optimised as it would be in clinical practice. The results of the trial may therefore not be generalisable to the outcomes that could be expected in UK clinical practice.

3.2.1.4 Outcome assessment

CMV viral load was assessed weekly and performed by a central virology laboratory to control variability. CMV viraemia clearance was defined as plasma CMV DNA concentrations < lower limit of quantitation (LLOQ, i.e. <137 IU/mL) in two consecutive post-baseline samples separated by at least 5 days. The primary outcome of SOLSTICE was clearance at week 8. The clearance data informing the economic model is clearance at week 4 and week 8. However, the data informing the model for both week 4 and week 8 are based on retrospective *post hoc* analyses with the week 8 data based on patients who did not have clearance at week 4 rather than the ITT population. The ERG considers the

analysis of the primary outcome from SOLSTICE the most robust data source for the clinical effectiveness of maribavir and for the economic analysis.

Recurrence was captured based on patients achieving clearance at any time during the study, but also based on those who achieved the primary outcome: clearance at week 8. The rational for assessing recurrence based on clearance at week 8 was provided in the CSR where the company states that,

"[redacted]" The ERG notes that this is likely to apply also to clearance and thereby strengthens the case for focusing on the primary outcome over the retrospective *post hoc* analyses of clearance at week 4 and 8.

Recurrence of CMV viraemia was defined as plasma CMV DNA concentrations ≥LLOQ in 2 consecutive plasma samples separated by at least 5 days after achieving confirmed viraemia clearance. In addition, clinically relevant recurrence, defined as recurrence needing alternative CMV-treatment, was captured. The latter is the recurrence outcome used in the model: clinically relevant recurrence at week 8 for those who had clearance at week 4 (*post hoc* analysis) and clinically relevant recurrence at week 20 for those with clearance at week 8 (pre-specified outcome).

In the CSR the company acknowledges that: "[redacted] At clarification the company further clarified that no specific definition was supplied regarding recurrence requiring treatment beyond the definition of initial infection requiring treatment. That is, the company expects the requirement for recurrence requiring treatment to be the same as the inclusion criterion of CMV infection (≥2,730 IU/mL in whole blood or ≥910 IU/mL in plasma). However, according to the CSR, "[redacted] and therefore, [redacted]" The ERG highlights the subjective nature of this outcome, which although clinically relevant, is likely to be biased, especially as the patients and trial investigators were not blinded.

3.2.1.5 Rescue arm

The treatment period in the trial was 8 weeks in both trial arms but patients in the IAT arm could discontinue IAT from week 3 at the investigator's discretion (lack of efficacy or toxicity) and instead receive maribavir. The ERG's clinical experts advised that in clinical practice it is very rare that a patient would stay on any of the anti-CMV treatments given in the IAT arm for as long as 8 weeks and that the long treatment period in the trial may accentuate the favourable toxicity profile of maribavir compared with the treatments in the IAT arm. The long treatment phase may also lead to an inflated cessation of therapy in the IAT arm. However, the experts also not that 3 weeks of treatment may not be enough to assess lack of efficacy. In clinical practice patients are likely to stay on anti-CMV treatment for closer to 4 weeks before discontinuing a treatment due to lack of efficacy.

It is not clear how many patients discontinued IAT at week 3 or how many continued for longer than 5 or 6 weeks, and thus how well the IAT arm reflects the use of these anti-CMV treatments in clinical practice. This may confound the efficacy in the IAT arm. However, it is not possible to quantify the effect of this potential difference between the trial design and clinical practice.

The company states that, "*Inclusion of the rescue arm for the IAT group introduced selection bias by removing subjects who were failing IAT. As a result, subjects who continued in the IAT arm represented those who were able to tolerate better and more likely to respond to treatment with IAT*." The ERG notes that the selection bias in the IAT arm due to the option of crossing over to the rescue arm won't affect clearance or recurrence (as these patients will not contribute to the recurrence data as they are non-responders to the randomised treatment). However, the outcomes which may be affected by the crossover to the maribavir rescue arm are mortality, graft function, QoL, and hospitalisations. For mortality, graft function and hospitalisations there were very few events and therefore substantial uncertainty around the results, which is unlikely to be markedly affected by the inclusion/exclusion of the rescue arm. However, for mortality the company provided results of advanced treatment switching methods which are mentioned in Section 3.2.2.4.

3.2.1.6 Handling of missing data

The primary approach for handling of missing data was described for each outcome reported in the CS. For the primary outcome of clearance at week 8, patients who received an alternative anti-CMV treatment before week 8 and patients with missing data due to early discontinuation were assumed

to be non-responders. The ERG considers the approach to be appropriate and likely to provide a conservative estimate of the rate of responders in both treatment arms.

For recurrence, the company states that all CMV DNA measurements after achieving confirmed CMV viraemia clearance, regardless of rescue or alternative treatment, were included in the assessment. The ERG assumes that data for clinically relevant recurrence included all CMV DNA measurements after achieving confirmed CMV viraemia clearance for all patients who received rescue or alternative treatment. For recurrence, the ERG considers the approach of handling missing data likely to lead to overly optimistic rather than conservative results as patients without the measured outcome (recurrence) were assumed not to have that outcome. An analysis of response rates is only conservative if the missing data is assumed to be a negative outcome – or more accurately if only positive events are measured. The ERG, therefore, has a strong preference for using KM data instead of response rates for both clearance and recurrence, as the KM data will take into account the change in number of patients contributing to the outcome at each time points by censoring patients when having an event other than clearance or recurrence, such as a missing CMV measurement.

3.2.2 *Critique of the clinical effectiveness analysis*

3.2.2.1 *CMV viraemia clearance*

The results for the primary endpoint, clearance at week 8, showed that a greater proportion of patients in the maribavir arm (55.7%) achieved confirmed CMV viraemia clearance compared with IAT (23.9%) in the ITT population (Table 18). At the end of the study (week 20) the clearance rates were [redacted]

In the model the company use the *post hoc* outcomes of clearance at week 4 and clearance at week 8 based on patients who did not have clearance at week 4. Clearance for the ITT population at week 4 was [redacted] Clearance at week 8 for patients who didn't have clearance at week 4 was [redacted]

Table 18. CMV viraemia clearance at week 4, 8 and 20.

	IAT	Maribavir			

Number at baseline	117		235				
	n/N	%	n/N	%	Adjusted[$] Diff. % (95% CI)	Unadjusted Diff. % (95% CI)	p
Clearance at 4 wks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clearance at 8 wks (primary outcome)	28/117	23.9	131/235	55.7	32.8 (22.8 to 42.7)	[redacted]*	<0.001
Clearance at 8 wks based on no clearance at 4 wks	[redacted]	[redacted]	[redacted]	[redacted]	NR	[redacted]	NR
Clearance at 20 wks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; Diff, difference; IAT, Investigator-assigned anti-CMV treatment; NR, not reported; wks, weeks

[$] adjusted for the stratification factors transplant type (SOT vs. HSCT) and baseline plasma CMV DNA viral load (low vs. pooled intermediate/high),

*Unadjusted difference in proportion (Maribavir – IAT) and the corresponding 95% CI is computed by the normal approximation method by the company.

**Unadjusted difference in proportion (Maribavir – IAT) calculated by the ERG.

The company reported the results of various sensitivity analyses investigating the impact of early discontinuation (using alternate definitions of CMV clearance response) on the primary endpoint of clearance at the end of study week 8. Overall, the results of the sensitivity analyses were consistent with the primary analysis and are not reported here.

In the CSR data on clearance were also reported as KM curves for clearance at any time during the study period (Figure 3). The results of clearance at week 8 are very different between the primary outcome rates and the KM curve. This is likely to be due to censoring of patients who no longer contribute data in the KM curve, whereas the rates for the primary analysis are based on the randomised population (ITT population). Patients are likely to have been censored if they had missing CMV measurements or other reasons for clearance not to be captured, whereas these patients have been counted as non-responders in the primary analysis. For clearance this could be considered a conservative assumption – the estimate is based on measured clearance with all other patients (including those with missing data) implicitly assumed to be treatment failures. However, for recurrence, the same approach leads to a more optimistic outcomes (with patients with missing data implicitly assumed to **not** have recurrence). The proportion of patients for whom CMV measurements were missing at week 8 was 11% in the maribavir arm and 44% in the IAT arm, and at week 20 that had increased to 16% and 50%, respectively (see Section 3.2.2.3). The ERG therefore

has a strong preference for the use of the KM data rather than rates in the economic model, which is discussed in Section 4.2.6.

Figure 3. Cumulative probability of achieving first CMV viremia clearance at any time during the study by treatment group (randomised set) (reproduced from the CSR)

3.2.2.2 CMV viraemia clearance and CMV infection symptom control

The key secondary endpoint in the trial 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. CMV infection symptom control was defined as resolution or improvement of tissue-invasive disease or CMV syndrome for symptomatic patients at baseline, or no new symptoms for patients who were asymptomatic at baseline. Maintenance of benefit through week 16 was defined as maintenance of CMV viraemia clearance through week 16 determined by the absence of two consecutive positive CMV DNA viral load assessments through week 16. Symptom status for tissue invasive disease or CMV syndrome was adjudicated by an independent Endpoint Adjudication Committee (EAC).

Additional secondary endpoints included:

- Achievement of the confirmed CMV viraemia clearance and CMV infection symptom control after 8 weeks of receiving study-assigned treatment, and
- 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.

The results are presented in Table 19, which shows a large benefit in favour of maribavir in terms of CMV clearance and symptom control at week 8. However, the proportions of patients who maintain clearance and symptom control until week 12, 16 and 20 were substantially reduced in both treatment arms. The difference between maribavir and IAT was also substantially reduced at all timepoints after week 8.

Table 19. CMV viraemia clearance and CMV infection symptom control through week 12, 16 and 20

	IAT		Maribavir			
Number at baseline	117		235			
	n/N	%	n/N	%	Adjusted Diff. % (95% CI)	Unadjusted* Diff. % (95% CI)
Clearance at 8 wks	28/117	23.9	131/235	55.7	32.8 (22.8 to 42.7)	[redacted]
Clearance at 12 wks	[redacted]	10.3	[redacted]	22.6	13.5 (5.84 to 21.17)	[redacted]
Clearance at 20 wks	[redacted]	9.4	[redacted]	18.3	9.8 (2.58 to 17.06)	[redacted]

Abbreviations: CI, confidence interval; Diff, difference; IAT, Investigator-assigned anti-CMV treatment; wks, weeks

*Note: Unadjusted difference in proportion (Maribavir – IAT) and the corresponding 95% CI is computed by the normal approximation method.

3.2.2.3 CMV viral load

The CMV viral load of patients over time (i.e., plasma CMV DNA concentration assessed by the central laboratory) was an exploratory efficacy endpoint. In line with the clearance data, maribavir treatment leads to a larger reduction in viral load (Log10 plasma CMV viral load) at week 4 compared with IAT but from week 8 onwards there is little difference between the treatment arms. The company argues that the lack of difference at the later timepoints is likely due to the lower number of patients in the IAT arm with measurements compared with the maribavir arm as the

patients with missing measurements are more likely not to have achieved viral clearance. The ERG agrees with the company and notes that this will likely lead to a conservative estimate of the primary outcome, clearance at week 8. However, the ERG also notes that the opposite may be true for recurrence.

Table 20. SOLSTICE: Summary and analysis of change from baseline in Log_{10} plasma CMV viral load by study week and treatment group (randomised set) (reproduced from CS, appendix D.4.1.1)

	IAT (N=117)		Maribavir (N=235)	
	Observed Value	Change From Baseline	Observed Value	Change From Baseline
Baseline				
n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Median	[redacted]		[redacted]	
Week 4				
n	[redacted]		[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Week 8				
n	[redacted]		[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Week 20				
n	[redacted]		[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CMV cytomegalovirus; IAT, investigator-assigned anti-CMV treatment; LLOQ, lower limit of quantitation; SD, standard deviation; VL, viral load

3.2.2.4 Mortality

Few patients died during the study and no statistically significant difference was observed in all-cause mortality between the treatment arms during the study period (20 weeks) (Table 21). *Post hoc* subgroup analysis by transplant type showed that there were more deaths in the HSCT group than the SOT group, and there was a small numerical difference in favour of maribavir for SOT patients and in favour of IAT for HSCT patients but neither analysis reached statistically significance.

The ERG notes that the HR and 95% CIs reported for the full trial population and the HSCT subgroup are identical despite the difference in underlying data. The reported HR is likely correct for the ITT population and likely to be different for the HSCT subgroup.

From the analysis of all-cause mortality, the company concluded that neither treatment, health state (clearance or no clearance) nor transplant type had a statistically significant impact on mortality in the first 8 weeks of the trial. However, based on input from the company's clinical experts they use mortality data based on type of transplant for the first 8 weeks of the model and health state specific mortality, that is mortality based on response or no response rather than treatment or transplant type, in the model from week 8 to week 52. This was based on another *post hoc* analysis of mortality based on response, which shows that more patients who were non-responders than responders at week 8 had died by week 20. The merits of this are discussed in Section 4.2.6.3.

The ERG requested mortality data at 20 weeks for the safety population by treatment arm and separately for the rescue arm and for those randomised to IAT who did not cross over to the rescue arm. That is because mortality was analysed based on the ITT population and thus mortality may be biased by patients in the IAT arm crossing over to receive maribavir. The company reported results from additional analyses including censoring patients who received rescue maribavir or alternative CMV treatment and advanced methods adjusting for treatment switching (Table 21). These resulted in a numerical advantage in favour of maribavir but the difference was still not statistically significant.

Table 21. Mortality by treatment group

	IAT				Maribavir	
Number at baseline	117				235	
	n/N	%	HR (95% CI)	p	n/N	%
Mortality at week 8*	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
All-cause Mortality$ at week 20	13/117	11.1	[redacted]	[redacted]	27/235	11.5
Mortality at week 20*	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Mortality at week 20 Sensitivity analysis censoring patients who received rescue maribavir or alternative CMV treatment	[redacted]	[redacted]	[redacted]	NR	[redacted]	[redacted]

Mortality at week 20 in HSCT patients	[redacted]	[redacted]	[redacted]	NR	[redacted]	[redacted]
Mortality at week 20 in SOT patients	[redacted]	[redacted]	[redacted]	NR	[redacted]	[redacted]

Abbreviations: IAT, investigator-assigned anti-CMV treatment; CMV, cytomegalovirus; HSCT; hematopoietic stem cell transplant SOT, solid organ transplant.

* source: CSR Table 42

$ Includes 4 patients who died after 20 weeks but were followed up due to ongoing serious adverse events

3.2.2.5 Recurrence of CMV viraemia

In SOLSTICE, the proportion of patients with a recurrence (defined as plasma CMV DNA concentrations ≥LLOQ in 2 consecutive samples separated by at least 5 days) was higher with maribavir treatment compared with IAT. This was irrespective of looking at patients with clearance at any time in the trial or patients with clearance at week 8 (Table 22). As highlighted in the CSR, "[redacted]"

The company states that recurrence in the model is informed by the *post hoc* outcome of clinically relevant recurrence, i.e. recurrence needing treatment with an alternative anti-CMV treatment, at week 8 based on clearance at week 4 and clinically relevant recurrence during the follow up period (up to week 20) based on clearance at week 8. For clinically relevant recurrence maribavir treatment led to a higher proportion of patients with a recurrence compared with IAT at week 8 based on patients with clearance at week 4 (Table 22). At the end of the trial (week 20), the proportion of patients with a clinically relevant recurrence was lower with maribavir compared with IAT. However, at neither timepoint was the difference statistically significant. In addition, the data that feed into the model in order to capture recurrences from week 4 to week 8 differ from those presented in Table 22. In the model the clinically relevant recurrence rate in the maribavir and IAT arms are 19% and 31%, respectively. It is unclear to the ERG what these data are based on.

The ERG's clinical experts advised that there is no clinical rationale for a lingering effect of CMV treatment. That is, after clearance has been achieved and a patient has discontinued treatment, the risk of recurrence is the same irrespective of the anti-CMV treatment received to achieved

clearance. As such, the non-significant difference between maribavir and IAT for clinically relevant recurrence is not unexpected. As discussed in Section 3.2.1, the ERG also highlights the open label trial design and the lack of clear guidance of when and who would need alternative treatment for their CMV recurrence, which increases the risk of bias for this outcome.

Table 22. Analysis of recurrence of CMV viraemia at week 8 and 20 (randomised set)

	IAT		Maribavir			
Number at baseline	117		235			
	n/N	%	n/N	%	Unadjusted Diff. %	p
Recurrence during the first 8 weeks	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Recurrence during the follow-up period (between week 8 and week 20)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Recurrence any time on study	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Cr recurrence at week 8 among responders at week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cr recurrence at week 20 among responders at week 8	[redacted]	35.7	[redacted]	26.0	[redacted]	[redacted]

Abbreviations: CMV, cytomegalovirus; Cr, clinically relevant; Diff, difference; IAT, investigator-assigned anti-CMV treatment; N, number of patients; NR, not reported

*Unadjusted difference in proportion (Maribavir – IAT), calculated by the company.

In the CSR recurrence data were presented as KM curves showing the cumulative probability of recurrence in patients who achieve clearance at any time during the trial (Figure 4), and the cumulative probability of clinically relevant recurrence in patients who achieve clearance by week 8 (

Figure 5). The figures show [redacted]

[redacted] However, as with clearance, the rates of overall recurrence at the end of the study are very different between the KM data and the rates reported in Table 22. For clinically relevant recurrence the difference between the KM data and the rates reported in Table 22 were less pronounced. Patients are likely to have been censored from the KM analysis if they had missing CMV measurements or other reasons for recurrence not being captured (e.g. discontinuations, withdrawals from the study or death), whereas these patients have been counted as not having a recurrence in the rate analysis.

Data on viral load presented in the CS shows that at week 20, results of CMV measurements were missing for 50% of patients in the IAT arm but only 16% of patients in the maribavir arm (Table 23). Due to the large amount of missing data, especially in the IAT arm, the ERG has a strong preference for the use of the KM data rather than rates in the economic model, which is discussed in Section 4.2.6.

Figure 4. Cumulative probability of CMV viremia recurrence in patients who achieved viremia clearance by treatment group (randomised set) (reproduced from the CSR Figure 14.2.3.4.1)

Figure 5. Cumulative probability of first CMV viremia clearance at week 8 to CMV viremia recurrence requiring alternative treatment by treatment group (randomised set) (reproduced from the CSR Figure 14.2.3.4.2)

Table 23. SOLSTICE: Summary and analysis of change from baseline in Log_{10} plasma CMV viral load by study week and treatment group (randomised set) (adapted from the CS, appendix D.4, Table 22)

	IAT (N=117)		Maribavir (N=235)	
	Observed Value	**Change From Baseline**	**Observed Value**	**Change From Baseline**
Baseline				
n	[redacted]		[redacted]	

Mean (SD)	[redacted]		[redacted]	
Median	[redacted]		[redacted]	
Week 4				
n	[redacted]		[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Week 8				
n	[redacted]		[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Week 20				
n	[redacted]		[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CMV, cytomegalovirus; IAT, investigator-assigned anti-CMV treatment; LLOQ, lower limit of quantitation; SD, standard deviation; VL, viral load

3.2.2.6 Transplant graft function

In both treatment arms, few patients experienced adverse graft outcomes during the study. Among SOT patients, [redacted] had an acute rejection in the IAT arm and [redacted] in the maribavir arm. No SOT patients experienced chronic rejection or graft loss. Among HSCT patients there [redacted] and new GvHD was reported for [redacted] of HSCT patients in the maribavir arm and [redacted] of HSCT patients in the IAT arm.

Data on graft function from the trial did not inform the economic model. However, the company's and the ERG's clinical experts agree that graft preservation is an important factor for the treatment of CMV in SOT patients, and that graft loss events would be more likely to be observed over a longer time horizon than the trial duration, and with greater frequency in a CMV cohort. The company therefore used external data to inform the probability of graft loss in the model. This is discussed in Section 4.2.6.4.

3.2.2.7 Health-related quality of life

Health related quality of life (HRQoL) was assessed using the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) and the Short Form-36 version 2 (SF-36v2) instruments. EQ-5D-5L data based on the EQ-VAS scores [redacted]

[redacted] with a larger improvement in QoL in the IAT arm [redacted]. In contrast, the EQ-5D-5L Utility Index scores showed [redacted] The results of the SF-36v2 also indicates [redacted] in HRQoL from baseline to the end of treatment (week 8) for both treatment arms, with a larger improvement in the maribavir arm. However, the ERG agrees with the company that the observed changes in EQ-5D-5L and SF-36v2 were [redacted]

3.2.2.8 Hospitalisation

The proportions of patients who were hospitalised during the treatment phase (8 weeks) and the full trial duration (20 weeks) were relatively similar between the trial arms, with slightly lower proportions in the maribavir arm compared with the IAT arm (Appendix 9.2). Similarly, the mean length of hospital stay was relatively similar between the arms but slightly shorter with maribavir.

At the clarification stage the ERG requested data on hospitalisation by treatment arm, type of transplant, and response (clearance) at each timepoint. The ERG also requested a breakdown of the reasons for hospitalisation. Data on hospitalisations at week 4, and subgroup data by transplant type and response, were not available but the company report that the most common reasons for hospitalisation in the trial were CMV infection/disease ([redacted]) and CMV treatment, which was more common in the IAT arm ([redacted]) (Appendix 9.2). This difference may not be unexpected as several of the IATs (ganciclovir and foscarnet) are given intravenously and requires several administrations per day and close monitoring for the duration of treatment, often necessitating the hospitalisation of patients for the duration of treatment. However, the low use of foscarnet in the IAT arm may obscure what would be expected in terms of increased admissions and length of stay with IAT versus maribavir compared with UK clinical practice.

3.2.2.9 Subgroup analyses

The company presented subgroup analysis for the primary outcome (clearance at week 8) and mortality based on transplant type, as specified in the NICE final scope (Table 24). The results showed that the benefit of treatment with maribavir on clearance at week 8 was consistent with the benefit seen in the overall population, irrespective of transplant type. The result on mortality

indicates a potential difference depending on transplant type with [redacted] There was also [redacted]

The ERG notes that the HR and 95% CIs reported for the full trial population and the HSCT subgroup are identical despite the difference in underlying data. The ERG considers the reported HR is likely to be correct for the ITT population and likely to be different for the HSCT subgroup.

Table 24. Efficacy endpoint analysis by transplant type

Endpoint	IAT	Maribavir	
Confirmed CMV viraemia clearance at week 8, n (%)[a]			Adjusted difference in proportion (95% CI); p-value
HSCT	10 (20.8)	52 (55.9)	36.1 (21.1 to 51.2); [redacted]
SOT	18 (26.1)	79 (55.6)	30.5 (17.3 to 43.6); [redacted]
ITT population	(23.9)	(55.7)	32.8 (22.8 to 42.7); <0.001
Number of patients who died, n (%)[b]			**HR (95% CI)**
HSCT	[redacted]	[redacted]	[redacted]
SOT	[redacted]	[redacted]	[redacted]
ITT population	13 (11.1)	27 (11.5)	[redacted]

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; HR, hazard ratio; IAT, investigator-assigned anti-CMV treatment; N, number of patients; SOT, solid organ transplant

Note: Percentages are based on the number of patients in the Randomised Set

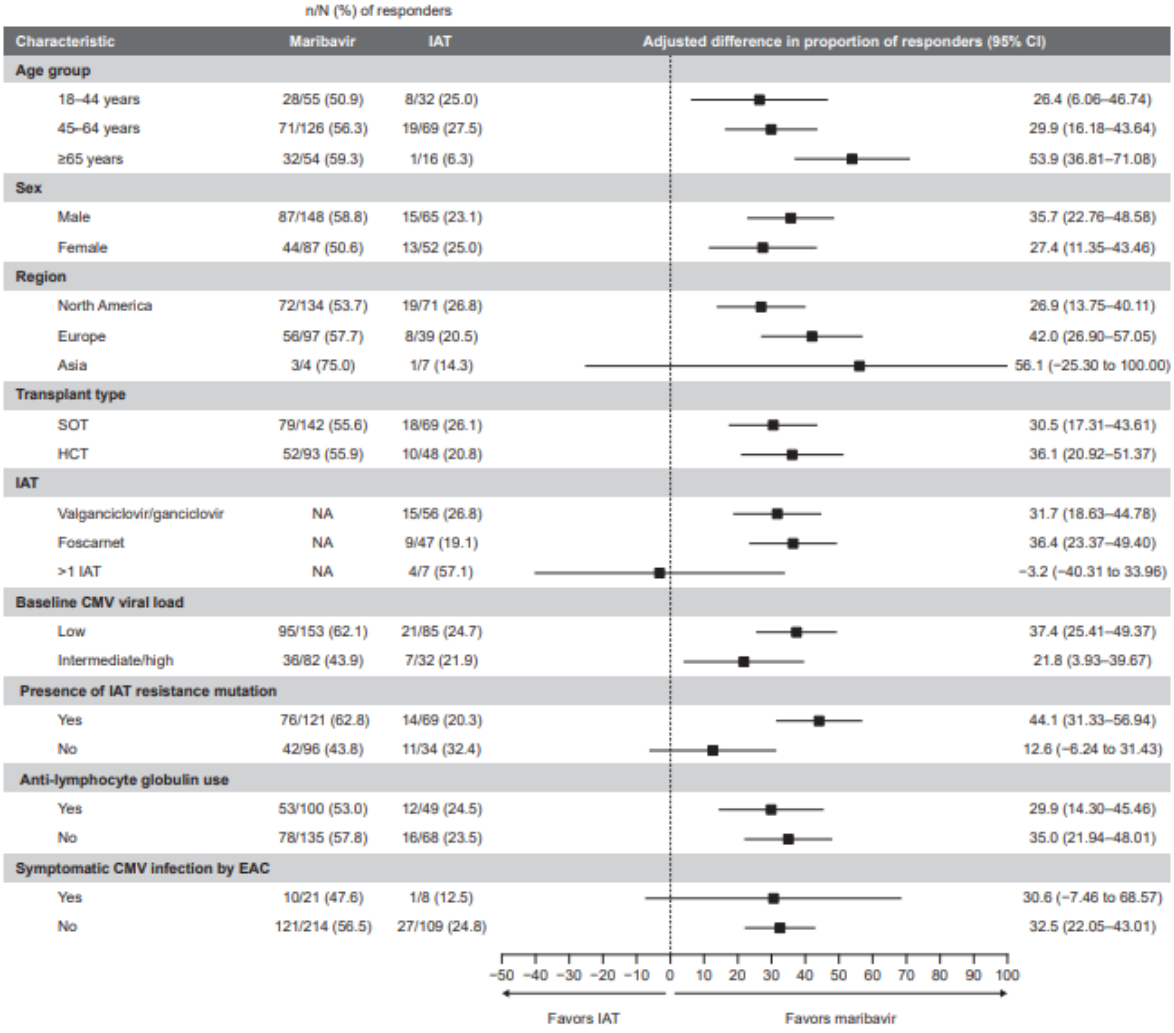
[a] Analysis was pre-specified

[b] *Post hoc* analysis

The results of other pre-specified subgroup analyses on the primary outcome were largely consistent with the results of the overall population (Figure 6). However, the ERG notes the difference in results based on the presence or not of an IAT resistance mutation, which indicates that IAT is less effective when resistance to a specific prior IAT is confirmed (resulting in a greater treatment effect for maribavir vs IAT). This goes against the company's argument that genetic testing for antiviral resistance in the trial may have resulted in the identification of the most appropriate treatment for patients in the IAT arm. The company also argues that the overall trial results may be conservative for maribavir because genetic testing is not part of routine UK practice for the management of CMV infection. The clinical experts advising the ERG do not agree with the company and state that genetic testing is a key part of routine practice but acknowledge that due to the time it takes to receive the results of the resistance test, any necessary change in treatment may be delayed. The ERG

speculates that the counterintuitive results for the subgroup of patients with confirmed resistance to an anti-CMV treatment is likely due to the large proportion of patients in the IAT arm with confirmed resistance to ganciclovir/valganciclovir who were assigned to these treatments in the trial (as reported in Section 3.2.1).

Figure 6. CMV viraemia clearance at week 8 overall in subgroups (reproduced from CS, Appendix E, Figure 5)



Abbreviations: CI confidence interval; CMV, cytomegalovirus; EAC, Endpoint Adjudication Committee; HCT, haematopoietic-cell transplant; IAT, investigator-assigned therapy; SOT, solid organ transplant

Note: Between-group differences for each subgroup in the randomised population adjusted for applicable stratification factor(s) of baseline CMV DNA level (low or intermediate/high) and SOT/HCT. Six patients received cidofovir as IAT (data not shown); one patient did not receive a dose of IAT.

As mentioned in Sections 2.3.5, 3.2.1.2 and 3.2.1.3, the ERG was concerned about potential differences in specific patient characteristics that may impact on the efficacy outcomes of maribavir compared with IAT. These include time since transplant and the number of prior CMV infection

episodes. The ERG also requested outcome data on the subgroup of patients in the IAT arm who received foscarnet as this is likely to be the key comparator for maribavir in the refractory and resistant setting in clinical practice.

The reasons for requesting results for these subgroups were:

- Time since transplant is an important prognostic factor which, although unlikely to have an effect on clearance, is likely to impact on recurrence, mortality and other outcomes as the risk of CMV infection, graft failure, etc., which diminish with an increased time since transplant.
- Number of CMV episodes (post-transplant) has also been shown to be a key prognostic factor of outcomes such as graft loss. In addition, a higher number of prior CMV episodes is likely to be associated with a longer time since transplant.
- Foscarnet is the key comparator in this setting and the IAT arm in SOLSTICE is very heterogeneous in terms of the treatments given. The results may be different and more generalisable if focused on the foscarnet subgroup.

The company did not provide subgroup results based on the current CMV infection being either the first or a later episode post-transplant. The company stated that, "*numerous sensitivity analyses were performed including baseline viral load, which may be predictive of whether the episode is first or later post-transplant, since earlier episodes tend to be characterised by higher viral loads. No difference was seen between results for either low or higher viral loads.*" However, the company did provide results for the subgroup of the IAT arm given foscarnet and by time since transplant. The ERG highlights that the results of these subgroup analyses are exploratory, as they are less reliable (due to breaking randomisation and likely at an increased risk of bias) and more uncertain (due to a smaller sample size) compared with the results for the ITT population.

The results for the subgroup of the IAT arm given foscarnet show no statistically significant difference or clear trend of a difference in results across clearance, recurrence, mortality or hospitalisations, compared with the overall IAT trial arm (Appendix 1.1). However, the reduced sample size of the foscarnet subgroup and the small number of events means that this assessment is likely to be underpowered to detect a true difference should one exist.

Subgroup results by time since transplant were made available by the company at a very late stage of the writing of this report. A full critique of the results has therefore not been possible in the time

available. Nevertheless, a summary of what was provided, and the ERG's initial assessment is presented below. As presented in Section 3.2.1.2, the mean number of days since transplant was [redacted] in the maribavir arm than in the IAT arm ([redacted] and time since transplant was [redacted] for SOT patients than HSCT patients (Table 25).

Table 25. Mean and median time since transplant (reproduced from clarification response to A2, Table 2)

	HSCT			SOT		
Time since transplant	IAT	Maribavir	Overall	IAT	Maribavir	Overall
Mean (days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HSCT, haematopoietic stem-cell transplant; IAT, investigator-assigned therapy; SOT, solid organ transplant

The ERG requested outcome data for clearance, clinically relevant recurrence, mortality and hospitalisations separately for patients with a time from transplant to randomisation of:

- ≤ 3 months;
- > 3 months to ≤ 6 months;
- > 6 months to ≤ 12 months;
- > 12 months.

Table 26 presents the results by treatment arm based on time since transplant. Data on clearance at 4 weeks and clinically relevant recurrence at week 8 for patients with clearance at 4 weeks were not provided as these were retrospective *post hoc* analyses for this submission and not pre-specified endpoints within the SOLSTICE trial.

The number of patients in each of the four time-categories were [redacted] in both treatment arms, indicating that the longer the mean time since transplant in the maribavir arm compared with the IAT arm could be due to skewed data, primarily in the > 12 months subgroup (Table 26). There was [redacted] linked to time since transplant based on the SOLSTICE subgroup data. As highlighted by both the company and the ERG, clearance is not expected to vary with increasing time since transplant as it is solely linked to the efficacy of the anti-CMV treatment to supress the infection. Similarly, hospitalisations in the IAT arm may be mainly driven by the anti-CMV treatment given, with more hospitalisations for patients on a treatment that needs to be administered several times per day in a hospital setting.

However, potential differences between the treatment arms could be obscured by the mix of HSCT and SOT patients in the trial.

The ERG expects the risk of a recurrence to decrease the longer time that has elapsed since transplant as the patient's immune system recovers. Subgroup data for recurrence was presented for clinically relevant recurrence after week 8 requiring anti-CMV therapy. The ERG notes that the denominator is therefore all patients rather than those in each subgroup with clearance at week 8. The difference in reporting makes it difficult to validate and compare the results with those reported in the CS and used in the economic model. However, if clearance does not vary with time since transplant, then it can be assumed that the number of patients with clearance at week 8 will be relatively evenly distributed between the subgroups (as the four subgroups roughly make up a quarter of patients). If time since transplant does impact on recurrence, the number of patients with a recurrence after week 8 would be expected to go down for each subgroup with a longer time since transplant. However, the results for recurrence do not indicate such a trend. The ERG does not consider these data to show an absence of a relationship between recurrence (or CMV infection) and time since transplant. Instead, the ERG notes (as highlighted by the company) that the number of events is low, resulting in a large uncertainty around these subgroup results. In addition, the ERG reiterates that clinically relevant recurrence, as assessed in the trial, is at an increased risk of bias due to the open label trial design and the need for alternative anti-CMV treatment was at the discretion of the trial investigators.

The subgroup results for mortality show [redacted] in risk of death with increasing time since transplant, but no clear difference in mortality between the treatment arms (Table 27). Mortality data for time since transplant based on transplant type show that the vast majority of deaths in the first 3 months after transplant were HSCT patients and the majority of deaths for patients who entered the trial more than 12 months after transplant were SOT patients. However, this may be a reflection of the time since transplant before entering the trial for HSCT and SOT patients, rather than indicating an increasing risk of mortality for SOT patients with an increasing time since transplant.

Table 26. CMV clearance, recurrence, mortality, and hospitalisations, based on time since transplant

	IAT			Maribavir			Difference		
	N	n	%	N	n	%	%	95% CI	p
Clearance									
<3 m	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3-6 m	[redacted]								
6-12 m	[redacted]								
12+	[redacted]								
Total	[redacted]								
Recurrence									
<3 m	[redacted]						NR	NR	NR
3-6 m	[redacted]						NR	NR	NR
6-12 m	[redacted]						NR	NR	NR
12+	[redacted]						NR	NR	NR
Total	[redacted]						NR	NR	NR
Mortality									
<3 m	[redacted]								
3-6 m	[redacted]								
6-12 m	[redacted]								
12+	[redacted]								
Total	116	13	11.2%	234	27	11.5%			
Hospitalisations									
<3 m	[redacted]								
3-6 m	[redacted]								
6-12 m	[redacted]								
12+	[redacted]								
Total	[redacted]								

Abbreviations: IAT, investigator-assigned therapy; m, month(s)

* Total updated by the ERG as the original stated 178, which does not equate to the sum of the subgroups

Table 27. Proportion of deaths split by transplant type and time since transplant

	HSCT		SOT	
	IAT	Maribavir	IAT	Maribavir
<3 m	[redacted]			
3-6 m	[redacted]			
6-12 m	[redacted]			
12+	[redacted]			

Abbreviations: HSCT, haematopoietic stem-cell transplant; IAT, investigator-assigned therapy; m, month(s); SOT, solid organ transplant

3.2.2.10 Safety

Treatment exposure

Mean time on treatment was substantially longer on maribavir than on IAT (Table 28). The ERG notes the difference in treatment with patients in the maribavir arm continuing treatment for eight weeks whereas patients randomised to 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 after three weeks of treatment.

The clinical experts advising the ERG consider that in clinical practice patients would be treated with available treatments until clearance (but not beyond), intolerance to the treatment or for up to around 4 weeks if there was a lack of clearance. It is unlikely for patients to stay on currently available anti-CMV treatments for 8 weeks.

Table 28: Treatment exposure of the safety population

	IAT (N=116)	Maribavir (N=234)
Exposure duration[a]		
n[b]	[redacted]	[redacted]
Mean (SD), days	[redacted]	[redacted]
Median, days	34.0	57.0
Actual exposure to study-assigned treatment[c]		
n[b]	[redacted]	[redacted]
Mean (SD), days	[redacted]	[redacted]
Median, days	[redacted]	[redacted]

Abbreviations: IAT, investigator-assigned anti-CMV treatment; max, maximum; min, minimum; N, number of patients; 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

Adverse events

Adverse events which occurred within the SOLSTICE trial during the on-treatment period were reported, by treatment arm, for the safety population (all randomised patients who received at least

one dose of study medication, n=350). The overall incidence of AEs was similar between patients randomised to the maribavir or to the IAT arm (Appendix 1.1). A majority of patients experienced at least one treatment-emergent adverse event (TEAE), [redacted] in the IAT arm and [redacted] in the maribavir arm. A total of 40 deaths were reported in SOLSTICE; 16 deaths due to serious TEAEs occurred in the maribavir arm and 6 occurred in the IAT arm. The most common serious TEAEs leading to death were due to respiratory failure or relapse or progression of underlying disease. 1 death in each arm was considered treatment-related by the investigator.

Dysgeusia (altered sense of taste) was the most frequently reported treatment emergent adverse event (TEAE) in the maribavir arm (maribavir 37.2% vs IAT 3.4%). The company reports that dysgeusia was mostly mild (88.5%), usually resolved either on treatment or shortly after the last dose of maribavir, and rarely led to treatment discontinuation (0.9% of patients in maribavir arm). Neutropenia was the most frequently reported TEAE in the IAT arm (maribavir 9.4% vs IAT 22.4%), with the highest frequency observed in patients treated with valganciclovir/ganciclovir (33.9%).

The majority of cases of dysgeusia with maribavir and neutropenia with valganciclovir/ganciclovir were classed as an AE of special interest (AESI) related to the treatment. For most other AESI there was no clinically meaningful difference between treatment arms. However, a larger proportion of patients in the maribavir arm had an increased concentration of immunosuppressants than in the IAT arm, and a large proportion of these were considered related to the treatment.

Most other frequently occurring adverse events (>10% of patients in either trial arm) were relatively similar between the maribavir and IAT arms. However, in comparison with foscarnet, which is likely to be the main comparator in clinical practice, maribavir therapy led to fewer cases of TEAE including acute kidney injury (maribavir: 8.5% vs foscarnet: 21.3%) and hypokalaemia (maribavir: 3.4% vs foscarnet: 19.1%), but more cases of CMV viraemia (maribavir: 10.3% vs foscarnet: 2.1%).

TEAEs leading to treatment discontinuation were reported for a greater proportion of patients in the IAT arm ([redacted]) than in the maribavir arm ([redacted]), and among the IATs discontinuations due to TEAEs were highest with foscarnet ([redacted]). The high rate of TEAEs leading to discontinuations in the IAT arm may reflect that giving 8 weeks of treatment with any of the IATs is more likely to bring dose-limiting toxicity than with maribavir. Giving 8 weeks of IAT is not compatible with UK clinical practice.

Most patients did not have CMV tissue invasive disease or CMV syndrome at baseline (maribavir: [redacted] vs IAT [redacted] A similar proportion of patients ([redacted]) developed tissue invasive CMV disease/syndrome during the on-treatment observation period.

3.3 Conclusions of the clinical effectiveness section

The evidence submitted by the company, based on the SOLSTICE trial, reflects the decision problem defined in the NICE final scope. However, because of differences in time since transplant, the population in the economic model may not be representative of the trial population or the population in clinical practice.

The SOLSTICE trial is generally of good quality for evaluating the primary outcome of clearance at week 8. However, the ERG has several conceráns around the design and conduct of the trial on secondary and *post hoc* outcomes and its generalisability to routine clinical practice:

- **Patient characteristics** – Time since transplant, which is a key prognostic factor for outcomes such as CMV infection (recurrence) and mortality, was imbalanced between the treatment arms at baseline and, at least for SOT patients, may not be representative of patients in UK practice.
- **IAT treatment assignment** – A large proportion of patients in the IAT arm was retreated with an anti-CMV treatment for which they had confirmed resistance, likely leading to an underestimate of clearance in the IAT arm compared with clinical practice. In addition, a lower proportion than would be expected in UK practice was assigned to foscarnet. However, subgroup results by type of IAT did not reveal any clear trends in difference in efficacy for the overall IAT arm and the subgroup given foscarnet. For safety the largest proportion of patients who discontinued treatment due to an adverse event were those on foscarnet.
- **Outcome assessment** – Outcome assessment of the primary outcome is robust and at a low risk of bias. However, clearance data informing the economic model are based on retrospective *post hoc* analyses which are associated with a higher risk of false positive findings or overestimating treatment effects. For clinically relevant recurrence, which informs the model, there is a high risk of bias due to the open label trial design and the lack of objective criteria for deciding who needed treatment for their CMV infection.
- **Outcome measure** – Focusing on response rates is likely to give conservative outcomes for clearance for both treatment arms, but for recurrence it may be the opposite when there is

a large amount of missing data. The ERG, therefore, has a strong preference for using KM data, which takes into account the number of patients at risk, over response rates, for use in the economic model.

Maribavir treatment leads to statistically significant increases in the incidence of clearance at week 4 (*post hoc*), week 8 (primary analysis), and week 20. This was supported by all sensitivity analyses and most subgroup analyses. However, the subgroup analysis by resistance status confirms the counterintuitive treatment assignment for a large proportion of patients in the IAT arm, which shows that the subgroup of patients with a confirmed resistance have a lower rate of clearance compared with maribavir, than the subgroup without a confirmed resistance. This indicates that the clearance data for the full trial population may be overestimating clearance with maribavir compared to IAT.

Maribavir therapy also seems to lead to numerically fewer clinically relevant recurrences at week 8 and week 20 compared with IAT. However, the difference versus IAT was not statistically significant, and the ERG's clinical experts highlight that there is no clinical rational for any anti-CMV treatment (including maribavir) to have an impact on the time to and risk of a subsequent CMV infection. The differences in mean time since transplant, the fact that patients continue maribavir treatment for 8 weeks, whereas patients in the IAT arm could discontinue treatment from week 3, and the potential bias introduced by further treatment being decided by the unblinded investigators, are all likely to affect the results of recurrence and are likely to lead to an overestimate of the efficacy of maribavir.

The ERG has a strong preference for using the primary outcome data for clearance and the pre-specified outcome data for clinically relevant recurrence over the data based on *post hoc* analyses to inform the economic model. In addition, the ERG highlights that the clearance data are relatively robust compared with the data on clinically relevant recurrence, which is likely to be at a high risk of bias due to the open label design of the study and the assignment of specific IATs at the start of the study.

There were few deaths or graft function issues in the study with no statistically significant difference between the treatment arms. The low number of events are likely due to the short follow up (20 weeks) but, at least for SOT patients, it's also likely due to the long time since transplant, i.e. on average after the initial 6 to 12 months high-risk period after transplant.

Adverse events (AEs) were generally mild and AEs leading to treatment discontinuation were more common among patients treated with an IAT (particularly foscarnet) than maribavir.

4 Cost effectiveness

The ERG considers that the key uncertainty around the company's cost effectiveness analysis is the assumption of time elapsed since transplant at baseline in the model. Currently, the model seems to estimate the cost-effectiveness for maribavir in refractory or resistant (r/r) patients when given immediately after surgery, despite the company submission (CS) stating that all patients enter the model at 1 year after surgery.

The evidence available in literature and clinical expert opinion provided to the ERG consistently reported that patients' clinical outcomes (such as mortality and risk of graft loss) vary as time from transplant elapses. Crucially, the ERG heard from its clinical experts that the probability of recurrence is unlikely to depend on the type of treatment on which patient achieved clearance (i.e., maribavir vs IAT), but instead to be dependent on time since transplant and on the level of lifelong immunosuppression needed by patients. Therefore, the ERG considers that time since surgery is a fundamental aspect of the cost effectiveness of maribavir.

During clarification, the company was unaware of the existence of data on time since transplant at baseline in SOLSTICE. Therefore, several clarification questions raised by the ERG remained unanswered. However, after the company's reply to the ERG's clarification questions was submitted, it came to light that time from transplant at baseline in SOLSTICE had been captured in the trial.

Based on the data shared by the company since then, the ERG learned that the mean time since surgery at baseline in SOLSTICE for SOT patients was [redacted] For HSCT patients mean time since transplant was [redacted] The ERG notes that there is a marked difference between mean and median times since transplant at baseline, with [redacted] and [redacted] Nonetheless, the ERG points out that a mean-based approach is a better reflection of the whole population under consideration rather than focusing on median values, particularly when dealing with a therapeutic area where there is a wide range of outcomes as is the case here with CMV infection occurring after transplant.

The data shared on mean time since surgery for SOT patients are, therefore, in direct contradiction with the ERG's inferred conclusion about the company's main modelling assumption - that no CMV

events occur 12 months after transplant. Furthermore, the company's model assumption that patients begin maribavir immediately after transplant fails not only to reflect time since transplant for the overall trial population (where the relative treatment effect of maribavir is sourced from), but also, a r/r population who initiates treatment with maribavir as soon as possible after transplant (and as a second line treatment).

Additionally, the ERG considers that the company's use of recurrence data from SOLSTICE to be fundamentally flawed and to introduce a bias in favour of maribavir. The company's assumption that the 4-weekly probability of recurrence at the end of the trial period remains the same until week 52 in the model, combined with the assumption that patients who achieved clearance with maribavir have a lower probability of recurrence (regardless of how long they have been off treatment), considerably overestimates recurrences in the model as well as the benefit associated with maribavir.

Given these concerns, the ERG concluded that the company's model is currently unfit for decision making. Throughout the following sections of the report, the ERG discusses the company's modelling approach and provides recommendations on the necessary alterations so that the economic model can accurately capture the cost effectiveness of maribavir. The three key elements of the analyses suggested by the ERG revolve around:

1. The company capturing the cost-effectiveness of maribavir in r/r patients from SOLSTICE, where the mean time from transplant at baseline in the trial is appropriately modelled. This population is referred to as the trial population from hereafter. The ERG notes that even though the company states that patients enter the model 1 year after all transplants, the ERG disagrees, and considers that the model assumes patients enter the analysis immediately after transplant (as discussed in Section 4.2.2).
2. The company clarifying the intended use for maribavir in the treatment pathway. If the company's value proposition is that maribavir should be given as early as possible for r/r patients, then:
    a. For SOT patients – clinical expert opinion should be used to inform the minimum time when patients, on average, would be eligible to start maribavir. The ERG has heard from its experts that this is likely to vary according to patients receiving prophylaxis (in which case the minimum period could be 4 months) or not (in which

case the minimum period could be 1 month). This population is referred to as the SOT UK population from hereafter.

b. For HSCT patients – since the approval of letermovir by NICE (TA591), the majority of patients receive at least 100 days of prophylaxis with letermovir before moving on to a first line treatment with IAT. Therefore, similar to SOT patients, the ERG recommends that clinical expert opinion is used by the company to inform the minimum time when patients, on average, would be eligible to start maribavir after HSCT in UK clinical practice. This population is hereafter referred to as the HSCT UK population. The ERG notes that the UK and the trial HSCT populations might be similar in terms of time since transplant when maribavir is initiated, nonetheless, this should be confirmed by the company.

1. The company limiting the number of recurrences in the first 52 weeks of the economic model. This issue is discussed in detail in Section 4.2.6.

4.1 ERG comment on the company's review of cost effectiveness evidence

The company performed three systematic literature reviews (SLRs) to identify published studies that could inform the cost effectiveness of maribavir for the treatment of refractory or resistant (r/r) CMV infection after haematopoietic stem cell transplantation (HSCT) or solid organ transplant (SOT). The first search (economic SLR) was conducted to identify published economic evaluations comparing treatments for CMV in SOT or HSCT recipients who were r/r to pre-emptive treatment or those on pre-emptive treatment. Economic studies where SOT or HSCT recipients received prophylactic treatment for CMV were excluded as the difference in disease staging would motivate different modelling assumptions. In light of the discrepancies surrounding disease staging at baseline in SOLSTICE (see Section 4.2.2), the ERG disagrees with this exclusion criteria.

The second search (HRQoL) SLR sought to identify studies reporting utility data in the same population, as well as disutilities associated with treatments and treatment-related adverse events (AEs). The third search [health cost resource use (HCRU) SLR] identified studies and prior economic evaluations which reported cost and resource use data for the same population as the other two searches. All database searches were first run in 2017, in 2020 and most recently updated in September 2021. The cost effectiveness review was restricted to studies published after 1 January 2007, while the HRQoL and HCRU reviews were not time restricted. Non-English language studies were excluded for all three reviews.

A summary of the ERG's assessment of the company's economic SLRs is presented in Table 29. Due to time constraints, the ERG was unable to replicate the company's searches.

Table 29. Systematic review summary

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Table 35 in Appendix G	Table 52 in Appendix H	Table 68 in Appendix I	Appropriate, though a grey literature search was not conducted. The company searched MEDLINE, Embase®, MEDLINE® In-Process, EconLit®, NHS EED, CENTRAL, and BIOSIS databases. CADTH and NICE websites were also searched.
Inclusion/exclusion criteria	Table 48 in Appendix G	Table 65 in Appendix H	Table 82 in Appendix I	The ERG disagrees with the exclusion of studies including prophylactic treatment for the rationale of differences in disease staging given the marked discrepancies surrounding the latter at baseline in SOLSTICE (Section 4.2.2).
Screening	Appendix G	Appendix H	Appendix I	Appropriate, PRISMA flow diagrams provided.
Data extraction	Table 49 in Appendix G	Table 66 in Appendix H	Tables 83 and 85 in Appendix I	Appropriate.
Quality assessment of included studies	Appendix G	Appendix H	Appendix I	Appropriate, Drummond checklist was completed by the company to assess the quality of the studies identified by the economic SLR.

Abbreviations: CS, company submission; ERG, evidence review group; HRQoL, health related quality of life; NHS EED, National Health Service Economic Evaluation Database; CENTRAL, Cochrane Central Register of Controlled trials; CADTH, Canadian Agency for Drugs and Technologies in Health; NICE, National Institute for Health and Care Excellence.

The economic SLR included one publication. Nuijten *et al.* 2016[28] assessed the cost-effectiveness of CMV-specific T-cell therapy for the management of CMV disease (second or third line) in patients after allogenic HSCT versus foscarnet and cidofovir. This study did not address the decision problem of the current appraisal. A Markov model was adopted but no further details were available. As such, this study was not used to inform the company's modelling approach. The company noted that NICE TA591,[29] which evaluated letermovir for prophylaxis of CMV in allogenic HSCT patients, was

excluded from the economic SLR for considering CMV prophylaxis. Nonetheless the company utilised TA591 to help inform the structure of a *de-novo* model for this appraisal.

The HRQoL SLR included 13 studies and 4 HTAs reporting relevant utility data, details of each are provided in Table 66 of the company submission appendices and summarised in Section B.3.4.2.1 of the CS. The company did not use any of the identified studies to inform the utility data used in the model base case instead opting to estimate health state utility values from SOLSTICE individual patient level data and a time-trade-off study conducted by the company. Two studies identified (Liem *et al*. (2008)[30] and Pidala *et al*. (2011)[31]) were however used to inform scenario analyses.

The HCRU SLR included 3 studies (from 5 publications) which reported health resource use data for CMV in SOT or HSCT recipients that is refractory or resistant to pre-emptive therapy. A further 14 studies (from 16 publications) which reported health resource use data for CMV in SOT or HSCT recipients on pre-emptive treatment. Details of each study are provided in Tables 83 and 85 of the company submission appendices and a summary is provided in Section B.3.5.1 of the CS. It was not clear whether any of the studies helped identify any unit cost data used in the model as all unit costs used were from standard UK sources. Resource use data used in the model was informed by the SOLSTICE trial or by UK clinical opinion.

The ERG notes that none of the data used in the model base case were identified by the economic, HRQoL or HCRU SLRs; however, data from TA591, which was outside the scope of the SLRs but identified independently by the company, was used to inform several parameter values in the model.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 30 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 30. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes.

Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes.
Synthesis of evidence on health effects	Based on systematic review	Yes.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.

Abbreviations: ERG, evidence review group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

4.2.2 Population

The population in the base case economic model consists of the ITT population from SOLSTICE, which included adults with CMV who were r/r to treatment after HSCT or SOT. The types of SOT included in the model were: heart (11%); kidney (50%); lung (29%); liver (3%); and other transplants (6%).

The company failed to clarify to the ERG what the assumption was on time elapsed since transplant in the model (clarification question B7). Therefore, this aspect of the model remains unclear to the ERG, with several contradicting statements and assumptions being reported in the CS. On one hand, the CS states that, "*patients are assumed to be 1-year post transplant on entering the model*". On the other hand, it can be inferred that the company's assumption is based on patients entering the

model (and therefore initiating treatment with maribavir) immediately after surgery. The ERG's inference is based on the following aspects:

- In their response to clarification question B7, the company states that the assumption on time since transplant in its model aligns with that in the NICE appraisal of letermovir (NICE TA591). In TA591 it was assumed that patients entered the model immediately after HSCT to start receiving prophylactic treatment with letermovir.
- The company's rationale for its model structure is based on the following argument: "*As patients move to the post-transplant maintenance phase (3–6 months), the dose of immunosuppression is reduced* […]*This results in natural clearance of CMV, which reduces the need for continued intervention. For this reason, the model assumes no further CMV events can occur after 12 months* [from cycle 0 in the model]*, with any remaining CMV assumed to be controlled by the patient's immune system without the need for further anti-CMV treatment*".
- The parameters used in the model to estimate mortality after solid organ transplant 1 year after cycle 0 in the model are those for patients who are in their second-year post-surgery (and not third), therefore, suggesting that patients entered the model immediately after surgery. The same is true for modelled HSCT patients.
- The parameters used to estimate graft loss in the model from cycle 1 are those corresponding to patients with risk of graft loss within 3 months of a first CMV event, during the first year since transplant from Hakimi *et al*. 2017.

The ERG is concerned with the lack of clarity on the company's intention regarding time elapsed since surgery in the model. Currently, the model seems to estimate the cost-effectiveness for maribavir in r/r patients when given immediately after surgery, which is 1) not an accurate reflection of a r/r population; and 2) is not reflective of the SOLSTICE trial.

Therefore, the ERG recommends that:

1. The company captures the cost-effectiveness of maribavir in the trial population;
2. If the company's proposition is that maribavir is given as early as possible in the treatment pathway for r/r patients, then the cost-effectiveness of maribavir for the SOT and HSCT UK population should be estimated (please see introductory paragraph in Section 4 for more details on this).

If the company's value proposition for maribavir is that the drug should be given as early as possible for r/r patients, then a case needs to be made for why the relative treatment effectiveness observed in the SOLSTICE SOT population is generalisable to maribavir given within the first year post-transplant and as a second line treatment. The ERG notes that the data provided by the company on 15 March suggests that the relative treatment effect of maribavir on clearance outcomes might not change with time elapsed since transplant.

It is also imperative that the company clarifies the rationale for their model structure, which is based on patients' immune system naturally resolving CMV infections 12 months after transplant. The company needs to reconcile this with the time from transplant at baseline in SOLSTICE when patients began treatment with maribavir or IATs. To note is that during the clarification stage, the ERG asked that the company to include a scenario analysis in the model where CMV recurrences could happen 1 year after transplant. The company did not conduct the requested analysis.

4.2.3 Interventions and comparators

The intervention included in the economic model was maribavir formulated as a 200mg tablet taken four times a day.

The comparator in the model consists of IATs modelled as a basket of drugs. The assumed proportions of each drug used in the IAT arm (based on SOLSTICE) is given in Table 31. The clinical experts advising the ERG noted that foscarnet would be the most relevant comparator to maribavir, as discussed in Section 2.3.2.

The company also assumed that both maribavir and IAT patients could be retreated in the model in case of recurrence or lack of clearance of CMV disease during the first 12 months of the model. The company assumed that patients could only be retreated with IATs and assumed that the distribution of treatments received in further lines would be the same as that received in first line in the model IAT arm (Table 31).

The ERG has several concerns with the company's approach:

1. The company's assumption that patients could not be retreated after 12 months in the model (and therefore, 12 months after transplant) – as discussed in Section 4.2.2, the population in SOLSTICE (particularly SOT patients) is reflective of a population who got treated, on average, [redacted] after transplant.

2. The assumption that patients could get retreated with the same IAT after first line IAT treatment in the model – the company did not ensure that patients getting, for example, first line foscarnet in the model were retreated with a different second line treatment. This is clinically implausible and likely to overestimate the retreatment costs in the IAT arm as foscarnet is the most expensive IAT. This issue would be overcome by the ERG's proposed reduction in the number of episodes of recurrence allowed in the model (Section 4.2.6).

Table 31 – Composition of the IAT arm

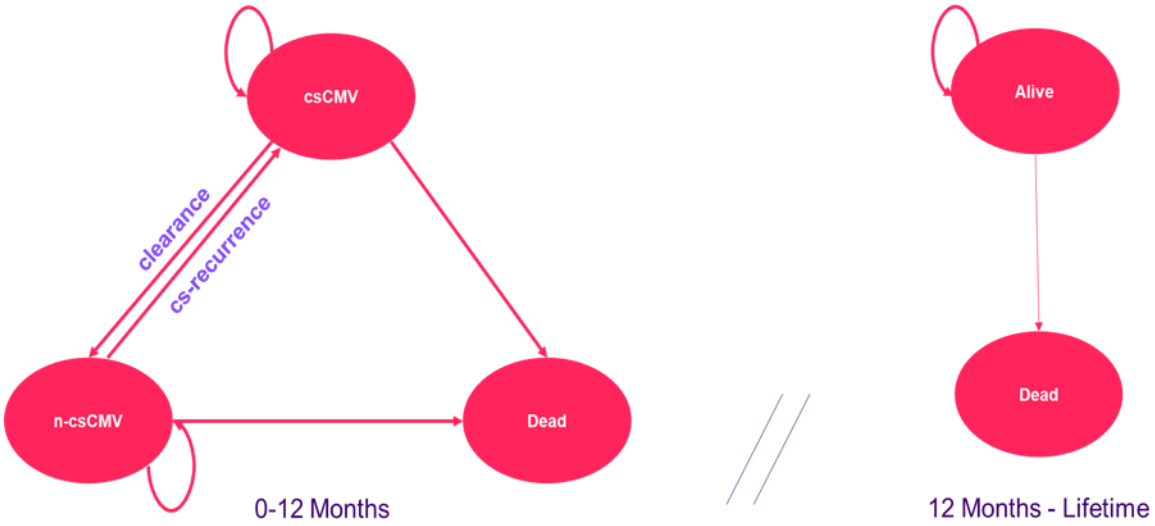
Drug	Proportion in the model
Ganciclovir	25.4%
Valganciclovir	25.9%
Foscarnet	43.5%
Cidofovir	5.2%

4.2.4 Modelling approach and model structure

The company developed a cohort state-transition model with two stages (Figure 7). The stage 1 Markov model included three health states and captured patients' transitions from month 0 to month 12 in the model. All patients entered the model in the clinically significant CMV infection (hereafter referred to as CMV) state and could then clear the infection and move to the no clinically significant CMV (nCMV) state or remain in the CMV state. Once patients cleared the infection, they could also experience a CMV recurrence. Patients could die at any point during the first 12 months of the model.

Stage 2 of the Markov model started after month 12 and lasted for 47 years. In this period, patients could transition from the alive or dead state only (Figure 7) and could not experience further CMV events. The company assumed that any remaining CMV after 12 months would be controlled by the patient's immune system without the need for further anti-CMV treatment.

Figure 7. Company's model structure (reproduced from Figure 14 in the CS)



4.2.4.1 ERG critique

The ERG has several concerns with the model structure and assumptions:

1. The stage 1 Markov model allows for multiple clearance and recurrence episodes per patient at various time points between week 8 and week 20, however the outcomes reported in SOLSTICE were clearance (week 8 clearance being the primary outcome in the trial and week 4 clearance being a *post-hoc* outcome); and recurrence after first clearance (i.e., only one episode of recurrence). The company did not present any evidence to substantiate why patients could have multiple recurrences in the model between week 8 and week 52. This issue would be overcome by the use of KM data from SOLSTICE and is further discussed in Section 4.2.6.
2. The ERG disagrees with the assumptions made after 20 weeks in the model until week 52. The company is using 20-week data from SOLSTICE to model recurrences outcomes up to week 52 based on the assumption that outcomes at 20 weeks would be the same as those observed 4-weekly throughout the rest of the model time horizon. As it stands, having the stage 1 Markov model extended to 52 weeks does not add any methodological or conceptual benefit to the economic analysis, and only introduces a bias in favour of maribavir as the estimates of treatment effectiveness used by the company at week 20 are in favour of maribavir. Even though the company assumed that patients switch to IATs after failing on maribavir, the company also assumed that the probability of a CMV recurrence was that associated with the most recent treatment received, which means that patients who achieved a first clearance with maribavir still experienced the lower probability of

recurrence associated with maribavir even when off treatment. If the company wanted to extrapolate trial outcomes beyond 20 weeks, then KM data from the trial could have been used. This issue is further discussed in Section 4.2.6.

3. The lack of clarity on the rationale for the model assumption that patients' immune system naturally resolves CMV infections 12 months after transplant. The company needs to reconcile this assumption with the time from transplant at baseline in SOLSTICE when patients began treatment with maribavir or IATs (as discussed in Section 4.2.2).
4. The switch from the stage 1 to the stage 2 Markov results in 35.56% of patients in the maribavir arm and 38.98% of patients the IAT arm having CMV at week 52 and being cured at week 56. The ERG considers that this stark drop lacks face validity and that it is more likely that the proportion of CMV cases decreases gradually over time, until all cases are resolved.
5. The lack of clarity on the company's assumption regarding time elapsed since surgery in the model. Currently, the ERG's conclusion is that the model seems to estimate the cost-effectiveness for maribavir in r/r patients when given immediately after surgery, which is not an accurate reflection of a r/r population, but also a poor reflection of the SOLSTICE population (particularly with regards to the SOT population).

The ERG recommends that the company considers the following changes to their economic model, for both HSCT and SOT patients:

1. Using the KM trial data, and some of the company's current assumptions it is possible to model patients' pathway through first clearance, first recurrence and second clearance for the model population without compromising data integrity (the ERG discussed this further in Section 4.2.6).
2. If the company does not use the recommended KM data, and instead uses the point estimates for the probability of clearance and recurrence at specific times in SOLTICE – the ERG recommends that the company changes the stage 1 Markov to be 20 weeks to effectively model the trial events only (the ERG discussed this further in Section 4.2.6).

4.2.5 Perspective, time horizon and discounting

A lifetime horizon (47 years) was adopted in the model and time was discretised into 4-week cycles for the first 3 years, following annual cycles after that. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE reference case.

The ERG agrees with the lifetime horizon used, and notes that patients' baseline age in the company's model was 53 years, therefore, at 47 years in the model patients would be 100.

The company chose a 4-week cycle length during the first 3 years of the model and a 1-year cycle length after year 3 and did not apply a half-cycle correction in the model. During clarification, the ERG requested that the company added the half-cycle correction to the model, however, the company considered that 4 weeks was a short enough time interval and therefore, did not apply the correction. The ERG disagrees that 4 weeks is a short enough time interval for the half-cycle correction to not be needed, and crucially, notes that after year 3 in the model the cycle length increases from 4 weeks to 12 months. Therefore, the ERG highly recommends that the company applies the correction to their model during TE.

4.2.6 Treatment effectiveness

4.2.6.1 Clearance

The primary outcome in the SOLSTICE trial was viral clearance at week 8. However, the company considered that SOLSTICE showed evidence that patients treated with maribavir achieved faster clearance compared with IAT (i.e., before completion of the 8-week treatment duration) and therefore used 4-week clearance outcomes in the economic model. The probability of clearance at week 4 was estimated as the proportion of patients in SOLSTICE with CMV clearance at week 4 out of the total of patients entering the trial, in the maribavir and the IAT arms, respectively.

The company also modelled clearance at week 8 based on response at week 4. The probability of clearance at week 8 was estimated as the proportion of patients in SOLSTICE with CMV clearance at week 8 who had not achieved clearance at week 4.

The company reported using individual patient-level data (IPD) from SOLSTICE to estimate clearance in the model at week 4 and at week 8. During the clarification stage, the ERG requested that the company provided the raw data showing the proportion of patients with clarence at week 4 and with clearance at week 8 depending on week 4 outcomes (Table 32). The company provided the data requested and the ERG discusses these in Section 3 of the report.

From week 8 to week 52, the company assumed that the probability of clearance in the maribavir and in the IAT arms were the same and based on the data from the IAT arm in SOLSTICE. The company's rationale was that patients with unresolved or new CMV after 8 weeks of maribavir

treatment would switch to treatment with an IAT. The probability of clearance from week 8 onwards was estimated as the proportion of patients in SOLSTICE with CMV clearance from week 0 to week 8 in the IAT arm, out of all patients entering the trial, regardless of outcomes at week 4. The probability of clearance observed from week 0 to 8 in the trial was converted into a 4-week transition probability and used from week 8 to week 52 in the model (Table 32).

Table 32. Clearance outcomes used in the model

Outcome	IAT	Maribavir
Clearance at week 4	37/117 (31.6%)	127/235 (54.0%)
Clearance at week 8 for patients not cleared at week 4	9/80 (11.2%)	34/108 (31.5%)
Clearance at week 12 onwards for patients not achieving clearance in the previous model cycle*	28/117 (23.9%) converted into a 4-week probability of 13%	same as in the IAT arm

Abbreviations: IAT, investigator-assigned antiviral therapy

*taken from the probability of clearance observed from week 0 to 8 in the trial for the IAT arm

4.2.6.2 Recurrence

Recurrence in the model was based on clinical outcomes from SOLSTICE defined as CMV viremia recurrence requiring alternative treatment. Given that the earliest that patients could achieve clearance in the model was 4 weeks, recurrence could not happen before week 8 (but could happen at week 8 and onwards).

The pre-specified outcome in the SOLSTICE trial concerning recurrence was CMV viremia recurrence requiring alternative treatment after first CMV viremia clearance at week 8. However, the company used recurrence outcomes based on 4-week clearance status. The probability of recurrence at week 8 in the model was estimated from the IPD data as the proportion of patients in SOLSTICE with CMV recurrence requiring alternative treatment who had achieved clearance at week 4.

From week 8 to week 20, the company estimated the probability of recurrence as the proportion of patients in SOLSTICE with CMV recurrence at week 20 requiring alternative treatment who had achieved clearance at week 8, for the maribavir and the IAT arm, respectively. The probability of recurrence observed from week 8 to week 20 in the trial was converted into a 4-week transition probability to be used in the model. From week 20 to week 52, the company used the same 4-week transition probabilities estimated for week 8 to week 20 (Table 33).

Table 33. Recurrence outcomes used in the model

Outcome	IAT	Maribavir
Recurrence at week 8	9/29 (31%)	23/124 (19%)
Recurrence at week 12 onwards*	10/28 (36%) converted into a 4-week probability of 14%	34/131 (26%) converted into a 4-week probability of 10%

Abbreviations: IAT, investigator-assigned antiviral therapy

*taken from the probability of recurrence between week 8 and week 20 in the trial

Furthermore, the company assumed that the probability of patients having a CMV recurrence was the probability of recurrence associated with the most recent treatment received. The implication of this is that patients who are on treatment and off treatment after first clearance were assumed to have the same probability of recurrence.

4.2.6.2.1 ERG critique

As discussed in Section 4.2.4, the ERG has several concerns with the estimation of treatment effectiveness in the model.

One of the ERG's biggest concerns is the company's assumption that patients could have multiple episodes of recurrences in the model when the trial outcomes only captured first clearance and first recurrence episodes. This assumption, in combination with the data used by the company results in model outcomes which are either not consistent with the clinical data from SOLSTICE or are impossible to validate.

Treatment effectiveness data on multiple episodes of recurrence

Before week 8 in the model, the company uses the *post-hoc* IPD data to estimate recurrences in the maribavir and IAT arms (19% and 31%, respectively). As explained in Section 3, the ERG considers these to be the wrong estimates, and notes that the company should be using the 8.1% (3/37) and 12.6% (16/127) estimates for IAT and maribavir, respectively, in order to capture recurrences from week 4 to week 8. The ERG's preferred estimates portray the opposite scenario of the estimates used by the company, where the ERG's preferred estimates show that patients on IATs have a lower probability of recurrence from week 4 to week 8 than maribavir patients. The company's approach therefore, contributes to the overestimation of recurrences in the IAT arm compared to the trial data.

After week 8 in the model, the company used the following probabilities:

1. For maribavir patients who achieved first disease clearance and remained in the nCMV state after week 8 (thus, off any treatment) - the probability of recurrence was estimated differently for maribavir and IAT patients (10% and 14% per model cycle, respectively) as the company assumed that the probability of patients having a CMV recurrence was that associated with the most recent treatment received. This means that a patient who had been cleared of CMV with maribavir for example, 6 months ago, still experienced the probability of recurrence associated with maribavir.

   The ERG disagrees with the company's assumption which implies that the probability of recurrence depends on the type of treatment received (i.e., maribavir vs IATs) and is independent of time since surgery, or even of time since the clearance event. The ERG heard from its clinical experts that the probability of recurrence is unlikely to depend on the type of treatment on which patient achieved clearance, but instead to be dependent on time since transplant and on the level of lifelong immunosuppression needed by the patient. As discussed in Section 3, the data provided by the company on 15 March are too uncertain to confirm or deny the clinical experts' expectations on the effect of time elapsed since transplant on recurrences.

   Furthermore, the KM data on time to recurrence after first clearance at week 8 from the SOLSTICE CSR (

   Figure 8) suggests no statistically significant difference between recurrence for maribavir and IAT patients. When the difference in baseline numbers for the two groups are considered, it is likely that the separation of the curves after week 4 is due to the number of patients at risk in the IAT arm compared to the number of patients at risk in the maribavir arm.

   Crucially, the difference in curves is also likely to be cofounded by the difference in time since transplant across treatment arms at baseline. As discussed in Section 3, patients in the maribavir arm entered the trial considerably later (on average) after transplant than IAT patients. Nonetheless, the opposite was demonstrated when median time since surgery was considered. Given that the probability of CMV recurrence is likely to be dependent on time since transplant, it is unclear to the ERG to which extent the recurrence outcomes in SOLSTICE were confounded by these differences in treatment arms at baseline.

Figure 8. KM data on time to recurrence requiring alternative treatment after clearance at week 8 (shaded areas represent the confidence interval around the curves)

As a result of these concerns, at clarification, the ERG asked that the company conducted a scenario analysis where patients in the maribavir and the IAT arms of the model in the nCMV state (off treatment) had the same background probability of experiencing events in the model. The company did not conduct the analysis as it considered that the trial data demonstrated that maribavir is associated with a reduction in the proportion of patients requiring subsequent anti-CMV therapy to treat a recurrence following clearance of their initial CMV episode.

The ERG conducted two simplified scenario analyses whereby the probability of recurrence in the model after week 8 (when patients are no longer on treatment with maribavir) was assumed to be the same for the IAT and the maribavir arms. In the first scenario the ERG assumed that the probability of recurrence in both treatment arms was that used in the IAT arm (14%); and in the second scenario the ERG assumed that the probability was that associated with maribavir (10%). Both scenarios increased the company's ICER. The first scenario increased the ICER from £15,337 to £70,964; whereas the second scenario increased the ICER to £47,704.

2. For maribavir patients who did not achieve disease clearance or had a recurrence and therefore started an IAT – the company used a probability of recurrence of 14% for both treatment arms, which was the probability of recurrence observed between week 8 and week 20 in the trial for the IAT arm, given that after 8 weeks patients would no longer be on maribavir.

   The ERG disagrees with the company's assumption which implies that the probability of first recurrence observed in the trial is the same as the probability of subsequent recurrences and also the same until week 52 in the model. The ERG's clinical experts have explained that the probability of CMV recurrence is dependent on time since surgery, with the initial 3 months representing the highest risk, followed by the next 3 months of lower, but still considerable risk. For HSCT patients, it is expected that most CMV are resolved within 6 months after transplant, whereas for SOT patients this will depended on the immunosuppression regimen for each patient. Given the issues raised by the ERG around time since surgery at baseline in SOLSTICE (see Section 4.2.2 and Section 4.2.4), there is a high degree of uncertainty associated with making any assumptions beyond what the trial data have captured in terms of number of subsequent recurrences for patients.

   Using the SOLSTICE KM data reported in the CSR (Table 34), it can be observed that the percentage of patients with clearances at week 8 was of 82% and 68% for maribavir and IATs, respectively, (to note is that these estimates include the proportion of patients who might have achieved clearance before week 8 and since then have lost response). Taking into account the proportion of patients alive (93% in both arms) at week 8, then the proportion of patients who have not cleared their first episode of CMV was approximately 11% for maribavir and 25% for IATs.

   The estimates from the model are not directly comparable to the estimates from SOLSTICE, given that the company's model combines patients who have not achieved clearance (like the trial outcomes) plus patients with first recurrences from week 4 to week 8. However, given that at week 8 in the model, there were 39% (maribavir) and 66% (IAT) of patients with CMV, in comparison with the KM data, the model outcomes would suggest a very high number of patients with recurrences between week 4 and week 8, especially in the IAT arm. However, data from the trial suggest the opposite with 12.6% (16/127) and 8.1% (3/37) recurrences from week 4 to week 8 in the maribavir and IAT arms, respectively (Table 34).

This reinforces the ERG's view that recurrences are likely to be considerably overestimated in the model.

Table 34. Clinical outcomes from SOLSTICE

Outcome	IAT	maribavir
Total number of Subjects with CMV Viremia Recurrence Requiring Alternative Treatment (at any point) after clearance at week 8	10/28 (36%)	34/131 (26%)
Total number of Subjects with CMV Viremia Recurrence (at week 8) requiring Alternative Treatment after clearance at week 4	3/37 (8.1%)	16/127 (12.6%)
KM data for first CMV clearance (cumulative) at week 8^	68%	82%
KM data for first CMV clearance (cumulative) at week 12^	85%	85%
KM data for first CMV clearance (cumulative) at week 20^	88%	90%
KM data for first CMV Viremia Recurrence Requiring Alternative Treatment (at week 12 of study) from first viraemia clearance at week 8^	25%	21%
KM data for first CMV Viremia Recurrence Requiring Alternative Treatment (at week 20 of study) from first viraemia clearance at week 8^	38%	25%

Abbreviations: IAT, investigator-assigned antiviral therapy

^approximated values based on visual inspection of the KM curves

Given the likely sensitivity of recurrences to time since transplant; the apparent overestimation of recurrences in the model; and the lack of trial data to justify modelling multiple episodes of recurrence per patient, the ERG advises that the company uses the SOLSTICE KM to estimate a "full cycle" of events consisting of a maximum of 2 episodes of clearances and one episode of recurrence per patient in the stage 1 Markov model. Patients entering the model with CMV could therefore experience one clearance; followed by one potential recurrence; followed by another clearance. The company could maintain its

current base case assumption that maribavir patients entering the model receive 8 weeks of treatment, after which they will change to an IAT if needed. Given that clearance is likely to be independent of time since surgery and related only to treatment received, the combination of the SOLSTICE trial data with the company's base case assumption will allow the company to estimate a "full cycle" of first clearance, first recurrence and second clearance in the model. The company should then obtain clinical expert opinion and/or external data to validate the average frequency of subsequent "full cycles" of events.

Treatment effectiveness data on multiple episodes of clearance

In order to estimate multiple clearance events, the company used the *post-hoc* IPD analysis on the proportion of patients with clearance at week 4 and at week 8 (conditional on week 4 outcomes). As discussed in Section x, the ERG is unsure on the validity of using the *post-hoc* 4-week outcomes from SOLSTICE. The trial CSR states that, "*recurrence during the 8-week treatment phase is not always clinically relevant, as patients may have transient fluctuations in viral load that are considered by many physicians to be inconsequential*." Furthermore, the company's rationale for using 4-week outcomes is that SOLSTICE showed evidence that patients treated with maribavir achieved faster clearance compared with IAT before completion of the 8-week treatment duration. Nonetheless, as recognised in the company's CSR, changes in DNA concertation of the CMV virus during the first 4 weeks of treatment might represent flections. Furthermore, the data in Table 35 show that the additional clearances associated with maribavir at week 8 (31.8%) were higher than those observed at week 4 (22.4%). Therefore, the ERG considers that using the 8-week primary outcome from SOLSTICE would have been a more robust source for the economic analysis, and it would not bias the analysis against maribavir.

Table 35. Clinical outcomes from SOLSTICE

Outcomes	IAT	maribavir
Clearance at week 4	37/117 (31.6%)	127/235 (54.0%)
Total number of Subjects with CMV Viremia Recurrence at week 8 requiring Alternative Treatment after clearance at week 4	3/37 (8.1%)	16/127 (12.6%)
Deaths at week 8	5 /116* (4.3%)	14/235 (6.0%)
Discontinuations before week 8	79/116 (67.5%)	51/234 (21.7%)
Clearance at week 8	28/117 (23.9%)	131/235 (55.7%)
Clearance at week 8 maintained through week 12	12/28 (42.9%%)	53/131(40.5%)
Clearance at week 12 maintained through week 20	11/28(39.3%)	43/131 (32.8%)

Abbreviations: IAT, investigator-assigned antiviral therapy
*Deaths only reported for safety set

From week 8 to week 52, for patients who had CMV disease (unresolved first episode or recurrent), the company assumed that the probability of clearance in the maribavir and in the IAT arms was the same (based on the data from the IAT arm in SOLSTICE) as all maribavir patients with a second CMV episode would be on treatment with an IAT. The probability of clearance with an IAT retreatment was taken from the proportion of patients in SOLSTICE with CM clearance at week 8 in the IAT arm, out of all patients entering the trial, regardless of outcomes at week 4. Therefore, the company assumed that the probability of clearance is independent of time since surgery. The ERG does not have particular concerns with this assumption as clearance outcomes are unlikely to be affected by time since surgery, and more likely to depend on the drug's effectiveness and on patients' resistance to the drug.

The ERG notes that for second clearances; or first clearances of unresolved CMV with the first treatment after week 8 in the model, the company did not use 4-week clearance outcomes from the IPD *post-hoc* analysis. Instead, the company used the primary outcome 8-week clearance outcomes. There was no justification provided by the company for this inconsistency. The ERG reinforces its view that 8 weeks outcomes would have been a more appropriate outcome to use throughout the analysis.

Finally, the ERG notes that the data in Table 35 shows that maribavir was less effective than IATs at maintaining patients' clearance outcomes from week 8 until the end of the study (39% vs 33%, respectively). However, the company's model and assumptions imply the opposite. The company modelled the probability of patients remaining in the clearance state achieved at week 8 as 1 minus the probability of recurrence (with the probability of recurrence being based on the total number of recurrences requiring alternative treatment after clearance at week 8, up to week 20). However, 1 minus the latter provides the proportion of all patients who between week 8 and week 20 in the trial achieved a first clearance plus the proportion of patients who might have discontinued the trial or died between the same time period.

Overall, the ERG considers that the model structure; assumptions; and data used fail to:

- Accurately represent and model the effectiveness data captured in SOLSTICE;
- Appropriately estimate the cost effectiveness of maribavir compared to IATs.

4.2.6.2.1.1 ERG's suggested approach for TE

As discussed in previous sections, the ERG recommends that:

1. The company captures the cost-effectiveness of maribavir in the trial population;
2. If the company's proposition is that maribavir is given as early as possible in the treatment pathway for r/r patients, then the cost-effectiveness of maribavir for the SOT and HSCT UK population should be estimated (please see introductory paragraph in Section 4 for more details on this);
3. The company addresses the impact of the imbalances of mean time since surgery at baseline across treatment arms in SOLSTICE (or provide a robust rationale for why this imbalance isn't clinically meaningful);
4. The company clarifies the rationale for their model structure which is based on patients' immune system naturally resolving CMV infections 12 months after transplant. The company needs to reconcile this with the time from transplant at baseline in SOLSTICE and change the structure of the model to account or the fact that SOT patients do indeed have CMV recurrences 1 year after transplant.

Additionally, the ERG recommends the following changes to the economic model:

5. Using the available SOLSTICE data on clearance at week 8 (instead of week 4) to model clearance and using the recurrence after first clearance (at week 8) requiring an alternative treatment data to model recurrence in the model.
6. By maintaining its current base case assumption that maribavir and IAT patients entering the model receive 8 weeks of treatment, after which they will change to an IAT, or a new IAT dose, respectively, if they do not achieve clearance, the company can model a "full cycle" events (i.e., a maximum of 2 episodes of clearances and one episode of recurrence per patient).
7. The company should obtain clinical expert opinion and/or external data to validate the average frequency of subsequent cycles of "full events" in order to capture the possibility that SOT patients are likely to have multiple episodes of CMV recurrences throughout their lives. The duration of the stage 1 Markov model should be determined by the duration of these cycles. The company can then repeat these cycles of events as appropriate in the model.

8. The ERG recommends that the SOLSTICE KM data are used to estimate a "full cycle" of events:
    a. The KM data on clearance at week 8 associated with maribavir and IAT would determine the proportion of patients achieving first clearance in the model before or at week 8, in each treatment arm, respectively;
    b. The KM data on recurrence after first clearance (at week 8) requiring an alternative treatment would determine the proportion of patients with a first recurrence in the model. If the company wishes to use the KM data for maribavir and IAT arms separately, the ERG recommends running a scenario analysis where the data are pooled, therefore assuming the same probability of recurrence across treatment arms;
    c. The KM data on clearance at week 8 associated with IAT would determine the proportion of patients with second clearance in both treatment arms.
9. The ERG recommends that the company fits and extrapolates the KM data for at least the second clearance event in order to account for 100% of patients having cleared their second recurrence. This will ensure that patients can leave the second CMV event state at a clinically plausible rate.
    a. If the company does not use the recommended KM data, and instead uses the point estimates for the probability of clearance and recurrence at specific times in SOLTICE – the ERG recommends that the company changes the stage 1 Markov to be 20 weeks to effectively model the trial events only. The company should correct the estimates being incorrectly used as detailed by the ERG's critique in Section 4.2.6.2.1. and should allow 100% of patients to clear their recurrence at a clinically plausible rate in the model.

Regardless of the company's proposition for when in the disease pathway maribavir should be placed, the ERG notes that it is crucial that the company estimates the cost effectiveness of maribavir for the average population included in SOLSTICE given that the evidence available consistently shows that patients' clinical outcomes (such as risk of CMV infection; mortality; and risk of graft loss) vary as time from transplant elapses. Due to this, it is possible that the cost-effectiveness of maribavir changes depending on how long after transplant the treatment is given.

4.2.6.3 Mortality

4.2.6.3.1 Week 0 to week 8 in the model

Upon analysis of the IPD, the company concluded that, "*neither treatment, health state nor transplant type had a statistically significant impact on mortality in the first 8 weeks*" of SOLSTICE. However, due to clinical expert advice, the company decided to include transplant-specific mortality rates in the first 8 weeks of the model. Furthermore, the company decided to estimate the risk of mortality by transplant type separately for weeks 0 to 4 and weeks 4 to 8, and used these directly as transition probabilities in the model (Table 36). In addition to the transplant specific mortality probabilities, background sex- and age-specific general population mortality was added to the transplant-specific mortality rates.

Table 36. Mortality rates in first 8 weeks of the model

Time period	Solid organ transplant (SE)	Haematopoietic stem transplantation (SE)
Week 0 to week 4	[redacted]	[redacted]
Week 4 to week 8	[redacted]	[redacted]

4.2.6.3.2 Week 8 to week 52 in the model

From week 8 to the end of the first year in the model, the company assumed that mortality varied by CMV status. The company used the IPD analysis to define CMV presence at week 8 (as per the primary outcome in SOLSTICE) to then estimate the number of deaths in the CMV and nCMV states, per treatment arm. The data used by the company captured the total number of deaths at week 20 (from week 8). This generated 12-week probabilities of death, which the company converted into 4-week probabilities to be used in the model from week 8 to week 52 (Table 37). Similar to the mortality rates for weeks 4 and 8, the company added background sex- and age-specific general population mortality to the CMV states mortality.

The company decided to not estimate mortality rates by type of transplant (in addition to CMV status) for this period of the model due to sample size, as "*patient numbers became too low in each respective category to provide robust and plausible estimates*". The observed proportion of deaths at week 20 by type of transplant and by CMV response at week 8 were [redacted] and [redacted] for the nCMV and CMV states, respectively, for SOT patients and [redacted] and [redacted] for HSCT patients, respectively.

Table 37. Mortality rates in week 8 to week 52 in the model

Time period	CMV state (SE)	nCMV state (SE)
Week 8 to week 52	[redacted]	[redacted]

4.2.6.3.3 ERG critique

The company's IPD analysis showed that neither treatment, CMV status or transplant type had a statistically significant impact on mortality in the first 8 weeks of the trial. Nonetheless the company decided to model a differential in mortality by type of transplant in the same period of the model (i.e. the first 8 weeks); and by presence of CMV disease in the remaining 44 weeks of the stage 1 Markov model, without providing a justification for the different approaches.

In SOLSTICE, the same percentage of deaths occurred in both treatment arms – 27 deaths in the maribavir arm and 13 deaths in the IAT arm (11.5% and 11.1%, respectively). Additionally, the KM data on all-cause mortality from the trial (Figure 9) shows that there [redacted].

Therefore, the ERG disagrees with the company's approach of using SOLSTICE data to model a differential in survival related to CMV status. The trial data (which, by default, incorporates the difference in CMV events across treatment arms) shows no difference in overall mortality for maribavir and IAT patients, thus suggesting that the CMV-related mortality in the trial was also not significantly different across treatment arms. The company's approach biases the analysis in favour of maribavir given the overall overestimation of CMV recurrences in the first 52 weeks of the model (as discussed in Section 4.2.6), and with the overestimation of the benefit associated with maribavir in preventing recurrences.

During clarification, the ERG noted that the company's approach to estimating survival in week 8 to week 52 in the model indirectly assumed a survival benefit associated with maribavir through separation of survival rates by CMV status. Given that survival in SOLSTICE was not statistically significantly different between treatment arms (and showed a numerical advantage in the IAT arm), the ERG asked that the company conducted a scenario analysis where mortality in the model from week 8 to week 52 was estimated in the same way as for week 4 to week 8 (i.e., differing only by type of surgery and not by CMV status and using data from SOLSTICE). The company did not conduct

the analysis and stated that the economic model was designed to capture the relationship between CMV and mortality.

Figure 9. KM data on all-cause mortality by treatment group, randomised set (reproduced from the CSR Figure 6)

The ERG agrees with the company's clinical experts' view that CMV occurrence is a key prognostic factor of mortality; however, likely to be dependent on how long after transplant the CMV event occurs. The ERG did not have access to the KM mortality data by type of transplant (i.e., SOT vs HSCT) but notes that clinical experts and external data suggest that time since transplant is a key driver of mortality. The ERG discusses the data available for mortality post-transplant, for SOT and HSCT patients, respectively, in the subsections below.

Finally, the ERG disagrees with the company's methodological approach of summing sex- and age-specific general population mortality rates to the mortality rates observed in SOLSTICE given these are competing risks. During clarification, the ERG asked that the company removed the former from the analysis. The impact on the final ICER was small.

Solid organ transplant

The Hakimi *et al*. 2017 paper looked at the risk of mortality over 12 months following the index date of a CMV infection for SOT patients. The index dates included patients with a CMV event within the first 3 months after transplant, between 3-12 months; and between 6 -12 months. The results of the study show that the annual probability of death during the first year after transplant depended on: type of organ transplanted; presence or absence of CMV; and time of CMV event (Table 38). A trend can also be noted where having CMV events later after transplant are associated with a lower risk of death vs having CMV events earlier after transplant (7.12% if CMV occurs within 3 months after surgery vs 4.10% if CMV occurs 6 months after surgery). The same trend is observed for patients without CMV (2.84% vs 0.96%), suggesting that the risk of mortality (when no CMV is present) also decreases over the first-year post-transplant.[32]

Despite the presence of CMV being a determinant predictor of mortality over the first-year post-transplant in Hakimi *et al*., the data from SOLSTICE indicated that CMV did not impact mortality. For SOT patients, the results of the IPD analysis could potentially be explained by the mean time since transplant at baseline in SOLSTICE ([redacted] for maribavir and [redacted] for IAT patients, respectively).

The ERG calculated the 4-weekly probabilities of death from the Hakimi data and provided estimates in Table 38. The ERG notes that the equivalent estimates derived from SOLSTICE for SOT patients (2.37% for the first 4 weeks and 0.97% for week 4 to week 8) are considerably higher than all the estimates observed in Hakimi *et al*. during the first year since transplant (the highest being 0.567% for CMV patients' events occurring within 3 months after transplant). The ERG is surprised with these results considering the mean time since transplant at baseline for SOT patients.

Table 39 reports the survival estimates from the NHS Organ Donation Annual Activity Report for 1-;2-;5-; and 10-years after SOT.[33] The ERG estimated the 4-weekly probability of death in each year, weighed by the proportion of type of transplants observed in SOLSTICE. In the first year after surgery, the overall 4-weekly probably of death observed was of 0.82% (for CMV and non CMV patients); which is higher than the rates observed in Hakimi *et al*. (even when only CMV events within the first 3 months post-transplant patient are considered – 0.57%). Nonetheless, the rates in SOLSTICE are still higher than those in year 1 of the NHS blood transplant report. Furthermore, at approximately 6 months in SOLSTICE, there were 90% of patients alive in both treatment arms for both SOT and HSCT populations (Figure 9), which compares to 97% still alive at the end of year 1 in the NHS Organ Donation Annual Activity Report.

Table 38. Probability of death over 12 months for patients with or without CMV at different points since transplant

Organ	First 3 months post-transplant			Beyond 3 months post-transplant			Beyond 6 months post-transplant		
	CMV	No CMV	p-value	CMV	No CMV	p-value	CMV	No CMV	p-value
Overall	77/1082 (7.12)	61/2146 (2.84)	<.0001	51/962 (5.30)	27/2028 (1.33)	<.0001	24/586 (4.10)	12/1245 (0.96)	<.0001
Kidney	19/740 (2.57)	26/1444 (1.80)	NS	17/647 (2.63)	13/1362 (0.95)	.004	10/383 (2.61)	3/812 (0.37)	.0005
Liver	32/211 (15.17)	23/430 (5.35)	<.0001	21/143 (14.69)	9/303 (2.97)	<.0001	9/75 (12.00)	5/160 (3.13)	.01
Lung	12/48 (25.00)	10/104 (9.62)	.01	8/89 (8.99)	3/191 (1.57)	.003	2/68 (2.94)	2/148 (1.35)	NS
Other*	14/83 (16.87)	2/168 (1.19)	<.0001	5/83 (6.02)	2/172 (1.16)	.03	3/60 (5.00)	2/125 (1.60)	NS
Total 4-weekly probability	0.567%	0.221%	-	0.418%	0.103%	-	0.322%	0.074%	-

Abbreviations: NS, not statistically significant

* Heart, pancreas, double organ, and intestine.

Table 39. KM survival data from the NHS Blood and Transplant 2021 report

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[a]	N/A
Liver	DBD	94	92	84	68
Weighted total 4-week probability of death in specific year	-	0.786%	0.392%	0.333%	0.326%

DBD=Donor after brain death; DCD=Donor after circulatory death, N/A=Not applicable; SOT=Solid organ transplant

[a] 3-year survival estimate used as the 5-year survival estimate was not available

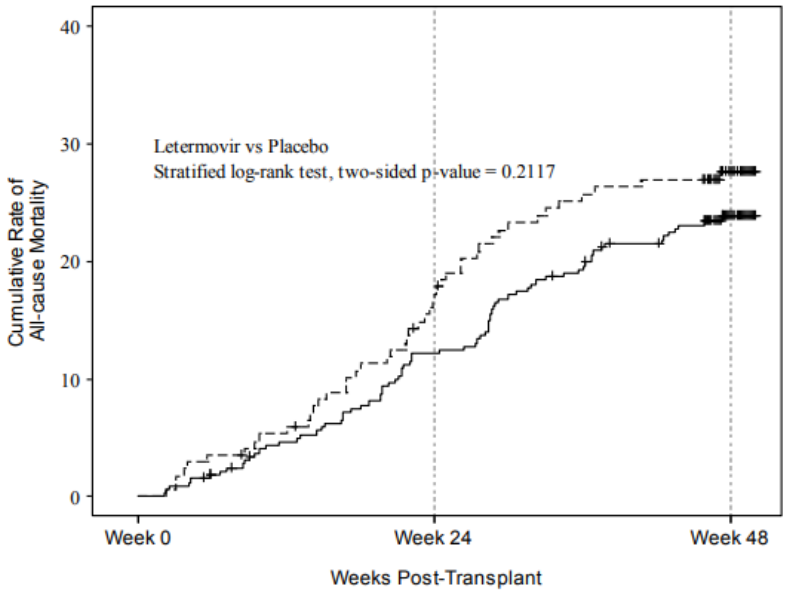
Furthermore, the company assumed that after week 8, the 4-weekly probability of death was 2.5% for SOT patients with CMV and 1.3% for patients without CMV. This represents an increase in the probability of death from week 4-8 (of 0.97%) for both patients with and without CMV. This increase does not seem clinically plausible in light of the data observed in Hakimi *et al.*; the NHS blood and transplant report and clinical expert opinion and again, overestimates the benefit associated with maribavir on survival in the model.

Stem cell transplant

The data on survival post HSCT transplant provided in TA591 (Figure 10) shows that the rate in mortality decreases over the first-year post HSCT, with about 28% of patients having died at the end of year 1. Figure 10 also shows that at approximately 6 months, 15% of patients in the placebo arm had died, which compares to about 10% of patients being dead at the end of SOLSTICE (for SOT and HSCT patients overall).

The ERG notes that the mortality in TA591 for HSCT patients is more closely aligned to the mortality observed in SOLSTICE than the mortality observed in Hakimi *et al*. and in the NHS blood and transplant report for SOT patients. Nonetheless, KM mortality data from SOLSTICE has not been provided by type of transplant, therefore, the ERG strongly recommends that the company provides KM data on mortality in SOLSTICE by type of transplant (i.e., HSCT vs SOT) so that the committee can understand the difference in mortality in both populations.

Figure 10. Reproduced from Figure 6 of CS in TA591



No. at risk: KM estimates % (95% CI)			
— Letermovir	325	282: 12.1 (8.6, 15.7)	165: 23.8 (19.1, 28.5)
- - - Placebo	170	139: 17.2 (11.5, 22.9)	81: 27.6 (20.8, 34.4)

4.2.6.3.3.1 ERG's suggested approach for TE

As discussed in previous sections, the ERG recommends that:

1. The company captures the cost-effectiveness of maribavir in the trial population. For this scenario the ERG recommends the following approach to estimate mortality:
    a. The use of the company's KM data on survival for the stage 1 Markov model. The KM data should be separated only by type of surgery (i.e., SOT vs HSCT). The company should fit survival curves and extrapolate the KM data (according to TSD 19) in order to estimate survival until the end of the stage 1 Markov (see further recommendations in Section 4.2.6.2.1.1).
    b. If the company can substantiate, with existent data available in literature, that approximately over 1 year after SOT, CMV still impacts patients' mortality, then the company should use these data to conduct a scenario analysis to estimate a differential in mortality according to CMV in the SOT population. The same is applicable for HSCT patients, although, for approximately over 100 days since transplant.
2. If the company's proposition is that maribavir is given as early as possible in the treatment pathway for r/r patients, then the cost-effectiveness of maribavir for the SOT and HSCT UK population should be estimated. For this population, the mortality observed in SOLSTICE could in theory be underestimated. While this could be the case for HSCT patients; the opposite seems to be true for SOT patients. Comparison of the SOT mortality rates in SOLSTICE with Hakimi *et al*. and the NHS blood and transplant reports shows that the mortality observed in SOLSTICE is higher than what would be expected for patients who had transplants more recently. Therefore, the ERG recommends:
        i. That the company provides a justification for why the mortality observed for SOT patients is higher in the trial than in the other sources;
        ii. The use of the company's KM data on survival for the stage 1 Markov model. The KM data should be separated by type of surgery (i.e., SOT vs HSCT) with possible adjustments included to reflect mortality earlier after transplant; and by CMV status being sourced from available literature (e.g., for SOT patients, the company could use the HRs estimated in Hakimi *et al*. on the impact of mortality on

presence of CMV vs no CMV). The company should fit survival curves and extrapolate the KM data (according to TSD 19) in order to estimate survival until the end of the stage 1 Markov.

3. If the company does not use the recommended KM data, and instead uses the point estimates for the probability of death at specific times in SOLTICE – the ERG recommends that the company changes the stage 1 Markov to be 20 weeks to effectively model only one cycle of 2 clearances and 1 recurrence (as per trial data and assumption that clearance is independent of time since surgery).
4. Removes the background sex- and age-specific general population mortality rates from the estimates of mortality in the first 12 months of the model.

4.2.6.3.4 Mortality in the stage 2 Markov model

Solid organ transplant patients

After year 1 in the model, mortality was assumed to differ by the type of transplant received by patients. For SOT patients, mortality was estimated based on data from the NHS Organ Donation Annual Activity Report.[33] One-, two-, five-, and 10-year post-transplant survival estimates for first non-paediatric heart, lung, liver and kidney transplants of all donor were converted into their corresponding annual conditional survival probabilities. The company then estimated a weighted average of the annual probability of survival for SOT patients considering the type of SOT at baseline in the model. Finally, the company ensured that the maximum mortality rate was taken every year, between the SOT-specific mortality and the general population mortality adjusted for age and sex.

To account for years where there were no published data available, a constant rate of mortality was assumed between the most recent available year and the next available year.

For lung transplants with donation after circulatory death (DCD) donor types, the survival probabilities were available only for the first 3 years after transplant, thus, the company assumed the same survival as that observed for DBD (donation after brain death) lung donors.

After 10 years, the company assumed that the mortality rate was the same as that observed at 10 years, until the age and gender matched mortality in the general population was higher than the former.

Haematopoietic stem cell transplant

The CS states that data from the Haematological Malignancy Research Network (HMRN) was used to estimate mortality in the first 5 years post-HSCT and that due to high attrition seen on the data after year 5, the 5-year mortality was continued for the remaining model years (Table 40). The company ensured that the maximum mortality rate was taken every year after year 5, between the HSCT-specific mortality and the general population mortality adjusted for age and sex. The HMRN data provided mortality estimates for year 2, 3, 4 and 5 post-transplant. The mortality for year 1 was assumed to be the same as the closest year with available data (year 2).

Table 40. HMRN mortality data for HSCT patients

Years	Annual probability of death %
2-years post-transplant	17.3
3-years post-transplant	10.4
4-years post-transplant	4.9
5-years post-transplant	5.8

4.2.6.3.5 ERG critique

The ERG generally agrees with the sources of data used to estimate the mortality parameters in the stage 2 Markov model. Nonetheless, as discussed in previous sections, the company needs to ensure consistency between the data used and when patients are assumed to enter the economic model after transplant.

During clarification, the ERG noted to the company that the transition from the mortality in the stage 1 Markov model to the stage 2 Markov model for HSCT patients implied an increase in mortality rates from 1.3% to 1.5%, which did not reflect a clinically plausible scenario (given that data suggests the opposite trend). The company replied by undertaking a scenario analysis where, "*the background HSCT mortality from the HMRN data was applied from week 0 rather than week 52*" (therefore, excluding the SOLSTICE mortality data from the model). This scenario increased the company's base case ICER from £15,337 to £18,884. Nonetheless, the ERG is unclear if this means that the company also removed the differential in mortality by CMV status from the model.

The ERG also disagrees with the long-term assumption made for both the SOT and the HSCT populations that the mortality estimate observed for the last year of data available in the NHS Organ Donation Annual Activity Report and in the HMRN data, respectively, would be observed for the remainder of the model (or until general mortality background rates were higher than the

transplant-specific rates). Given that the data available indicates that transplant-specific mortality decreases with time since transplant, the company's approach is likely to overestimate the mortality of transplanted patients.

In TA591, the ERG noted that the life expectancy of patients in the long-term Markov phase of the model was a key driver of incremental QALYs and hence cost-effectiveness. The ERG for TA591 used the same HMRN data to estimate mortality in the first 5 years post-HSCT, however, after 5 years the ERG ran two scenario analyses assuming different relative risks (RR) in relation to the general population mortality to estimate mortality. The more relevant scenario for this current STA is the scenario using the RR applied to general population mortality from Martin *et al.* (RR 4.5).[34]

The ERG anticipates that the same issue would apply to SOT patients, although possibly to a lesser extent, given that the company assumed that the 10-year mortality rate (as opposed for the 5-year rate for HSCT patients) would be observed for patients' lifetime (or until the general population background mortality rate is higher).

4.2.6.3.5.1 ERG's suggested approach for TE

In addition to the changes proposed by the ERG to the company's estimation of mortality in the stage 1 Markov model, the ERG recommends that the company changes its approach to estimating mortality in the stage 2 Markov model to ensure:

1. That the cost-effectiveness of maribavir in the trial population in captured and that mortality in the phase 2 Markov model reflects the appropriate population and time surgery.
2. If the company's proposition is that maribavir is given as early as possible in the treatment pathway for r/r patients, then the cost-effectiveness of maribavir for the SOT and HSCT UK population should be estimated to ensure that mortality in the phase 2 Markov model reflects the appropriate population and time surgery.
3. That overall survival is not overestimated after 5 years for HSCT patients and after 10 years for SOT patients. In order to do this the ERG recommends that the company investigates the possibility of using a RR to adjust background survival for patients in the long term (similar to what has been done by the ERG in TA591).
4. A clinically plausible transition between mortality rates from the stage 1 to the stage 2 Markov models.

4.2.6.4 *Graft loss*

As no graft losses occurred in the 20-week follow-up period of SOLSTICE, the company decided to use the Hakimi *et al.* study to estimate graft failure in the model (defined in the study as a re-transplantation procedure or at least one dialysis procedure).[32] During the clarification stage, the ERG raised the fact that the company was erroneously using the 1-year outcomes reported in the study as 2-year outcomes. The company disagreed with the ERG as it considered that the study followed patients up to 2 years. Nonetheless, the company acknowledged some uncertainty around the follow up time in the study, therefore conducted a scenario analysis where the rates reflected annual events.

The company modelled graft failure by CMV status by using the probability of 9.41% for patients without CMV and the probability of 10.81% for patients with CMV provided in Hakimi *et al.* (Table 41). The company assumed that the estimates were 2-year probabilities and therefore converted them accordingly to 4-weekly probabilities to be used in the model. The distribution of organ transplant at baseline (11% for heart; 50% for kidney; 29% for lung; 3% for liver; and 6% for other organs) was used to estimate a weighted probability of graft loss in every model cycle. Graft failures were only assumed to occur in the stage 1 Markov model.

Although it was not clearly reported in the CS, the company implicitly assumed that patients with graft failure have a second transplant in the model, with respective costs and disutilities. The company also assumed that patients who suffered from graft failure in the model had an increased risk of mortality associated with a retransplant (vs first transplant). The increase in mortality was applied by multiplying the organ-specific HR sourced from the literature (for each specific organ) by the relevant annual age- and sex-specific mortality.[35-38]

For kidney transplant failures, the company assumed that patients received dialysis before receiving a new transplant. Therefore, in the base-case, all renal transplant patients who experienced graft loss were assumed to have a retransplant, along with the additional cost of dialysis while waiting for a transplant.

The costs and the impact on patients' quality of life associated with graft failures are discussed in Section 4.2.10, and Section 4.2.8, respectively.

Table 41. Probability of graft loss over 12 months for patients with or without CMV at different points since transplant

Graft failure	CMV within 3 months post-transplant			CMV beyond 3 months post-transplant			CMV beyond 6 months post-transplant		
	With CMV	Without CMV	p-value	With CMV	Without CMV	p-value	With CMV	Without CMV	p-value
Overall	10.81%	9.41%	nss	6.34%	3.70%	0.001	5.12%	1.69%	0.0001
Kidney	13.24%	11.77%	nss	6.65%	4.48%	0.04	4.70%	2.22%	0.02
Liver	4.27%	3.72%	nss	4.90%	0.99%	0.01	6.67%	1.25%	0.04
Lung	6.25%	8.65%	nss	5.62%	4.71%	nss	4.41%	0.00%	0.03
Other*	8.43%	4.17%	nss	7.23%	1.16%	0.01	6.67%	0.80%	0.02

nss: not statistically significant

*heart, pancreas, double organ, intestine

4.2.6.4.1 ERG critique

During clarification, the ERG asked the company to discuss the potential relationship between the absence of graft loss events in SOLSTICE and time since transplant for SOT patients enrolling in the trial; however, during their initial response, the company was not aware that trial data on time since surgery at baseline was available and therefore did not explore this relationship. The ERG therefore recommends that the company explores this relationship TE.

Furthermore, the ERG asked the company to explain why in the model graft loss could occur as early as week 4, given that it heard from clinical experts that the earliest that graft failure occurs is usually around 3 months post-transplant. The company replied that it took a pragmatic approach in the modelling of graft loss events and that assuming events started at a specific point after transplant (i.e., later than in the first cycle) would require a robust clinical explanation and that it had not heard or come across any such evidence.

The ERG also asked the company to conduct a scenario analysis where graft failure could only start occurring 3 months after patients' surgery in the model. The company replied that such analysis was not possible to conduct as time since surgery was unknown at baseline in SOLSTICE. The ERG notes the inconsistency in the company's answer as the company's base case model assumes that patients entered the analysis immediately after transplant. Therefore, the scenario analysis requested by the ERG would simply entail not allowing patients to have graft failure events for the first 3 months of the economic model.

The ERG also considers that the company's approach is biased in favour of maribavir as graft failure events in the model were higher for patients experiencing CMV. The ERG acknowledges the evidence by Hakimi *et al*. which shows a higher risk of graft failure for patients with CMV compared with patients without CMV. However, no graft loss events were observed in SOLSTICE, and no evidence has been provided in the relevant r/r CMV population, comparing patients with r/r CMV who experienced 2 or more episodes with patients with r/r CMV who experienced only one, to support the company's application of a higher probability of graft failure to patients experiencing CMV. Therefore, assuming that patients only experienced graft failures 3 months after cycle 0 in the model would have reduced the benefit estimated for maribavir, thus increasing the company's ICER.

The ERG disagrees with the company's decision to assume that the rates of graft loss were based on 2 years follow up in their base case analysis. The Hakimi *et al.* study reports outcomes reflecting a 2-year and a 1-year follow up. However, in reference to the graft loss estimates used by the company, the study states, "*Recipients with L-CMV-3M* [CMV beyond 3 months post-transplant] *and L-CMV-6M* [CMV beyond 6 months post-transplant] *were more likely than controls to experience graft rejection and graft failure over 12 months following the index date*". Therefore, the ERG considers that the estimates provided in the study are annual (instead of biannual); however; reflect a period of time that goes beyond 1 year after transplant. For example, the graft failure rates estimated for L-CMV-6M patients reflect patients, who had CMV 6 month (or later) after transplant, were only followed up for graft failure events for 12 months after the CMV event.

Importantly, the ERG notes that the estimates from Hakimi *et al.* used by the company in their base case are mainly applicable to patients within their first-year post-surgery (as the rates chosen by the company are for patients who had a CMV event within 3 months after transplant – Table 41). As discussed throughout the report, the mean time since surgery for SOT patients in SOLSTICE exceeds [redacted] for both maribavir and IAT patients. Therefore, the Hakimi *et al.* estimates used by the company are not reflective of the risk of graft failure for the SOLSTICE population. The Hakimi *et al.* study reported KM data on graft failure by CMV events occurring within 3 months of surgery; 3 months post-surgery; and 6 months post-surgery up to 2 years after the index event. Visual inspection of the curves suggests that the risk of graft failure decreases with time since transplant (particularly for patients who experience CMV events within 3 months after transplant), however, the data needs to be analysed through the use of survival analysis to provide more robust conclusions. Therefore, the ERG recommends that the company uses the KM data from Hakimi *et al.* to fit and extrapolate survival curves according to the NICE DSU TSD 19 in order to estimate the

probability of graft failure for the initial years in the model and crucially, in accordance with the assumption made for time since surgery at baseline in the model.

The ERG's clinical experts advised that less than 5% of patients get a re-transplant after first graft failure. Therefore, during clarification, the ERG asked that the company conducted a scenario analysis where 0% of patients (instead of 100%) received a second transplant in the model. The company replied that, "g*iven that there are more graft loss events in the comparator arm, it could be reasonably argued that Takeda have taken a conservative approach when incorporating graft loss into the economic model.*" The ERG is confused by this statement, as it expects exactly the opposite to be true. Given the higher number of graft failure events in the comparator arm, an assumption of 100% of re-transplants (when in clinical practice less than 5% of patients are expected to experience a second transplant) will overestimate the costs in the IAT arm, and therefore bias the costs of re-transplantation in favour of maribavir. Nonetheless, the alternative to a second transplant seems to be dialysis for kidney patients and a likely increase in mortality overall, which would negatively impact the outcomes in the IAT arm.

The ERG asked that the company adjusted the mortality and the need for dialysis in the scenario analysis for 0% of patients having a re-transplant. The company undertook an analysis where the mortality risk following graft loss; re-transplant costs; and re-transplant utility decrements were all set to zero. The company also assumed all patients receiving a renal transplant required kidney dialysis. The ICER increased from £15,337 to £16,211. The company's scenario analysis failed to take into account the increase in mortality for patients with graft failure, therefore not appropriately capturing the negative impact that the lack of a second transplant would have in patients' survival.

Finally, in their base case, the company assumed that patients who have a re-transplant have an elevated risk of mortality by applying an organ-specific HR sourced from literature to the annual age- and sex-specific mortality. Nonetheless, the ERG notes that some of these HRs (such as the HR estimated for a kidney re-transplant) were estimated as the relative increase in the risk of mortality of a second transplant vs a first transplant (and not vs no transplant).

4.2.6.4.1.1 ERG's suggested approach for TE

As previously discussed for clearance; recurrence; and mortality outcomes, the ERG recommends that:

1. That the cost-effectiveness of maribavir in the trial population is captured and that the probability of graft failure events reflects time since surgery in this population. The company should use clinical expert advice and the available evidence base to substantiate if graft failure events are still likely to happen over [redacted] after transplant.
2. If the company's proposition is that maribavir is given as early as possible in the treatment pathway for r/r patients, then the cost-effectiveness of maribavir for the SOT and HSCT UK population should be estimated to ensure that graft failure events reflect time since surgery in this population. Furthermore, the ERG recommends that the company ensures that graft failures can only occur 3 months after patients' transplant.

Additionally, the ERG recommends that the company:

3. Explores the relationship between the lack of graft loss events in SOLSTICE and time since transplant for SOT patients enrolling in the trial.
4. Uses the KM data from Hakimi *et al.* to fit and extrapolate survival curves according to the NICE DSU TSD 19 in order to estimate the probability of graft failure in the model (taking time since transplant into consideration).
5. Assumes that the proportion of patients receiving a second transplant in the model is less than 5% (or 0% for simplification purposes), however:
    a. All kidney transplant patients with a graft failure should be assumed to receive dialysis;
    b. All patients with graft failure should have an increase in mortality. If the company decides to use the same HRs as those used in the base case to estimate the increase in patients' mortality, these HRs should be applied to patients SOT-specific mortality and not to background mortality.

4.2.6.5 Leukaemia recurrence and graft versus host disease

The company did not originally include graft versus host disease (GvHD) events or any leukaemia recurrences in the base case model. During clarification, the ERG requested that the company considered both of these events as scenarios analyses in the model.

Disease recurrence

During clarification, the ERG pointed out that in TA591 it was noted that, "*a significant proportion of people with haematological cancers will experience relapse in their underlying disease following a SCT. These people will incur additional resource use and experience lower quality of life*". The ERG for TA591 added that, "*This* [the omission of relapse from the model] *is problematic as the costs and QALY decrements associated with relapse will not impact evenly on the two groups due differences in the number of patients at risk in the two groups (different mortality rates)*" [29].

Therefore, the ERG requested that the company included a scenario analysis where recurrences of underlying disease for HSCT patients were included in the economic analysis.

The ERG notes that in SOLSTICE [redacted] of patients in the IAT arm and [redacted] of patients in the maribavir arm who had received an HSCT also had recurrence of underlying disease at baseline. This compares with the 47% of disease recurrences from the HMRN data reported in TA591.

The company's scenario analysis assumed a probability of relapse of 47% and a one-off impact was estimated for these patients at week 52. The utility decrement associated with a relapse was assumed to be 0.01 which was derived by taking the difference in reported utility score for patients with acute myeloid leukaemia from Leunis *et al*.[39] and the general population utility reported by Ara *et. al.*[40] The company assumed that the duration of the disutility for a patient would be 3-months, however, the costs of a relapse were assumed to be incurred for two years. The cost of a relapse (£55,529) was derived by taking the three-month cost of £6,375 for a HSCT relapse reported in TA451 (ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia) and inflating it to 2021 values. The company's scenario analysis increased the ICER from £15,337 to £16,471.

The company's approach is similar to the approach taken by the company in TA591 to estimate the long-term impact of HSCT. However, in TA591, the company also undertook a scenario to estimate the impact of disease recurrence, which is the more relevant scenario for the ERG's request of estimating the impact of disease recurrence after HSCT. In TA591, the company considered the impact of disease recurrence on survival; costs; and utilities. The company presented several scenarios, assuming survival was 6 months, one year or two years. In all scenarios, a relapse was assumed to be associated with a 0.0114 disutility and with a per-cycle cost of £6,460 (2015/2016 prices). The ERG-preferred scenario in TA591 included the assumption that 47% of patients have

disease relapse; and that during the 6-month survival period of these patients, a per cycle cost of £6,460 is applied, together with a per-cycle disutility of 0.0114.

In comparison to the ERG scenario in TA591, the company's current scenario underestimates the impact of disease recurrence on survival and quality of life for HSCT patients. With regards to costs, it is likely that the company's approach is overestimating costs, as the company in TA591 assumed a higher cost of disease relapse, but only for 6 months, whereas in this STA the company assumed a lower cost per cycle, however with a duration of 2 years.

Chronic graft versus host disease

During clarification, the ERG noted that clinical expert opinion indicated that HSCT patients with chronic GvHD (i.e., unresolved GvHD at 100 days post-surgery) have a higher probability of CMV recurrence due to intense immunosuppressant treatment and are not expected to survive beyond 2 years after surgery. Therefore, the ERG requested that the company incorporated the subgroup of HSCT patients with GvHD from SOLSTICE in the model assuming an equal proportion of events in both arms, based on pooled prevalence data from the trial. After clarification, the ERG realised that the company had included a scenario analysis in the original CS where GvHD was included.

Nonetheless, as a response to clarification, the company surprisingly did not point the ERG to the analysis already conducted and instead, stated that it considered that the causal relationship between GvHD and CMV is not well established in literature; and that the impact of having GvHD was already included in the mortality data from SOLSTICE (given that a subgroup of patients had the disease in the trial). The company added that the number of patients with GvHD was relatively low in the trial.

The ERG notes that while it can be considered that the impact of GvHD has been captured in the 20-week mortality data from SOLSTICE, its long-term impact was not, given that the company did not choose to extrapolate the KM mortality data from SOLSTICE. The ERG also notes that even if the relationship between CMV and GvHD cannot be included in the model, the increased mortality associated with GvHD patients should be modelled.

Out of the 141 HSCT patients in SOLSTICE, new GvHD was reported during the study for [redacted] maribavir patients and for [redacted] HSCT recipients in the IAT group. Furthermore, [redacted] patients and [redacted] patients had chronic GvHD at baseline, in the maribavir and the IAT arms,

respectively, while [redacted] patients and [redacted] patients had acute GvHD at baseline, in the in the maribavir and the IAT arms, respectively. It is not possible for the ERG to know which of the new cases of GvHD occurring during SOLSTICE became chronic cases; or which baseline acute cases also became chronic; however, given that HSCT patients entered the trial, on average, over [redacted] days after transplant [redacted] it would be clinically plausible that most new/acute GvHD cases during the trial became chronic.

If an assumption were to be included in the model whereby all patients in SOLSTICE with chronic GvHD were assumed to be dead at 2 years after entering the model, it is likely that the ICER associated with maribavir would increase, as fewer patients would contribute to the long-term benefits associated with the drug.

Even though the company considered that the relationship between CMV and GvHD unclear, in the scenario analysis included in the CS, a different 4-weekly rate of GvHD was assumed for CMV and nCMV patients. The company used a hazard ratio of 2.18 (95% CI: 1.30 to 3.65, p-value < 0.01) reported in Cantoni *et al*. which concluded that during phases of CMV replication, patients were at increased risk of developing acute GvHD. The ERG notes that the hazard ration reported in the study does not provide any information on the relationship between CMV and chronic GvHD. The costs and disutilities used by the company in their scenario analysis are discussed in Sections 4.2.9, and 4.2.8, respectively.[41]

4.2.6.5.1.1 ERG's suggested approach for TE

In order to estimate the impact of underlying disease recurrence for HSCT patients, the ERG recommends that the company runs a scenario analysis which is consistent with TA591, specifically:

1. Assumes that 47% of patients with a recurrence live for 6 months since recurrence;
2. Assumes that patients with disease recurrence experience a per-cycle disutility of 0.0114;
3. Updates the per-cycle cost of £6,460 (2015/2016 prices) to the correct price year and applies it in every cycle of the model for 6 months.

Additionally, the ERG recommends that the company:

4. Investigates further (if possible) how many cases of chronic GvHD were in SOLSTICE;
5. Runs a scenario analysis assuming that the pooled percentage (i.e. not differentiating by CMV or nCMV) of patients with chronic GvHD at baseline in SOLTICE were the only patients

who had chronic disease over 20 weeks; and another scenario where all acute and new cases in SOLSTICE (in addition to the chronic cases at baseline) are assumed to become chronic during the trial. These scenarios should assume that patients with chronic GvHD do not survive beyond 2 years after transplant;

6. Adapts the scenario analysis requested in point 5 according to the assumptions made around time since surgery at baseline (see ERG's recommendations for TE on Section 4.2.6 for more details).

4.2.7 *Adverse events*

Adverse events which occurred within the SOLSTICE clinical trial during the on-treatment observation period were reported, by treatment arm, for the safety population (all randomised patients who received at least one dose of study medication, n=350). The overall incidence of AEs was similar between patients randomised to the maribavir or to the IAT arm (Table 42). A majority of patients experienced at least one treatment-emergent adverse event (TEAE), 91.6% in the IAT arm and 97.4% in the maribavir arm. However, the company noted that, within the safety population, the mean exposure to maribavir ([redacted]) was longer than to IAT ([redacted]). A total of 40 deaths were reported in SOLSTICE; 16 deaths due to serious TEAEs occurred in the maribavir arm and 6 occurred in the IAT arm. The most common serious TEAEs leading to death were due to respiratory failure or relapse or progression of underlying disease. 1 death in each arm was considered treatment-related by the investigator.

Table 42. Summary of adverse events (safety population) (reproduced from CS appendices, Table 28)

	Maribavir		IAT	
	n	(%)	n	(%)
Participants in population	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to discontinuation of study-assigned treatment	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related TEAE leading to discontinuation of study-assigned treatment	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE leading to discontinuation of study-assigned treatment	[redacted]	[redacted]	[redacted]	[redacted]

Any treatment-related serious TEAE leading to discontinuation of study-assigned treatment	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to study discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE leading to study discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related serious TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE of special interest	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related TEAE of special interest	[redacted]	[redacted]	[redacted]	[redacted]

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

The most frequently reported TEAEs were [redacted] for those receiving maribavir, and [redacted] for those receiving IAT (Table 43). The company noted that although dysgeusia was more common in the maribavir group, most cases were mild (88.5%) and rarely lead to treatment discontinuation (0.9% of patients in the maribavir group). Neutropenia was more frequently observed in the IAT arm, as were hypokalaemia, hypomagnesemia, leukopenia and hypertension. Occurrence of all other TEAEs were similar in the maribavir and IAT arms. Of note, TEAEs leading to discontinuation of the study-assigned treatment were higher for the IAT arm than the maribavir arm (31.9% of patients in the IAT arm experienced a TEAE leading to discontinuation compared with 13.2% of patients in the maribavir arm). Tissue invasive CMV disease/syndrome (a TEAE of special interest) occurred in 3.4% of patients both the maribavir and IAT arms.

Table 43. Summary of most frequent TEAEs (incidence ≥ 10% in one or more treatment groups, safety population) (reproduced from CS, Table 27)

	Maribavir		IAT	
	n	**(%)**	**n**	**(%)**
Participants in population	[redacted]	[redacted]	[redacted]	[redacted]
with any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]

Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
CMV viraemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Taste disorder	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]

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

The costs and disutilities associated with adverse events were accounted for in the company's base case (Sections 4.2.8 and 4.2.9).

4.2.8 Health-related quality of life

Quality-adjusted life years (QALYs) accrued by the model cohort in each cycle are dependent on the utility attributable to each model health state; the disutility associated with adverse events or graft loss; and an age-related reduction in quality of life. These are discussed in detail in the following subsections.

4.2.8.1 Health state utilities

Health state utility values (HSUVs) were derived from EQ-5D-5L data from SOLSTICE for patients with and without a clinically significant CMV infection (CMV and nCMV, respectively). The EQ-5D-5L data collected was mapped to the EQ-5D-3L UK value set using the Van Hout *et al.* (2012)[42] algorithm. The CMV and nCMV utility values were also estimated separately for SOT and HSCT patients. The company estimated the nCMV health state utility values by averaging all utility measurements taken over the 20-week trial for patients who were week-8 responders to either maribavir or IAT treatment. Conversely, CMV health state utility values were estimated by averaging all utility measurements taken for patients who were non-responders at week 8. The resulting four health state utility value estimates were applied for the first 52 weeks of the model based on whether a patient was on/off treatment in a given cycle and whether they were a SOT or HSCT patient.

As no CMV events occurred in the stage 2 Markov model, the company estimated utility values for SOT and HSCT patients who remained alive by averaging all utility measurements taken throughout the 20-week SOLSTICE trial for SOT and HSCT patients. Table 44 provides a summary of the health state utility values applied in both phases of the company's economic model.

The company also included age-related utility decrements in the base case for the alive/dead phase of the model (stage 2 Markov). The company began by subtracting the SOT or HSCT utility values reported in Table 44 for alive patients from the UK general population utility at age 53 (the starting age of the model cohort), estimating 0.037 and 0.137 utility decrements for the SOT and HSCT populations, respectively. Subsequently, for every cycle of the stage 2 Markov model, the company subtracted the relevant utility decrement estimated from the UK general population utility at the relevant age. The application of age-related utility decrements was consistent with TA591, however, rather than using Ara *et al.* 2010[40] as a source of UK general population utilities, the company sourced the estimates from Szende *et al.* 2014.[43]

Table 44. Summary of utility values used in company base case

Health state	Utility Value (by transplant type)	
	SOT	HSCT
Weeks 0-52 (stage 1 Markov model)		
CMV	[redacted]	[redacted]
nCMV	[redacted]	[redacted]
Weeks 52+ (stage 2 Markov model)		
Alive	0.81*	0.71*

Abbreviations: SOT, solid organ transplant; HSCT, haematological stem cell transplant; csCMV, clinically significant cytomegalovirus; n-csCMV, non-clinically-significant cytomegalovirus.

*Patients are one year older when entering the alive-dead stage of the model and so the age adjustment is applied to the utility estimates derived from SOLSTICE IPD. The utilities estimated for the first cycle of the stage 2 Markov are 0.762 and 0.662 for SOT and HSCT patients, respectively.

4.2.8.2 Adverse event related disutilities

Adverse event-related disutilities were applied, disaggregated by type of AE, in each model cycle, for the proportion of patients in each treatment arm who remained on treatment (including IAT retreatment) up to 1 year, when all patients were assumed to cease treatment. The disutility applied in each 4-week cycle was based on the 20-week incidence of each AE in the maribavir or IAT arm of SOLSTICE, the mean duration of each AE, and disutility estimates sourced from existing literature

sources. Table 45 provides a summary of these inputs. Of note, the 4-week AE probabilities derived from the maribavir arm of SOLSTICE were applied in the maribavir model arm to patients on IAT retreatment after maribavir.

Table 45: Adverse Event unit disutilities and duration.

Adverse Event	Mean duration* (days)	Unit disutility	Source
Acute kidney injury	36.90	-0.1006	Sullivan *et al.* 2011[44]
Anaemia	10.80	-0.2500	Ossa et al. 2007[45]
Diarrhoea	15.92	-0.0725	Sullivan *et al.* 2011[44]
Dysgeusia	0	0	Assumption: No care required or disutility applicable
Fatigue	77.69	-0.0410	Nafees *et al.* 2017[46]
Febrile neutropenia	10.80	-0.0900	Nafees *et al.* 2008[47]
Headache	21.22	-0.0266	Sullivan *et al.* 2011[44]
Leukopenia	21.50	-0.0900	Bullement et al. 2019[48]
Nausea	19.36	-0.0250	Nafees *et al.* 2017[46]
Neutropenia	14.80	-0.0897	Nafees *et al.* 2008[47]
Pyrexia	11.77	-0.1100	Beusterien et al. 2010[49]
Renal impairment	29.50	-0.1006	Sullivan *et al.* 2011[44]
Thrombocytopenia	48.90	-0.1080	Tolley *et al.* 2013[50]
Vomiting	14.72	-0.0250	Nafees *et al.* 2017[46]

* Mean adverse event duration calculated from SOLSTICE patient level data.

4.2.8.3 Disutilities associated with disease complications

As no graft loss events were observed in SOLSTICE, the company conducted a vignette study to estimate utility values for patients with and without graft loss (of kidney or lung transplants). A total of [redacted] members of the UK general public were presented with a total of 12 health state vignettes developed in conjunction with UK clinicians. These described three clinical states for r/r CMV: clinically significant and symptomatic; clinically significant and asymptomatic; and non-clinically significant. For each clinical state, three add-on events of interest were described: kidney graft loss; lung graft loss; and GvHD. A time-trade-off methodology was used to value each health state and results are provided in Table 50 of the CS.

The company estimated the disutility associated with kidney graft failure based on the difference between utility estimates for the "asymptomatic CMV" and "asymptomatic CMV with kidney graft

loss" health state vignettes. The disutility associated with lung graft failure was similarly estimated. Graft loss disutilities (provided in Table 46 below) were applied to the proportion of patients who experienced graft loss in each 4-week cycle up to week 52. The impact on patients' quality of life of graft failure was assumed to last for 4 weeks.

The company also provided a scenario analysis wherein a dialysis disutility (-0.250 sourced from Liem *et al*.[30]) was applied based on a proportion of patients experiencing kidney graft loss in each 4-week cycle were assumed to receive lifetime dialysis.

Table 46. Disutilities applied in company base case for patients who experience graft loss

Transplant type/dialysis	Disutility applied	Source
Heart transplant	-0.279	Vignette study – assumed equal to lung transplant.
Kidney transplant	-0.166	Vignette study – decrement calculated as the difference between utility estimates for patients with asymptomatic CMV and patients with asymptomatic CMV with kidney graft loss.
Lung transplant	-0.279	Vignette study – decrement calculated as the difference between utility estimates for patients with asymptomatic CMV and patients with asymptomatic CMV with lung graft loss.
Liver transplant	-0.279	Vignette study – assumed equal to lung transplant.
Other transplant	-0.279	Vignette study – assumed equal to lung transplant.

Abbreviations: csCMV, clinically significant cytomegalovirus; n-csCMV, non-clinically-significant cytomegalovirus.

Note: each disutility is applied to the proportion of patients who experience graft failure in a given 4-week cycle, meaning that the disutility is implicitly assumed to last for 4 weeks.

Finally, the company also conducted a separate scenario analysis considering GvHD in the model, where a disutility of -0.090 was applied to the proportion of patients experiencing GvHD in the CMV or nCMV health states in a given cycle (see Section 4.2.6.5). The disutility applied was estimated from SF-36 HRQoL data from Pidala *et al*. 2011[18] and converted to EQ-5D-3L using a mapping algorithm by Ara and Brazier 2008.

4.2.8.4 ERG critique

The ERG considers the company's approach to estimating utility values to be flawed for the reasons discussed below. The ERG's requests for new utility analyses during the clarification stage were not adequately addressed by the company, and these analyses could not be conducted by the ERG due to the unavailability of IPD. As such, the ERG has provided guidance on the analyses and model adaptations needed to address the discussed limitations.

The company's approach of using simple averages of cross-walked EQ-5D-3L data to estimate health state utility values without consideration for the bias introduced by incomplete follow up is considered flawed by the ERG. Averaging utility measurements taken for patients at different points in time results in utility estimates which underweight patients for whom fewer utility measurements were taken before they were lost to follow up. For this reason, linear mixed effects regression models are regularly used for the estimation of utilities where the available data is longitudinal. A further concern is whether there is any differential loss to follow up between the treatment arms, as this can be an indicator that data is not missing at random.

Furthermore, given the company's statement that utilities were estimated based on week 0 to week 20 utilities for responders and non-responders at week 8, the ERG remains unclear if the company assessed response at week 8 and then retrospectively averaged utility measurements for responders and non-responder from week 0; or if the utilities were collected from the point of response until week 20.

The ERG also notes that averaging utility values across different time points does not provide any information of patients' change in utility from baseline.

Therefore, during the clarification stage the ERG requested the company to provide data on the number of respondents to each EQ-5D-5L assessment so that both the extent of loss to follow up, and changes in utility from baseline could be assessed.

The company partially provided the data requested in Table AB of the clarification document, however, did not provide the statistical significance for the change in utility data from baseline within each treatment arm, which considerably reduces the value of the analysis provided at clarification. The company provided the statistical difference for mean change at baseline at all available time points in SOLSTICE across treatment arms, and these were all [redacted].

The company also provided the data reported in Table 47, which show a higher loss to follow up in the IAT arm. Although data on reasons for loss to follow up was provided, the ERG note that the substantial difference observed between the maribavir and IAT arms are likely due to confounding factors and the data is likely to be missing not at random.

Table 47. EQ-5D questionnaires completed, and mean observed (crosswalked) EQ-5D-3L score, at each timepoint (adapted from CQ response Table AB).

Timepoint	Maribavir N=235		IAT N=117	
	Questionnaires completed (% of N)	Mean EQ-5D-3L score*	Questionnaires completed (% of N)	Mean EQ-5D-3L score*
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations; IAT, investigator-assigned treatment.

The ERG also requested the company to provide a scenario analysis wherein a linear mixed effects model was used to estimate the health state utility values. This was provided by the company; however, the ERG has several concerns regarding the implementation of these values in the model.

The company's linear mixed effects model included CMV status at 8-weeks; transplant type; and treatment arm as predictors. This analysis demonstrated a significant difference in utility between responders and non-responders to treatment at 8-weeks and between transplant groups, but no significant difference in utility was observed between treatment arms. This result was used to justify the company's application of treatment independent utility values. However, as the utility estimates by response status and transplant group were estimated for each treatment arm, the company produced a weighted average of the utility scores for patients treated with IAT and maribavir based on the number of EQ-5D-5L questionnaire responses informing each estimate. The ERG notes that a more appropriate method of analysis would have been to run a linear mixed effects model with only response status at 8-weeks and transplant type included as predictors, which may have yielded different results from the company's more indirect approach. However, the issue of data missing not at random remains an unaddressed issue for this analysis. The ERG, therefore, recommend that the company explore multiple imputation and pattern-mixture modelling methodologies which may limit or overcome the bias (of unknown magnitude and direction) introduced by the non-random loss to follow up.

The ERG also disagrees with the company's approach to estimating the transplant-specific utility values for the stage 2 Markov model as the estimated utility values included patients with and without CMV during the 20-week follow-up of SOLSTICE and led to an implausible transition from the utilities used in the stage 1 and the stage 2 parts of the economic model.

As demonstrated in Table 48 below, patients in the SOT CMV state prior to week 52 suffer a drop in utility when the model switches to an alive/dead model. This is inconsistent with the company's assumption that all patients cease CMV treatment due to patients' immune system recovering at 12 months and patients being free from CMV from that point onwards.

The ERG is also concerned that the utility values applied beyond 52 weeks in the company base case underestimate the quality of life experienced by nCMV patients. These patients suffer a considerable drop in their quality of life after week 52 without a plausible explanation, given that their CMV status was considered to not change after that point in time.

The ERG considered the application of age-adjusted utility values in the stage 2 Markov model appropriate. However, the ERG noted that the company's approach was inconsistent with TA591 as Szende *et al.* 2014[43] was used as the source of general population utilities rather than Ara *et al.* 2010.[40] The company did not provide rationale for this deviation from TA591. The ERG notes that Ara *et al.* 2010[40] has been used extensively in previous NICE technology appraisals and provides more granular utility estimates (by age rather than age ranges). As such, Ara *et al.* 2010[40] is preferred by the ERG.

Table 48. Transition in utility values applied to nCMV and CMV patients before and after entering the alive/dead stage of the model.

Transplant type	Utility value	
	Week 52	Week 56
SOT nCMV	[redacted]	0.762
SOT CMV	[redacted]	
HSCT nCMV	[redacted]	0.662
HSCT CMV	[redacted]	

Abbreviations; SOT, solid organ transplant; HSCT, haematological stem cell transplant, n-csCMV, non-clinically-significant cytomegalovirus.

The ERG also has several concerns regarding the company's approach to incorporating the quality-of-life impact of graft loss into the model. Firstly, the disutilities were applied only in the 4-week model cycle in which patients experienced graft failure, implicitly assuming that graft loss impacts

quality of life for only 4 weeks. The ERG considers this assumption inappropriate as graft loss is non-reversible and expected to have a long-lasting effect a patient's quality of life. As the ERG's clinical experts indicated that only a small minority of patients would receive a second transplant, the ERG considers that the disutility associated with graft failure should be applied until death (accounting for additional age-related reduction in quality of life). Furthermore, as patients who experience graft loss are unlikely to receive a second transplant, those with kidney graft loss are expected to receive lifelong dialysis and therefore the disutility associated with dialysis is applicable for these patients.

Additionally, the ERG is uncertain of why the company estimated graft loss disutilities based on utility estimates (with and without graft loss) for health state vignettes of only asymptomatic clinically significant CMV patients, rather than also including estimates for symptomatic clinically significant CMV patients and patients without clinically significant CMV. The ERG recommends that the company clarifies this assumption at TE.

Finally, the company's application of 4-week AE probabilities derived from the maribavir arm of SOLSTICE to patients receiving subsequent IAT retreatment after maribavir may have overestimated the true utility decrement attributable to the maribavir arm of the model. The ERG therefore considered the assumption conservative, though the impact of AE-related disutilities on the ICER was minimal.

4.2.8.4.1.1 ERG's suggested approach for TE

As previously discussed for clearance; recurrence; mortality; and graft loss outcomes, the ERG recommends that:

1. The cost-effectiveness of maribavir in the trial population is captured and that the probability of graft failure events and respective impact on patients' quality of life reflects time since surgery in this population.
2. If the company's proposition is that maribavir is given as early as possible in the treatment pathway for r/r patients, then the same should be ensured for the cost-effectiveness of maribavir for the SOT and HSCT UK population.

Additionally, the ERG recommends that the company:

3. Provides a formal assessment of whether the EQ-5D-5L data are missing at random and identify, if possible, the contributing factors to the differential loss to follow up observed between the maribavir and IAT arms.
4. Explores whether multiple imputation and pattern-mixture modelling methodologies can limit or overcome the bias (of unknown magnitude and direction) introduced to the utility estimates by the missing not at random EQ-5D data.
5. Re-evaluates the transitioning in utilities from week 52 to week 56 in the model so that these are consistent with model assumptions and also clinically plausible.
6. In line with TA591, it is recommended that the company utilises Ara *et al.* 2010[40] to estimate the age-related utility decrements applied in the model.
7. Applies utility decrements due to graft loss until death (adjusting for age-related utility) for all patients who experience graft loss. For kidney graft loss, it is recommended that the utility decrement associated with dialysis is applied.

4.2.9 Resource use and costs

Maribavir is given as two 200mg oral tablets twice daily (800mg total daily dose) for 8 weeks. The list price, provided by the company, is £[redacted] for a 56 x 200 mg pack. The total cost per 8-week treatment course is £[redacted]. The company has proposed a patient access scheme price for maribavir, bringing the cost of a 56 x 200 mg pack down to £[redacted] with an 8-week treatment course cost of £[redacted]. This cost is applied for all patients in the first model cycle, though it is adjusted for the observed time-on-treatment (ToT) from the maribavir arm of the SOLSTICE trial.

The unit acquisition costs for the basket of drugs included in the IAT arm (ganciclovir, valganciclovir, foscarnet, and cidofovir) were primarily sourced from the British National Formulary (BNF). For cidofovir the BNF did not provide a list price and the company sourced a USA cost using the Medi-Span® Price Rx® online drug pricing tool converted to GBP.

Based on advice from the company's clinical experts, patients receive a single dosing regimen until CMV has been cleared. As such, the company has applied the indicated loading dose for each IAT drug for the duration of treatment. Table 49 provides a breakdown of the 4-week treatment acquisition costs for IAT drugs. IV drug costs were calculated based on the mean patient weight from the SOLSTICE trial assuming vial sharing. A weighted average of these costs was applied in the model per 4-weeks of IAT treatment (£4,096.39) based on the proportion of patients who received each

drug in the IAT arm of the SOLSTICE clinical trial: 25.4% ganciclovir, 25.9% valganciclovir, 43.5% foscarnet, 5.2% cidofovir. As per the maribavir arm, patients were assumed to receive an 8-week treatment cycle, thus, the cost of 8-week treatment with IAT was applied in the first model cycle. An adjustment was made to the 8-week cost to reflect the observed ToT in the IAT arm of the SOLSTICE trial relative to the 8-week intended treatment period.

Patients who experience a recurrence of clinically significant CMV are assumed to restart treatment with IAT only (whether they first received maribavir or IAT as their first treatment in the model). As such, the 4-week IAT acquisition cost was applied for all patients in the CMV state after week 8, for every cycle of the model. These costs were also adjusted based on the observed ToT from SOLSTICE.

Acquisition costs were not included past week 52 of the model as all patients were assumed to have ceased treatment and transitioned to the stage 2 Markov model.

Table 49. Treatment costs of IAT component drugs (adapted from table 55 of the CS)

Treatment	Pack size	Cost per pack	4-week treatment cost	Source
Ganciclovir	5 x 500mg powder for concentrate for solution for infusion vials	£115.00	£963.42*	British national formulary[51]
Valganciclovir	60 x 450mg tablets	£865.17	£1,614.98	British national formulary[51]
Foscarnet	6g/250ml solution for infusion	£119.85	£7,530.42*	British national formulary[51]
Cidofovir	375mg/5ml concentrate for infusion vials	£760.05	£3,032.09*	US cost sourced from Medi-Span® Price Rx® online drug pricing tool and converted to GBP[52]

*4-week treatment cost for IV drugs calculated assuming vial sharing and the mean patient weight from the SOLSTICE clinical trial (74.8kg).

Note: the 4-week treatment costs exclude time-on-treatment adjustments made.

To account for the mean exposure time to maribavir or IAT in the SOLSTICE trial, the company applied ToT multipliers to the administration and acquisition costs included in the model. These multipliers (Table 50) were defined as the ratio of the mean time on maribavir, or on IAT, compared to the intended 8-week treatment period in SOLSTICE. The IAT multiplier was applied to all administration costs associated with IV treatments in the IAT arm. The multipliers were also applied to IAT retreatment in the maribavir and the IAT model arms.

Table 50: Mean time on treatment (adapted from Table 53 of the CS)

Drug	Mean time on treatment (Weeks)	ToT multiplier applied to acquisition and administration costs in model
Maribavir	[redacted]	[redacted]%
IAT	[redacted]	[redacted]%

Abbreviations: IAT, investigator-assigned treatment; ToT, time on treatment.

4.2.9.1 Administration costs

Administration costs for maribavir were based on the "Deliver Exclusively Oral Chemotherapy" activity cost code (SB11Z) from the NHS Reference Costs 2019-2020,[53] which is estimated as £210.79. This was applied as a one-off cost in the first model cycle, in line with the approach adopted by the ERG in TA591. This oral administration cost was also applied to valganciclovir, although as valganciclovir retreatment was also permitted in the model, this cost was applied in each 4-week model cycle for the proportion of patients who initiate valganciclovir treatment or retreatment in that cycle.

For IV drugs (ganciclovir, foscarnet, and cidofovir), administration costs were based on the "Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance" activity cost code,[53] of £403.84. This cost was applied for each day of IV treatment received (daily for ganciclovir and foscarnet, once weekly for cidofovir) to the proportion of patients receiving each type of IAT in the first model cycle, adjusted for ToT.

For subsequent IAT retreatment, 4-week administration costs (ToT adjusted) for each IAT, were applied to the proportion of patients in the csCMV state, after week 8 and up to week 52 of the model. Administration costs were not included past week 52 of the model as all patients were assumed to have ceased treatment and transitioned to an alive-dead model.

4.2.9.2 ERG critique

The company applied induction doses specified by the BNF for the duration of IAT treatments, however, reductions to maintenance doses were not applied. The company also noted that foscarnet is used off-license for CMV r/r patients and that the BNF dosing regimens specified for ganciclovir and valganciclovir are for prophylaxis use rather than for post-transplant CMV treatment.

The ERG's clinical experts agreed with the doses assumed in the company's base case for ganciclovir and valganciclovir dosing but noted that the BNF dosing regimen (including the maintenance dose) would be used for cidofovir and expressed preference for the dose escalation (at lower frequency) described in BNF regimen for foscarnet. The ERG notes that adopting the BNF dosing regimens for foscarnet and cidofovir would likely favour the IAT treatment arm as the less frequent maintenance dosing reduces acquisition and administration costs. During clarification, the ERG requested a scenario analysis applying the unadjusted dosing regimens specified by the BNF, however, this was not provided by the company.

Crucially, the ERG considers that the cost associated with IAT retreatment are overestimated in the model. The company captured treatment discontinuation by applying a ToT multiplier to the 4-week IAT acquisition and administration costs. However, no stopping rule was applied to retreatment with IATs, therefore, patients in the CMV state (with a recurrence event) were assumed to be on treatment until they exit the state or reach the end of 52-week stage 1 Markov model. Even though it could be argued that patients with a CMV infection after an 8-week round of treatment with one specific IAT would simply switch to another IAT, this is unlikely to happen with the frequency (and the duration) assumed in the company's model. This is related to the overestimation of recurrence episodes in the model (as discussed in Section 4.2.6).

The ERG notes that the company's application of constant CMV recurrence rates from week 20 to 52 in the base case results in 35.56% of patients in the maribavir arm and 38.98% of patients the IAT arm being on IAT retreatment at week 52. In the subsequent model cycle (week 56) these percentages drop to 0% in both arms due to the transition to the alive/dead stage 2 Markov model at 1 year. The ERG considers that this stark drop lacks face validity as there exists no one-year stopping rule for IAT retreatment. Instead, the ERG considers it likely that CMV recurrence rates would decline with time since transplant and as a result the proportion of patients requiring CMV retreatment would gradually approach 0%. The ERG proposed changes to the model structure and to the modelling of clearance and recurrence events (Section 4.2.4 and Section 4.2.6) resolves this issue as only 1 CMV recurrence, and hence one line of IAT retreatment would be considered in every round of CMV recurrences.

The ERG also has concerns that the administration costs applied for IV drugs in the IAT arm are overestimated as the company has assumed that the daily cost of IV administration is equal to an NHS reference cost for complex chemotherapy at first attendance (SB14Z).

The company noted that this approach was in line with TA591. However, the ERG notes that although the SB14Z reference cost was used in TA591, it was used in a much more restricted and temporary manner – for 5% of patients who received an initial IV infusion for the mean duration of IV letermovir within the PN001 trial. This was based on the assumption that a proportion of patients would not be able to tolerate the initial oral letermovir administration; and that all patients would switch to oral letermovir once the drug was tolerated.

In contrast, for this STA, the same reference cost is applied daily for all patients receiving IV treatment for the entire duration of treatment. The ERG therefore considers the company's use of the SB14Z first attendance cost as a daily administration cost inappropriate for the following reasons:

- The 2020/21 National cost collection guidance document notes that this cost applies to only the first administration of a chemotherapy cycle and that another lower reference cost for subsequent elements of a chemotherapy cycle (SB15Z) should be used for, *"Delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance"*.
- Feedback from the ERG's clinical experts suggested that administration of the IV treatments for CMV (ganciclovir, foscarnet, cidofovir) would utilise an existing central line and that approximately 4 hours of ICU nurse time would be required per administration of these IV drugs. As such, the application of a complex chemotherapy at first attendance cost means that costs associated with inserting catheters to facilitate IV treatment would be applied every day for the duration on treatment – this is inconsistent with the ERG's clinical expert feedback.

During clarification, the ERG requested that the company provided a scenario analysis wherein the daily administration costs for IV treatments were estimated based on the PSSRU hourly cost of a critical care nurse based on the ERG's clinical expert estimates that administration for 2 patients concurrently occupied 4 hours of a nurse's time (Guidelines for Provision of Intensive Care Services [FICM/ICS] outline a 2:1 patient to nurse ratio for level 2 patients). The company replied that the ERG's proposed approach would fail to capture the full costs of IV administration as it did not include the supply chain and hospital pharmacy time costs. The company did not provide the requested analysis.

The ERG acknowledges the company's point and therefore, recommends that 15 minutes of hospital pharmacist time be added to the nurse staff cost per IV administration originally suggested.

Finally, given the ERG's clinical experts' opinion that foscarnet is the most relevant comparator to maribavir, the ERG recommends that a scenario analysis is used where the first line IAT treatment consists of the cost of foscarnet only, with the other IATs being a retreatment option for further lines. As discussed in Section 2.3, there was no strong signal from the company's data that the response to foscarnet is different from the other IATs, therefore a change in the cost of the comparator arm will suffice for this analysis.

4.2.9.3 Monitoring costs

Treatment specific monitoring costs were included in the model to account for the cost of diagnostic tests conducted during CMV-related treatment. The company estimated the frequency of each diagnostic test based on the SmPCs for ganciclovir, valganciclovir, foscarnet, and cidofovir. Maribavir monitoring resources were assumed equal to that of valganciclovir as this is also an oral drug. Unit costs for each diagnostic test (complete blood count, renal function, electrolytes, and neutrophils) were sourced from the NHS Reference Costs 2019-2020.[53] The unit costs and further details of the estimated monitoring test frequencies are provided in Tables 56-58 of the CS. The total 4-weekly treatment-specific monitoring costs were applied in each model cycle for the proportion of patients on each treatment. In the maribavir arm this cost was £7.64, whereas for the IAT arm £26.40 was the weighted average (by SOLSTICE IAT treatment proportions) of the monitoring costs for the component drugs.

In addition, the company has also assumed that patients in the CMV health state of the model would have twice weekly viral load tests to monitor the progression of disease, with a unit test cost of £33.15. As such, a cost of £265.20 was applied per model cycle to the proportion of patients in the CMV state, regardless of treatment arm.

Monitoring costs were not included past week 52 of the model as all patients were assumed to have ceased treatment and transitioned to an alive/dead model.

4.2.9.4 Hospitalisation costs

Hospitalisation costs were applied in the model based on the 20-week hospitalisation rates (converted to 4-week probabilities) from SOLSTICE (split by SOT and HSCT patients). Rates of

hospitalisation were estimated, separately, for patients who responded to CMV treatment and those who did not; and treatment response was used as a proxy for clinically significant CMV status. The 4-week probabilities of hospitalisation (Table 51) were applied to the proportion of patients in the CMV and nCMV health states in the model, accordingly.

The total cost of each hospitalisation was estimated from NHS Reference Costs 2019-2020,[53] with a higher cost applied for hospitalisations which occur in patients with clinically significant CMV. The CMV cost corresponded to a weighted average for non-elective long stay costs for major infectious diseases with interventions, whereas the nCMV cost corresponded to a weighted average of non-elective long stay costs for major infectious diseases without interventions. Hospitalisation costs were not included past week 52 of the model as all patients transitioned to an alive/dead model.

Table 51. Hospitalisation costs (adapted from Table 59 and 60 of the CS)

Health state	4-week probability of hospitalisation (SE)		Unit cost	Source
	SOT	HSCT		
csCMV (response)	0.259 (0.026)	0.241 (0.024)	£7,019.85	SOLSTICE IPD, NHS Reference Costs 2019-2020[53] – weighted average of WJ02A and WJ02B
n-csCMV (no response)	0.153 (0.015)	0.217 (0.022)	£1,969.53	SOLSTICE IPD, NHS Reference Costs 2019-2020[53] – weighted average of WJ02C to WJ02E

Abbreviations: SE, standard error; SOT, solid organ transplant; HSCT, haematological stem cell transplant; csCMV, clinically significant cytomegalovirus; n-csCMV, non-clinically-significant cytomegalovirus; IPD, individual patient level data; NHS, national health service.

4.2.9.5 ERG Critique

The ERG notes that company has applied substantially higher unit hospitalisation costs to patients in the CMV health state compared to the nCMV state. This was based on weighted average NHS reference costs for non-elective long stay for infectious diseases with or without interventions (£7,019.85 versus £1,969.53). The ERG notes that application of the higher cost (with interventions) has resulted in double counting the CMV intervention costs given that acquisition and administration costs for CMV treatment are independently included in the model. As such, the ERG considers the company's approach inappropriate and recommends that the company captures the cost of a CMV-related hospitalisation by weighting average NHS reference costs for non-elective long stay for

infectious diseases without interventions (WJ02C to WJ02E) and applies the cost to hospitalisations occurring for both the CMV and nCMV health states.

4.2.9.6 Adverse event costs

The unit costs of treating AEs are given in Table 61 of the CS. Treatment emergent adverse events which occurred in ≥10% of patients in either the maribavir or IAT arms of the SOLSTICE trial were considered. Unit costs were derived from NHS Reference Costs 2019-2020.[53] The unit costs were multiplied by the 4-week probability of each AE occurring (provided in Table 45 of the CS) and applied to the proportion of patients receiving maribavir or IAT in each model cycle, up to 52 weeks. The 4-weekly AE management cost applied to patients on maribavir and IAT were: £431.49 and £542.10, respectively. Of note, when patients received retreatment with IAT after maribavir, the IAT AE costs were applied.

The ERG considered the company's approach to estimating AE-related costs generally appropriate. The company's application of 4-week AE probabilities derived from the maribavir arm of SOLSTICE to patients receiving subsequent IAT retreatment after maribavir may have overestimated the true AE-management costs attributable to the maribavir arm of the model. The ERG therefore considered the assumption conservative, though the impact of AE-related costs on the ICER was minimal.

4.2.9.7 Disease complication costs

Graft failure

The cost of a second transplant was applied to all patients who experienced graft loss in the model. Unit costs of re-transplantation by organ requiring transplant were sourced from the NHS Reference Costs 2019-2020[53] and are provided in Table 62 of the CS. The organ-specific transplant costs are applied based on the distribution of organ transplants observed at baseline of SOLSTICE. The ERG's critique of the company's approach to estimating the probability of graft loss in the model is discussed in Section 4.2.6.4. of the report.

In line with the transition to the alive-dead phase of the model, graft loss and its associated costs are assumed to cease at week 52.

Graft-versus-host disease

The company's scenario analysis considered a cost of £11,448 per GvHD event. The cost was based on the inflation-adjusted average cost of acute and chronic GvHD accepted by the NICE committee for TA591.[29]

4.2.9.8 ERG's suggested approach for TE

The ERG has several concerns with the company's approach to estimating unit costs and resource use in the model. Requests for new analyses at the clarification stage were not adequately addressed by the company. As such, the ERG recommends that the company:

1. Implements the ERG proposed model structure, limiting the occurrence of CMV recurrences to only one event followed by clearance (per each recurrence cycle - please see Section 4.2.4 and Section 4.2.5 for more details), thus, only estimating one line of IAT retreatment for every recurrence.
2. Estimates the administration cost for IV treatments based on the PSSRU hourly staff cost for a critical care staff nurse (band 5) and a hospital pharmacist, with 4 hours nurse time costed per administration of treatment to 2 patients; and 15 minutes hospital pharmacist time per administration.
3. Applies the weighted average of NHS reference costs for non-elective long stay for infectious diseases without interventions (WJ02C to WJ02E) for hospitalisations occurring from both the CMV and nCMV health states.
4. Runs a scenario analysis whereby first line IAT treatment costs consist of foscarnet only, with the other IATs being a retreatment option for further lines.

5 Cost effectiveness results

5.1.1 *Company's cost effectiveness results*

The results included in this section are based on list prices, except for maribavir, where a patient access scheme (PAS) price of £[redacted] for a 56 x 200 mg is used. Results including the comparator prices agreed with the national Commercial Medicines Unit (CMU) be found in the confidential appendix.

5.1.1.1 Deterministic results

The company's deterministic base case results are given in Table 52. In the company's base case, maribavir is associated with higher costs and higher quality-adjusted life years (QALYs) compared with IATs, resulting in an ICER of £15,337 per QALY gained.

Table 52. Company's deterministic base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Maribavir	[redacted]	8.386	6.021	-	-	-	-
IAT	[redacted]	8.226	5.890	£2,004	0.16	0.13	£15,337

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; LYG, life-years gained

5.1.1.2 Probabilistic results

The company performed a probabilistic sensitivity analysis (PSA), where all inputs were varied simultaneously over 10,000 iterations based on their distributional information (reported in Table 65 of the CS). Generally, costs were varied using a gamma distribution and probabilities using a beta-distribution.

The company's mean probabilistic results are reported in Table 53 and these are consistent with the company's deterministic results. The company also provided a cost-effectiveness plane (Figure 11) which shows that most iterations lie in the north-east. The company also noted in the CS that there is a probability that maribavir has a 51.83% probability of being cost-effective at a WTP threshold of £20,000 and 61.72% at a WTP threshold of £30,000.

The ERG considers the distributions assigned to each parameter reasonable. However, upon inspection of the model the ERG found that +/-10% of the mean value was assumed for the standard error (SE) when measures of uncertainty were not reported. A variation of 10% can be considered

low. Typically, a SE of 20% is used when measures of uncertainty are unavailable. This may explain the relatively narrow eclipse of iterations in Figure 11. The ERG notes that even with a lower variation around the mean values, the probability of maribavir being cost effective at the higher threshold of £30,000 was only 61.72%. The ERG recommends that the company uses a 20% variation around means to conduct PSA during TE.

Table 53. Company's probabilistic base case results

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Maribavir	[redacted]	6.03	-	-	-
IAT	[redacted]	5.91	£2,176	0.127	£17,156

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; LYG, life-years gained

Figure 11. Cost-effectiveness plane (reproduced from Figure 21 of the CS)

Key: CS, company submission; QALYs, quality-adjusted life years.

5.1.2 Company's scenario analysis

The company varied a number of model inputs in scenario analysis. The results of these scenarios are outlined in Table 68 of the CS. All the results reported by the company resulted in an ICER for maribavir vs IATs below £25,000 per QALY gained.

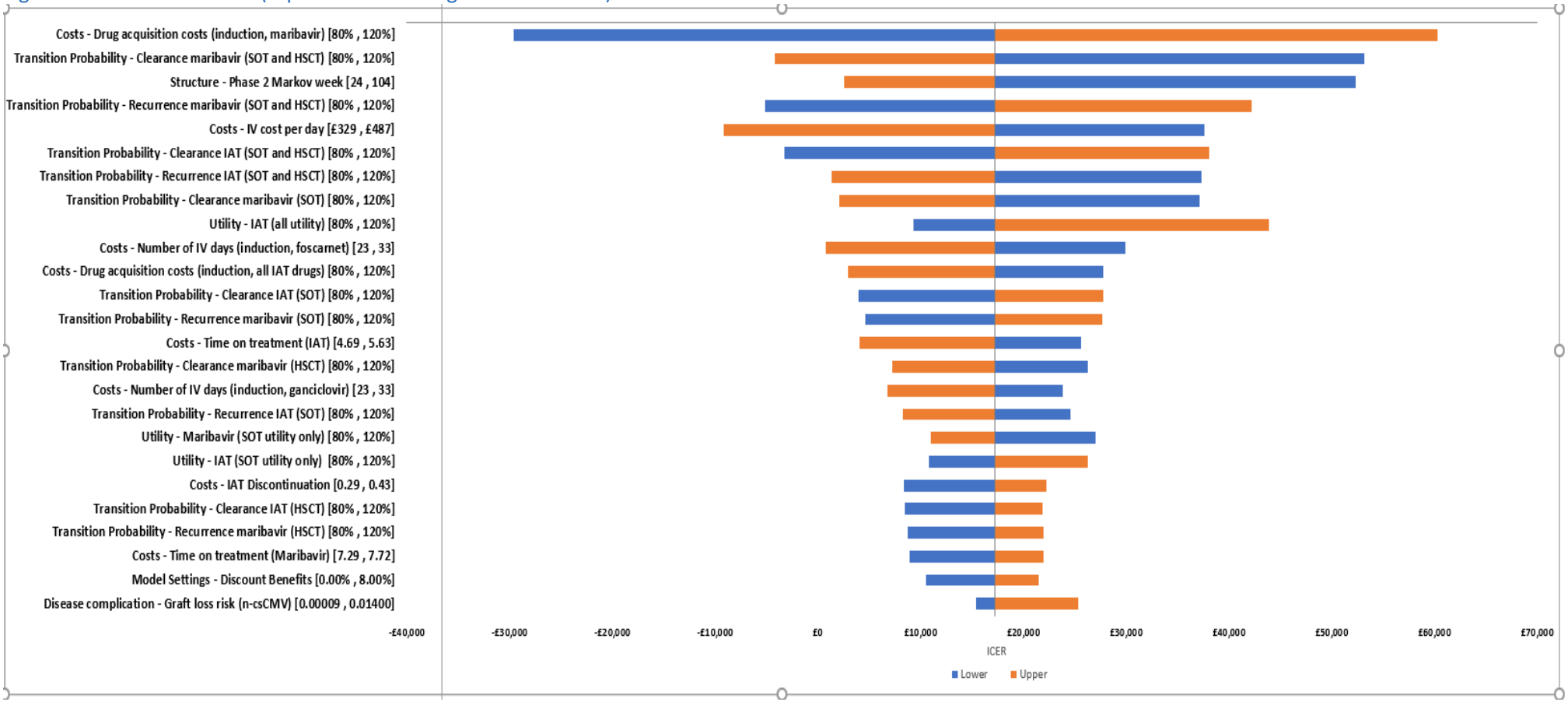
5.1.3 *Company's one-way sensitivity analysis (OWSA)*

The company conducted deterministic sensitivity analysis by varying parameters by their standard error; 95% CI; or +/- 20% of the mean values depending on data availability.

As shown in Figure 12, the company included the cost of drugs in the OWSA. This is a flawed approach as the price of drugs is set externally and is not at risk of containing any uncertainty. Not surprisingly, the parameters with the greatest impact on the ICER (excluding costs) are the probability of clearance assumed for maribavir; followed by when the stage 2 Markov model begins (the company varied the mean 52 weeks by a minimum of 24 weeks and a maximum of 104 weeks) ; followed by the probability of recurrence associated with maribavir.

The company also reported separate ICERs for SOT and HSCT patients, amounting to £9,303 and £29,471 per QALY gain, respectively.

Figure 12. Results of OWSA (reproduced from Figure 24 of the CS)



6 Additional economic analysis undertaken by the ERG

Given the ERG's concerns around the company's cost-effectiveness model, and the ERG's conclusion that the company's model is currently unfit for decision making, the ERG does not have a preferred ICER.

In this section, the ERG summarises the recommendations on the necessary alterations to the economic model so that it can accurately capture the cost effectiveness of maribavir.

6.1 ERG's recommendations for technical engagement

As per the ERG's request during clarification, the ERG asks that all the scenario analysis undertaken by the company are implemented in the model as user-selectable options so that these can be combined.

The ERG recommends that the company clarifies/investigates the following issues:

1. The company's intended use for maribavir in the treatment pathway, in relation to time since transplant and previous lines of treatments received.
2. The rationale for the assumption underpinning the company's model structure that patients' immune system naturally resolves CMV infections 12 months after transplant. The company needs to reconcile this with the mean time from transplant at baseline in SOLSTICE and change the structure of the model to account or the fact that [redacted].
3. The potential impact of the imbalances of mean time since surgery at baseline across treatment arms in SOLSTICE.
4. The potential clinical justification for why the mortality observed in SOLSTICE for SOT patients is higher in the trial than in Hakimi *et al.* and the NHS blood and transplant report.
5. The potential relationship between the lack of graft loss events in SOLSTICE and time since transplant for SOT patients enrolling in the trial.
6. Investigating further (if possible) how many cases of chronic GvHD were in SOLSTICE.
7. The ERG strongly recommends that the company provides KM data on mortality in SOLSTICE by type of transplant (i.e., HSCT vs SOT) so that the committee can understand the difference in mortality in both populations.

8. Providing a formal assessment of whether the EQ-5D-5L data are missing at random and identifying, if possible, the contributing factors to the differential loss to follow up observed between the maribavir and IAT arms.

The key elements of the analyses suggested by the ERG, for both the trial and the UK populations revolve around:

1. Using the available SOLSTICE data on clearance at week 8 (instead of week 4) to model clearance and using the recurrence after first clearance (at week 8) requiring an alternative treatment data to model recurrence in the model.
2. Modelling a "full cycle" of events (i.e., a maximum of 2 episodes of clearances and one episode of recurrence per patient):
    a. The KM data on clearance at week 8 associated with maribavir and IAT would determine the proportion of patients achieving first clearance in the model before or at week 8, in each treatment arm, respectively;
    b. The KM data on recurrence after first clearance (at week 8) requiring an alternative treatment would determine the proportion of patients with a first recurrence in the model. If the company decides to use the KM data for maribavir and IAT arms separately, the ERG recommends running a scenario analysis where the data are pooled, therefore assuming the same probability of recurrence across treatment arms;
    c. The KM data on clearance at week 8 associated with IAT would determine the proportion of patients with second clearance in both treatment arms.
3. Obtaining clinical expert opinion and/or external data to validate the mean frequency of subsequent "full cycles" in order to capture the possibility that SOT patients are likely to have multiple episodes of CMV recurrences throughout their lives. The duration of the stage 1 Markov model should be determined by the duration of these cycles. The company can then repeat these cycles of events as appropriate in the model.
4. Fitting and extrapolating the KM data for at least the second clearance event (but ideally for all clearance and recurrence events in one "full cycle") in order to account for 100% of patients having cleared their second recurrence. This will ensure that patients can leave the second CMV event state at a clinically plausible rate.
5. If the company decides to not use the recommended KM data, and instead uses the point estimates for the probability of clearance and recurrence at specific times in SOLTICE – the

ERG recommends that the company changes the stage 1 Markov to be 20 weeks to effectively model the trial events only. The company should correct the estimates being incorrectly used as detailed by the ERG's critique in Section 4.2.6.2.1. and should allow 100% of patients to clear their recurrence at a clinically plausible rate in the model.

6. Applying a half-cycle correction throughout the time horizon of the economic model.
7. Removing the background sex- and age-specific general population mortality rates from the estimates of mortality in the first 12 months of the model.
8. Ensuring that overall survival is not overestimated after 5 years for HSCT patients and after 10 years for SOT patients. In order to do this the ERG recommends that the company investigates the possibility of using a RR to adjust background survival for patients in the long term (similar to what has been done by the ERG in TA591).
9. Ensuring a clinically plausible transition between mortality rates from the stage 1 to the stage 2 Markov models.
10. Assuming that the proportion of patients receiving a second transplant in the model is less than 5% (or 0% for simplification purposes), however:
    a. All kidney transplant patients with a graft failure should be assumed to receive dialysis;
    b. All patients with graft failure should have an increase in mortality. If the company decides to use the same HRs as those used in the base case to estimate the increase in patients' mortality, these HRs should be applied to patients SOT-specific mortality and not to background mortality.
11. In order to estimate the impact of underlying disease recurrence for HSCT patients, the ERG recommends that the company runs a scenario analysis which:
    a. Assumes that 47% of patients with a recurrence live for 6 months since recurrence;
    b. Assumes that patients with disease recurrence experience a per-cycle disutility of 0.0114;
    c. Updates the per-cycle cost of £6,460 (2015/2016 prices) to the correct price year and applies it in every cycle of the model for 6 months.
12. Including a scenario analysis assuming that the pooled percentage (i.e. not differentiating by CMV or nCMV) of patients with chronic GvHD at baseline in SOLTICE were the only patients who had chronic disease over 20 weeks; and another scenario where all acute and new cases in SOLSTICE (in addition to the chronic cases at baseline) are assumed to become

chronic during the trial. These scenarios should assume that patients with chronic do not survive beyond 2 years after transplant;

13. Exploring whether multiple imputation and pattern-mixture modelling methodologies can limit or overcome the bias (of unknown magnitude and direction) introduced to the utility estimates by the missing not at random EQ-5D data.
14. Re-evaluating the transitioning in utilities from week 52 to week 56 in the model so that these are consistent with model assumptions and also clinically plausible.
15. In line with TA591, it is recommended that the company utilises Ara *et al.* 2010[40] to estimate the age-related utility decrements applied in the model.
16. Estimating the administration cost for IV treatments based on the PSSRU hourly staff cost for a critical care staff nurse (band 5) and a hospital pharmacist, with 4 hours nurse time costed per administration of treatment to 2 patients; and 15 minutes hospital pharmacist time per administration.
17. Applying the weighted average of NHS reference costs for non-elective long stay for infectious diseases without interventions (WJ02C to WJ02E) for hospitalisations occurring for both the CMV and nCMV health states.
18. Running a scenario analysis whereby first line IAT treatment costs consist of foscarnet only, with the other IATs being a retreatment option for further lines.

In addition to the recommendations above (which should be incorporated into the two populations described below), the ERG recommends that the company:

1. Captures the cost-effectiveness of maribavir in r/r patients from SOLSTICE, where the mean time from transplant at baseline in the trial is appropriately modelled. For this scenario the ERG recommends the following approach to estimating specific parameters:
    a. Mortality:
        i. Using SOLSTICE KM data to model survival for the stage 1 Markov model. The KM data should be separated only by type of surgery (i.e., SOT vs HSCT). The company should fit survival curves and extrapolate the KM data in order to estimate survival until the end of the stage 1 Markov.
        ii. If the company can substantiate, with existent data available in literature, that approximately over [redacted] after SOT, CMV still impacts patients' mortality, then the company should use these data to conduct a scenario

analysis to estimate a differential in mortality according to CMV in the SOT population. The same is applicable for HSCT patients, although, for approximately over 100 days since transplant.

iii. Ensuring that the mortality in the phase 2 Markov model reflects the appropriate time since surgery.

b. Graft loss: The company should use clinical expert advice and the available evidence base to ascertain if graft failure events are still likely to happen [redacted] after transplant and only model graft failure events if this can be substantiated by external evidence.

2. If the company's value proposition is that maribavir should be given as early as possible for r/r patients, then the ERG recommends that clinical expert opinion is sought to inform the minimum time when patients, on average, would be eligible to start maribavir. The ERG has heard from its experts that this is likely to vary according to type of transplant (i.e., HSCT or SOT); to patients receiving prophylaxis (which since the approval of letermovir is established for the majority of HSCT patients for at least 100 days post-surgery); and according to the minimum period of treatment when clinicians would consider patients to be r/r in clinical practice. In addition, for this population, the ERG recommends the following approach to estimating specific parameters:

Mortality:

a. The use of the company's KM data on survival for the stage 1 Markov model. The KM data should be separated by type of surgery (i.e., SOT vs HSCT) with possible adjustments included to reflect mortality earlier after transplant; and by CMV status being sourced from available literature (e.g., for SOT patients, the company could use the HRs estimated in Hakimi *et al*. on the impact of mortality on presence of CMV vs no CMV). The company should fit survival curves and extrapolate the KM data in order to estimate survival until the end of the stage 1 Markov.

b. Ensuring that mortality in the phase 2 Markov model reflects the appropriate time since surgery.

Graft loss:

c. The company should ensure that graft failure events reflect time since surgery in this population. Furthermore, the ERG recommends that the company ensures that graft failures can only occur 3 months after patients' transplant;

d. The ERG recommends that the company uses the KM data from Hakimi *et al.* to fit and extrapolate survival curves in order to estimate the probability of graft failure in the model (taking time since transplant into consideration);

e. Utility decrements due to graft loss should be applied until death (adjusting for age-related utility). For kidney graft loss, it is recommended that the utility decrement associated with dialysis is applied.

6.2 Conclusions of the cost effectiveness sections

The key uncertainty around the company's cost effectiveness analysis is the assumption of time elapsed since transplant at baseline in the model. Currently, the model seems to estimate the cost effectiveness for maribavir in r/r patients when given immediately after surgery, which fails not only to reflect time since transplant for the overall trial population (where the treatment effect of maribavir is sourced from), but also, a r/r population who initiates treatment with maribavir as soon as possible after transplant (and as a second line treatment). Furthermore, SOLSTICE data on mean time since surgery for SOT patients are in direct contradiction with the company's main modelling assumption that no CMV events occur 12 months after transplant.

The evidence available in literature and clinical expert opinion provided to the ERG consistently reported that patients' clinical outcomes (such as mortality and risk of graft loss) vary as time from transplant elapses. Crucially, the ERG heard from its clinical experts that the probability of recurrence is unlikely to depend on the type of treatment on which patient achieved clearance (i.e., maribavir or IAT), but instead to be dependent on time since transplant and on the level of lifelong immunosuppression needed by patients. Therefore, the ERG considers that time since surgery is a fundamental aspect of the cost effectiveness of maribavir.

Additionally, the ERG considers the company's use of recurrence data from SOLSTICE to be fundamentally flawed and to introduce a bias in favour of maribavir given that:

1. Before week 8 in the model – the ERG considers that the company should base recurrences of the primary outcome of SOLSTICE (where recurrences could not happen before week 8), instead of the *post-hoc* IPD analysis (based on 4-week clearance outcomes). Crucially, the ERG considers that the company's model uses the wrong estimates for recurrence and notes that the ERG's preferred estimates portray the opposite scenario of the estimates used by

the company, where the ERG's preferred estimates show that patients on IATs have a lower probability of recurrence from week 4 to week 8 than maribavir patients.

2. Between week 8 and week 52 – for maribavir patients who achieved first disease clearance and remained in the nCMV state after week 8 (thus, off any treatment), the probability of recurrence was estimated differently for maribavir and IAT patients (10% vs 14%, respectively) per model cycle. This means that a patient who had been cleared of CMV with maribavir for example, 6 months ago, still experienced the probability of recurrence associated with maribavir. For maribavir patients who did not achieve disease clearance during the initial 8 weeks or had a recurrence and therefore started an IAT, the company used a probability of recurrence of 14% for both treatment arms. The company's assumptions imply that the probability of recurrence is dependent on the type of treatment on which patients achieved clearance; and that the probability of first recurrence observed in SOLSTICE is the same as the probability of subsequent recurrences and also the same until week 52 in the model

The ERG heard from its clinical experts that the probability of recurrence is unlikely to depend on the type of treatment on which patient achieved clearance, but instead to be dependent on time since transplant and on the level of lifelong immunosuppression needed by the patient. Furthermore, the KM data on time to recurrence after first clearance at week 4 from the SOLSTICE CSR suggests no statistically significant difference between recurrence for maribavir and IAT patients.

The ERG conducted two simplified scenario analyses whereby the probability of recurrence in the model after week 8 (when patients are no longer on treatment with maribavir) was assumed to be the same for the IAT and the maribavir arms. In the first scenario the ERG assumed that the probability of recurrence in both treatment arms was that used in the IAT arm (14%); and in the second scenario the ERG assumed that the probability was that associated with maribavir (10%). Both scenarios increased the company's ICER. The first scenario increased the ICER from £15,337 to £70,964; whereas the second scenario increased the ICER to £47,704.

There is, therefore, a high degree of uncertainty associated with making any assumptions beyond what the trial data have captured in terms of number of subsequent recurrences for patients.

7 End of Life

The company has not made a case for committee to consider maribavir as an end of life treatment and the Evidence Review Group (ERG) agrees with this assessment.

8 References

1. Gupta M, Shorman M. Cytomegalovirus. Treasure Island, FL: StatPearls Publishing 2021.
2. Humar A, Snydman D. Cytomegalovirus in solid organ transplant recipients. *American Journal of Transplantation* 2009;9(s4)
3. De la Hoz RE, Stephens G, Sherlock C. Diagnosis and treatment approaches of CMV infections in adult patients. *Journal of clinical virology* 2002;25:1-12.
4. Razonable RR, Emery VC. Management of CMV infection and disease in transplant patients. 27-29 February 2004. *Herpes: the journal of the IHMF* 2004;11(3):77-86.
5. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clinical Infectious Diseases* 2016:ciw668.
6. Fisher CE, Knudsen JL, Lease ED, et al. Risk factors and outcomes of ganciclovir-resistant cytomegalovirus infection in solid organ transplant recipients. *Clinical Infectious Diseases* 2017;65(1):57-63.
7. Dropulic LK. The impact of cytomegalovirus infection on solid organ transplantation. *ADVANCED STUDIES IN MEDICINE* 2006;6(7):319.
8. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. *Clinical infectious diseases* 2002;34(8):1094-97.
9. Cho SY, Lee DG, Kim HJ. Cytomegalovirus Infections after Hematopoietic Stem Cell Transplantation: Current Status and Future Immunotherapy. *Int J Mol Sci* 2019;20(11) doi: 10.3390/ijms20112666
10. Takeda. Data on file. OTUS SOT Interim analysis study results. 2021
11. Takeda. Data on file. OTUS HSCT Interim analysis study results. 2021
12. Azevedo Ls Fau - Pierrotti LC, Pierrotti Lc Fau - Abdala E, Abdala E Fau - Costa SF, et al. Cytomegalovirus infection in transplant recipients. (1980-5322 (Electronic))
13. Fishman JA, Emery V Fau - Freeman R, Freeman R Fau - Pascual M, et al. Cytomegalovirus in transplantation - challenging the status quo. (0902-0063 (Print))
14. Simon DM, Levin S. Infectious complications of solid organ transplantations. (0891-5520 (Print))
15. Piret J, Boivin G. Clinical development of letermovir and maribavir: Overview of human cytomegalovirus drug resistance. *Antiviral Res* 2019;163:91-105. doi: 10.1016/j.antiviral.2019.01.011
16. National Institue for Health and Care Excellence (NICE). **Final scope for the appraisal of maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]**. 2021. https://www.nice.org.uk/guidance/gid-ta10792/documents/final-scope (accessed Feb 2022).
17. Maribavir vs. investigator-assigned therapy (IAT) for the treatment of transplant recipients with refractory/resistant (R/R) cytomegalovirus infection: Efficacy data from a randomized phase 3 open-label study. 47th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT); 2021.
18. Hantz S, Garnier-Geoffroy F, Mazeron MC, et al. Drug-resistant cytomegalovirus in transplant recipients: a French cohort study. *J Antimicrob Chemother* 2010;65(12):2628-40. doi: 10.1093/jac/dkq368 [published Online First: 2010/10/22]
19. Papanicolaou GA, Silveira FP, Langston AA, 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. *Clinical Infectious Diseases* 2019;68(8):1255-64. doi: 10.1093/cid/ciy706
20. Yin Z, Xu N., Jiang L., Shi P., Fan Z., Huang F., Liu Q., Sun J., Yu G. Cidofovir, a Choice for Salvage Treatment of CMV Infection in the Patients with Haploidentical Hematopoitic Stem Cell Transplantation. *Blood* 2020;136:40-41.

21. Veit T, Munker, D.,Barton, J.,Milger, K.,Kauke, T.,Meiser, B.,Michel, S.,Zoller, M.,Nitschko, H.,Keppler, O. T.,Behr, J.,Kneidinger, N. Letermovir in lung transplant recipients with cytomegalovirus infection: A retrospective observational study. *Am J Transplant* 2021;21(10):3449-55. doi: 10.1111/ajt.16718 [published Online First: 2021/06/13]
22. Pierce B, Richardson, C. L.,Lacloche, L.,Allen, A.,Ison, M. G. Safety and efficacy of foscarnet for the management of ganciclovir-resistant or refractory cytomegalovirus infections: A single-center study. *Transpl Infect Dis* 2018;20(2):e12852. doi: 10.1111/tid.12852 [published Online First: 2018/01/31]
23. Avery RK, Arav-Boger, R., Marr, K. A., Kraus, E., Shoham, S., Lees, L., Trollinger, B.,Shah, P., Ambinder, R.,Neofytos, D.,Ostrander, D.,Forman, M.,Valsamakis, A. Outcomes in Transplant Recipients Treated With Foscarnet for Ganciclovir-Resistant or Refractory Cytomegalovirus Infection. *Transplantation* 2016;100(10):e74-80. doi: 10.1097/TP.0000000000001418 [published Online First: 2016/08/09]
24. Myhre HA, Haug Dorenberg, D.,Kristiansen, K. I.,Rollag, H.,Leivestad, T.,Asberg, A.,Hartmann, A. Incidence and outcomes of ganciclovir-resistant cytomegalovirus infections in 1244 kidney transplant recipients. *Transplantation* 2011;92(2):217-23. doi: 10.1097/TP.0b013e31821fad25 [published Online First: 2011/06/21]
25. Foresto RD, Hazin M.A., Zapata A., Santos D.W.C. Safety and efficacy of management of refractory cytomegalovirus infection in kidney transplant recipients treated with foscarnet and conversion from antimetabolite to mtor inhibitor. *Journal of the American Society of Nephrology* 2018;29
26. Kohlschmidt M, Christopeit M., Wolschke C., Ayuk F., Kröger N., Langebrake C. Efficacy and toxicity of ganciclovir and foscarnet combination therapy for refractory Cytomegalovirus reactivation in adult allogeneic stem cell transplant recipients. *Bone Marrow Transplantation* 2019;53:555-56.
27. British Transplantation Society. The prevention and management of CMV disease after solid organ transplantation, 2015.
28. Nuijten M, Kielar C., Peggs K. Cost-effectiveness analysis of a directly selected CMV-specific t cell therapy for management of CMV disease in patients post allogeneic stem cell transplantation: A UK analysis. *Haematologica* 2016;101:594-95.
29. NICE. Letermovir for preventing cytomegalovirus disease after a stem cell transplant: Appraisal consultation committee papers (TA591) 2019 [Available from: https://www.nice.org.uk/guidance/ta591/chapter/1-Recommendations accessed December 2021.
30. 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 in Health* 2008;11(4):733-41. doi: https://doi.org/10.1111/j.1524-4733.2007.00308.x
31. Pidala J, Kurland B, Chai X, 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;117(17):4651-57. doi: 10.1182/blood-2010-11-319509 [published Online First: 2011/02/25]
32. Hakimi Z, Aballéa S, Ferchichi S, et al. Burden of cytomegalovirus disease in solid organ transplant recipients: a national matched cohort study in an inpatient setting. *Transplant Infectious Disease* 2017;19(5):e12732.
33. NHS Blood and Transplant. Organ and Tissue Donation and Transplantation Annual Activity Report 2020/2021 2021 [Available from: https://www.odt.nhs.uk/statistics-and-reports/annual-activity-report/ accessed December 2021.
34. Martin PJ, Counts GW, Jr., Appelbaum FR, et al. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. *Journal of clinical oncology : official journal of*

the American Society of Clinical Oncology 2010;28(6):1011-16. doi: 10.1200/JCO.2009.25.6693 [published Online First: 2010/01/11]
35. Miller RJH, Clarke BA, Howlett JG, et al. Outcomes in patients undergoing cardiac retransplantation: A propensity matched cohort analysis of the UNOS Registry. *J Heart Lung Transplant* 2019;38(10):1067-74. doi: 10.1016/j.healun.2019.07.001 [published Online First: 2019/08/06]
36. Panchal H, Muskovich J, Patterson J, et al. Expanded criteria donor kidneys for retransplantation United Network for Organ Sharing update: proceed with caution. *Transpl Int* 2015;28(8):990-9. doi: 10.1111/tri.12584 [published Online First: 2015/04/14]
37. Kawut SM, Lederer DJ, Keshavjee S, et al. Outcomes after lung retransplantation in the modern era. *Am J Respir Crit Care Med* 2008;177(1):114-20. doi: 10.1164/rccm.200707-1132OC [published Online First: 2007/09/29]
38. Kim HJ, Larson JJ, Lim YS, et al. Impact of MELD on waitlist outcome of retransplant candidates. *Am J Transplant* 2010;10(12):2652-7. doi: 10.1111/j.1600-6143.2010.03315.x [published Online First: 2010/11/13]
39. Leunis A, Redekop, W. K., Uyl-de Groot, C. A., Lowenberg, B. Impaired health-related quality of life in acute myeloid leukemia survivors: a single-center study. *Eur J Haematol* 2014;93(3):198-206. doi: 10.1111/ejh.12324 [published Online First: 2014/03/29]
40. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;13(5):509-18. doi: 10.1111/j.1524-4733.2010.00700.x [published Online First: 2010/03/17]
41. Cantoni N, Hirsch HH, Khanna N, et al. Evidence for a bidirectional relationship between cytomegalovirus replication and acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2010;16(9):1309-14. doi: 10.1016/j.bbmt.2010.03.020 [published Online First: 2010/04/01]
42. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15(5):708-15. doi: 10.1016/j.jval.2012.02.008 [published Online First: 2012/08/08]
43. Szende A, Janssen MF, Cabases JM. Self-Reported Population Health: An International Perspective based on EQ-5D2014.
44. Sullivan PW, Slejko JF, Sculpher MJ, et al. Catalogue of EQ-5D Scores for the United Kingdom. *Medical Decision Making* 2011;31(6):800-04. doi: 10.1177/0272989X11401031
45. Ossa DF, Briggs A, McIntosh E, et al. Recombinant Erythropoietin for Chemotherapy-Related Anaemia. *PharmacoEconomics* 2007;25(3):223-37. doi: 10.2165/00019053-200725030-00005
46. Nafees B, Lloyd AJ, Dewilde S, et al. Health state utilities in non–small cell lung cancer: An international study. *Asia-Pacific Journal of Clinical Oncology* 2017;13(5):e195-e203. doi: https://doi.org/10.1111/ajco.12477
47. Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. *Health and quality of life outcomes* 2008;6:84-84. doi: 10.1186/1477-7525-6-84
48. Bullement A, Nathan P, Willis A, et al. Cost Effectiveness of Avelumab for Metastatic Merkel Cell Carcinoma. *Pharmacoecon Open* 2019;3(3):377-90. doi: 10.1007/s41669-018-0115-y
49. Beusterien KM, Davies J, Leach M, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. *Health and quality of life outcomes* 2010;8:50-50. doi: 10.1186/1477-7525-8-50
50. Tolley K, Goad C, Yi Y, et al. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *The European Journal of Health Economics* 2013;14(5):749-59. doi: 10.1007/s10198-012-0419-2
51. National Institute for Health and Care Excellence (NICE). British National Formulary (BNF). 2021. https://bnf.nice.org.uk/ (accessed 10/06/2021).

52. Wolters Kluwer Health Inc. Medi-Span Price Rx. Cidofovir Intravenous Solution 75 MG/ML 2021 [Available from: https://pricerx.medispan.com accessed 15 December 2021.
53. NHS Improvement. NHS Reference Costs 2019/20. 2020. https://improvement.nhs.uk/resources/national-cost-collection/ (accessed 10/06/2021).
54. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare. *Available at https://wwwyorkacuk/media/crd/Systematic_Reviewspdf (Accessed 21 March 2016)* 2011

9 Appendices

9.1 Baseline characteristics

Table 54. Demographics and baseline disease characteristics by treatment group (randomised set) (adapted from CS Table 31 with additional information from the company's clarification response)

Characteristic	IAT (N=117)	Maribavir 400 mg BID (N=235)
Age (year)		
Median (range)	54.0 (19, 77)	57.0 (19, 79)
Male sex, n (%)	65 (55.6)	148 (63.0)
Weight, n	115	232
Median (range)	70.0 (39, 131)	74.1 (36, 124)
Race, n (%)		
White	87 (74.4)	179 (76.2)
Black or African American	18 (15.4)	29 (12.3)
Asian	7 (6.0)	9 (3.8)
Other	5 (4.3)	16 (6.8)
Missing	0	2 (0.9)
Region, n (%)		
North America	71 (60.7)	134 (57.0)
Europe	39 (33.3)	97 (41.3)
Asia	7 (6.0)	4 (1.7)
SOT, n (%)	69 (59.0)	142 (60.4)
Kidney	32 (46.4)	74 (52.1)
Lung	22 (31.9)	40 (28.2)
Heart	9 (13.0)	14 (9.9)
Multiple	5 (7.2)	5 (3.5)
Liver	1 (1.4)	6 (4.2)
Pancreas	0	2 (1.4)
Intestine	0	1 (0.7)
HSCT, n (%)	48 (41.0)	93 (39.6)
Allogeneic	48 (100.0)	92 (98.9)
Donor type,		
HLA identical sibling	2 (4.2)	13 (14.1)
HLA matched other relative	10 (20.8)	12 (13.0)
HLA mismatched relative	7 (14.6)	11 (12.0)
Unrelated donor	29 (60.4)	56 (60.9)
Stem cell source		
Peripheral blood stem cell	30 (62.5)	71 (77.2)

Bone marrow	13 (27.1)	16 (17.4)
Cord blood	5 (10.4)	5 (5.4)
Presence of acute GvHD confirmed for HSCT recipients	8 (17.0)	23 (25.0)
Presence of chronic GvHD confirmed for HSCT recipients	5 (10.6)	6 (6.5)
CMV DNA levels by central laboratory at baseline, IU/mL		
Median (IQR)	2869.0 (927, 11,636)	3377.0 (1036, 12,544)
Patients with or without CMV mutations known to confer resistance to ganciclovir, foscarnet, and/or cidofovir, n (%)		
Refractory CMV infection with resistance	69 (59.0)	121 (51.5)
Refractory CMV infection without resistance	34 (29.1)	96 (40.9)
Missing resistance results	14 (12.0)	18 (7.7)
Prior use of CMV prophylaxis, n (%)	45 (38.5)	100 (42.6)
Letermovir prophylaxis	[redacted]	[redacted]
Current CMV infection is the first episode post-transplant, n (%)	78 (66.7)	162 (68.9)
Most recent anti-CMV agent prior to randomisation, n (%)		
Ganciclovir/Valganciclovir	98 (83.8)	204 (86.8)
Foscarnet	18 (15.4)	27 (11.5)
Cidofovir	1 (0.9)	4 (1.7)
Prior direct-acting anti-CMV agents at any time, n (%)	n=116	n=234
Valganciclovir	96 (82.8)	178 (76.1)
Ganciclovir	82 (70.7)	147 (62.8)
Foscarnet	37 (31.9)	49 (20.9)
Letermovir	5 (4.3)	12 (5.1)
Cidofovir	5 (4.3)	7 (3.0)
Time since transplant		
Mean, days (SD)	[redacted]	[redacted]
Median, days	[redacted]	[redacted]

Abbreviations: BID=Twice daily; BMI=Body mass index; CMV=Cytomegalovirus; DNA=Deoxyribonucleic acid; GvHD=Graft-versus-host-disease; HSCT=Haematopoietic stem cell transplant; HLA=human leukocyte antigen; IAT=Investigator-assigned anti-CMV treatment; IQR=Interquartile range; LLOQ=Lower limit of quantification; max=Maximum; mg=Milligrams; min=Minimum; N=Number of patients; SD=Standard deviation; SOT=Solid organ transplant

Table 55. Demographics and baseline disease characteristics by treatment group and transplant type (adapted from the CS, Appendix E, Table 25 with additional information from the company's clarification response)

	HSCT			SOT		
	IAT [redacted]	Maribavir 400 mg BID [redacted]	Total [redacted]	IAT [redacted]	Maribavir 400 mg BID [redacted]	Total [redacted]

Age (years)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age category (years), n (%)						
12-17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)						
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enrolling regions, n (%)						
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current transplant type						
SOT, n (%)						
Heart	-	-	-	[redacted]	[redacted]	[redacted]
Lung	-	-	-	[redacted]	[redacted]	[redacted]
Liver	-	-	-	[redacted]	[redacted]	[redacted]
Pancreas	-	-	-	[redacted]	[redacted]	[redacted]
Intestine	-	-	-	[redacted]	[redacted]	[redacted]
Kidney	-	-	-	[redacted]	[redacted]	[redacted]
Multiple	-	-	-	[redacted]	[redacted]	[redacted]
HSCT, n (%)						
Autologous	[redacted]	[redacted]	[redacted]	-	-	-
Allogeneic	[redacted]	[redacted]	[redacted]	-	-	-

Underlying disease, n (%)						
Leukaemia (acute myeloid)	[redacted]	[redacted]	[redacted]	-	-	-
Leukaemia (chronic myeloid)	[redacted]	[redacted]	[redacted]	-	-	-
Leukaemia (acute lymphocytic)	[redacted]	[redacted]	[redacted]	-	-	-
Lymphoma (non-Hodgkin's)	[redacted]	[redacted]	[redacted]	-	-	-
Myelodysplastic syndrome	[redacted]	[redacted]	[redacted]	-	-	-
Other myeloid malignancy	[redacted]	[redacted]	[redacted]	-	-	-
Other	[redacted]	[redacted]	[redacted]	-	-	-
Current graft status at baseline						
SOT, n (%)						
Functioning with complications	-	-	-	[redacted]	[redacted]	[redacted]
Functioning	-	-	-	[redacted]	[redacted]	[redacted]
Other	-	-	-	[redacted]	[redacted]	[redacted]
HSCT, n (%)						
Partially engrafted	[redacted]	[redacted]	[redacted]	-	-	-
Functioning with complications	[redacted]	[redacted]	[redacted]	-	-	-
Functioning	[redacted]	[redacted]	[redacted]	-	-	-
Acute GvHD confirmed, n (%)						
No	[redacted]	[redacted]	[redacted]	-	-	-
Yes	[redacted]	[redacted]	[redacted]	-	-	-
Chronic GvHD confirmed, n (%)						
No	[redacted]	[redacted]	[redacted]	-	-	-
Yes	[redacted]	[redacted]	[redacted]	-	-	-
Type of preparative conditioning regimen, n (%)						
Myeloablative	[redacted]	[redacted]	[redacted]	-	-	-
Non-myeloablative	[redacted]	[redacted]	[redacted]	-	-	-
Reduced intensity conditioning regimen	[redacted]	[redacted]	[redacted]	-	-	-
NA	[redacted]	[redacted]	[redacted]	-	-	-
Missing	[redacted]	[redacted]	[redacted]	-	-	-
Net immunosuppression use changed prior to the study, n (%)						
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Yes	[redacted]					
Missing	[redacted]					
Antilymphocyte use, n (%)						
No	[redacted]					
Yes	[redacted]					
Renal impairment, n (%)						
No impairment	[redacted]					
Mild	[redacted]					
Moderate	[redacted]					
Severe	[redacted]					
Missing	[redacted]					
Hepatic impairment, n (%)						
No impairment	[redacted]					
Grade 1	[redacted]					
Grade 2	[redacted]					
Missing	[redacted]					
Karnofsky Scale Performance Status, n (%)						
100	[redacted]					
90	[redacted]					
80	[redacted]					
70	[redacted]					
60	[redacted]					
50	[redacted]					
40	[redacted]					
30	[redacted]					
20	[redacted]					
Missing	[redacted]					
Prior use of CMV prophylaxis, n (%)			[redacted]			[redacted]
Time since transplant						
Mean, days (SD)	[redacted]	[redacted]		[redacted]	[redacted]	
Median, days	[redacted]	[redacted]		[redacted]	[redacted]	

Abbreviations: BID twice daily; BMI body mass index; CMV cytomegalovirus; GvHD graft-versus-host-disease; HSCT haematopoietic stem cell transplant; IAT investigator-assigned anti-CMV treatment; max maximum; mg milligrams; min minimum; N number of patients; SD standard deviation; SOT solid organ transplant

9.2 Hospitalisation data

Table 56. Hospitalisations (adapted from clarification response to A9, Table D)

	IAT	Maribavir
Number at baseline	117	235
Number of patients hospitalised during on-treatment phase, n (%)	[redacted]	[redacted]
Number of patients hospitalised during full study period, n (%)	[redacted]	[redacted]
LOS per patient during on-treatment phase, mean days (SD)	[redacted]	[redacted]
LOS per patient during full study period, mean days (SD)	[redacted]	[redacted]

Abbreviations: IAT investigator-assigned anti-CMV treatment; LOS length of stay; SD standard deviation

Table 57. Reason for hospitalisations by treatment arm (adapted from clarification response to A9, Table E)

Reason for hospitalisation	IAT	Maribavir
Number at baseline	117	235
CMV infection/disease	[redacted]	[redacted]
CMV treatment	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Transplant or graft complications	[redacted]	[redacted]
GVHD	[redacted]	[redacted]
AE (unspecified)	[redacted]	[redacted]
Multiple reasons listed	[redacted]	[redacted]

Abbreviations: CMV cytomegalovirus; GvHD graft-versus-host-disease; IAT investigator-assigned anti-CMV treatment

9.3 Subgroup analysis – foscarnet

Table 58. Clearance and clinically relevant recurrence by treatment arm, transplant type and resistance status (adapted from clarification question A5, Table 2)

	IAT (total)				IAT (foscarnet)				Mar	
Number at baseline	117				47				235	
	n/N	%	Diff.	p	n/N	%	Diff.	p	n/N	%
Clearance at week 4	[redacted]									
Clearance at week 8	[redacted]									
Clearance at week 20	[redacted]									
Clinically relevant recurrence at week 8 for patients with clearance at week 4	[redacted]									
Clinically relevant recurrence after week 8 for patients with clearance at week 8	[redacted]									
Mortality at week 8	[redacted]									
Mortality at week 20	[redacted]									
Number of patients hospitalised	[redacted]									

Abbreviations: Diff, difference (versus maribavir); IAT investigator-assigned anti-CMV treatment; NR, not reported

*Deaths only reported for safety set

**denominator updated by the ERG as the original stated the number of patients randomised rather than the number of patients with clearance at week 4

9.4 Safety

Table 59. Summary of adverse events (safety population) (reproduced from CS appendices, Table 28)

	Maribavir		IAT	
	n	(%)	n	(%)
Participants in population	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to discontinuation of study-assigned treatment	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related TEAE leading to discontinuation of study-assigned treatment	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE leading to discontinuation of study-assigned treatment	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related serious TEAE leading to discontinuation of study-assigned treatment	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to study discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE leading to study discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related serious TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE of special interest	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related TEAE of special interest	[redacted]	[redacted]	[redacted]	[redacted]

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

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 28 March** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Assumption of time elapsed since transplant at baseline in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 4, issue 3 page 18/19 “The ERG remains unclear on the company’s assumption of mean time elapsed since transplant at baseline in the model. Currently, the model seems to estimate the cost effectiveness for maribavir in r/r patients when given immediately after surgery, which fails to...	The model has a time since transplant parameter that has been set to 12 months in the base case, not 0 months as suggested in Table 4 on page 18/19. The ERG report should be amended to reflect this. Please amend the text on page 18/19 to say: “currently, the model seems to estimate the cost effectiveness for maribavir in r/r patients when given 12 months after transplant”	To accurately reflect the model structure and the submission document. Please note the economic model sheet “model control” has average time since transplant (years) – SOT and HSCT set to 1. Section B.3.6.1 Table 63 (p98) of Document B of the Company submission also states average time since transplant is 1 year for both SOT and HSCT. This misunderstanding around starting time in the model has led to numerous other issues throughout the ERG report.	The ERG has provided reasons, in Section 4.2.2, why the inference can be made that patients enter the model (and therefore initiate treatment with maribavir) immediately (or within a few months) after transplant. If the company believes that the model does, in fact, capture patients entering the model 12 months post-transplant the inconsistencies raised in Section 4.2.2 should be addressed and the risks applied in the model (mortality and graft loss) should reflect this timeframe.
Page 79 “The data shared on mean time since surgery for SOT patients are, therefore, in direct contradiction with the company’s main modelling assumption that no CMV events occur 12 months after transplant.”	Please amend the text on page 79 to say: “The data shared on mean time since surgery for SOT patients are, therefore, in direct contradiction with the ERG’s inferred conclusion around the main modelling assumption that no CMV events occur 12 months after transplant”		Amended to: “The data shared on mean time since surgery for SOT patients are, therefore, in direct contradiction with the ERG’s inferred conclusion about the company’s main modelling assumption - that no CMV events occur 12 months after transplant”

Table 2, page 17. “Mean time since transplant was imbalanced between the treatment arms in SOLSTICE”	Please amend to: “The ERG consider that mean time since transplant was imbalanced between the treatment arms in SOLSTICE”	Takeda consider there was no meaningful difference between treatment arms regarding time since transplant. Median time was very similar.	No factual inaccuracy.
Page 17. The ERG state “Company needs to re-analyse its clinical data taking account of time since transplant”	Please consider removing this statement.	Takeda provided an analysis to the ERG on 16 March which we believe demonstrates no significant difference between arms based on time since surgery, and that the outcomes showed that the overall composition of patient groups and time since surgery are balanced between IAT vs MBV. Takeda accept that time on transplant data was provided after the deadline for response to ERG clarification questions, however an analysis of the clinical data taking into account time since transplant has been provided.	No factual inaccuracy. However, text has been added to provide context around the suggested re-analysis.

Issue 2 AE incidence rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 121. The ERG notes that the frequency of AEs from the maribavir and IAT arms of the SOLSTICE trial were not correctly captured in the economic model.	Please consider removing this statement.	The incidence rate of AEs used in the model has been calculated using m (the number of events) rather than n (the number of subjects experiencing an event). For example, while the incidence rate of anaemia for maribavir is	The ERG report has been amended removing all references to this issue.

		shown as 15.0% in Table 23 of the SOLSTICE IPD Appendix, the model uses the number of anaemia events (41) divided by the total number of maribavir patients (234) for an incidence rate of 17.5%. The number of events rather than the number of subjects experiencing an event was used to define the rate of AEs, this was then converted to a probability.	

Issue 3 Structural assumptions in the company's model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 20. The ERG state "The switch from the stage 1 to the stage 2 Markov (dead/alive) model after week 52 results in 35.1% of patients in the maribavir arm and 38.3% of patients the IAT arm having CMV at week 52 and being cured at week 56.	Please modify to state: "The switch from the stage 1 to the stage 2 Markov (dead/alive) model after week 52 results in 35.56% of patients in the maribavir arm and 38.98% of patients the IAT arm having CMV at week 52 and being cured at week 56"	To accurately reflect the data in the submitted model. However, Takeda recognise the impact of this on the ICER is minor.	These data have been amended throughout the ERG report. The ERG's critique, which these data support, remains unaffected.
Page 20. The ERG state "Finally, the company's assumption that no CMV events occur after 12 months in the model is in contradiction of the SOLSTICE data for SOT patients, and of clinical expert opinion"	Please modify to state: "Finally, the ERG's inferred assumption that no CMV events occur after 12 months in the model is in contradiction of the SOLSTICE data for SOT patients, and of clinical expert opinion"	The model has a time since transplant parameter that has been set to 12 months in the base case, not 0 months, therefore modelled CMV events can happen 12 months since initiation of treatment for R/R CMV. The model changes to alive/dead state at 12 months from the	Amended to: "Finally, the company's implicit assumption that no CMV events occur after 12 months in the model is in contradiction of the SOLSTICE data for SOT patients, and of clinical expert opinion."

		initiation of R/R treatment based on direct feedback from clinicians as most patients would be cleared of CMV by this time.	

Issue 4 Modelling of graft failure

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 25 states "Given the absence of graft loss events in SOLSTICE and clinical expert opinion provided to the ERG that graft failure is only likely to occur from 3 months after patients' transplant, the ERG disagrees with the company's assumption that patients could have graft failure after 4 weeks in the model"	Please amend to: "Given the absence of graft loss events in SOLSTICE and clinical expert opinion provided to the ERG that graft failure is only likely to occur from 3 months after patients' transplant, the ERG disagrees with the inferred assumption that patients could have graft failure after 4 weeks in the model"	The model has a time since transplant parameter that has been set to 12 months in the base case, not 0 months. Within the model, patients do not have graft failure after 4 weeks post-transplant as they enter the model at initiation of treatment for R/R CMV, not at the point of transplant. Therefore, if graft loss occurs at 4 weeks in the model this is 4 weeks post-R/R infection, not 4 weeks post-transplant.	Amended to: "Given the absence of graft loss events in SOLSTICE and clinical expert opinion provided to the ERG that graft failure is only likely to occur from 3 months after patients' transplant, the ERG disagrees with the company's implicit assumption that patients could have graft failure after 4 weeks in the model."
Page 25 also states "The ERG also notes that the company's approach is biased in favour of maribavir as the probability of graft failure events in the model is higher for patients experiencing CMV"	Please amend to: "The ERG considers that the company's approach is biased in favour of maribavir as the probability of graft failure events in the model is higher for patients experiencing CMV"	Clearance in SOLSTICE was defined as plasma CMV DNA concentrations <LLOQ (i.e., <137 IU/mL), when assessed by central specialty laboratory, in two consecutive post-baseline samples separated by at least 5 days. Elevated CMV viraemia levels are associated with mortality and graft loss outcomes, and maribavir demonstrates reduction in viraemia	Amended, text has also been added to page 113 to contextualise the statement.

		therefore we do not consider this to be bias	

Issue 5 Overestimation of recurrence in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 22, Page 94, page 149. The first scenario increased the ICER from £15,337 to £74,314; whereas the second scenario increased the ICER to £50,186.	Takeda are unable to replicate these results, and there could be a potential factual error.	To accurately reflect the ICER in the scenario	These results have been amended in the ERG report. The corrected ICERs are £70,964.24, and £47.703.76 respectively.

Issue 6 Estimation of utilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 29. The ERG state "Furthermore, given the company's statement that utilities were estimated based on week 0 to week 20 utilities for responders and non-responders at week 8, the ERG remains unclear if the company assessed response at week 8 and then retrospectively averaged utility measurements for responders and non-responder from week 0; or if the utilities were collected from the point of response until	Please consider revising to state: "Furthermore, in a scenario that assesses utilities based on week 20 data, given the company's statement that utilities were estimated based on week 0 to week 20 utilities for responders and non-responders at week 8, the ERG remains unclear if the company assessed response at week 8 and then retrospectively averaged utility measurements for responders and non-responder from week 0; or if the	Takeda wish to clarify this is not the base case setting in the economic model. The Company submission Document B (page 88, section B.3.4.4.1.1.1) states 'For this reason, in the base case analysis, transplant and health-state specific utility values at week 8 were selected (Table 48). This is also emphasised on Page 100 (Table 64).	The ERG does not consider there to be any factual inaccuracy in the quoted statement unless the data in Table 26 of the company's IPD analysis is misleading or incorrect. Further detail provided below.

<table>
<tr>
<td>week 20.”</td>
<td>utilities were collected from the point of response until week 20.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Page 122:

“The company estimated the nCMV health state utility values by averaging all utility measurements taken over the 20-week trial for patients who were week-8 responders to either maribavir or IAT treatment. Conversely, CMV health state utility values were estimated by averaging all utility measurements taken for patients who were non-responders at week 8.”</td>
<td>Please consider revising to state:

“The company estimated the nCMV and CMV health state utility values based EQ-5D utility measurements at week 8 based on response status”</td>
<td>Takeda used EQ-5D score at week 8 based on response status, and this was not averaged over 20 weeks in the base case.

The same approach was used to estimate utility values for both nCMV and CMV health states.</td>
<td>The ERG note that the source of these estimates was Table 26 of the company’s IPD analyses which provides mean utility measured. Provided below is a simplified version of the relevant table with only the relevant information included.

<table>
<tr><td rowspan="2"></td><td colspan="2">SOT</td><td colspan="2">HSCT</td></tr>
<tr><td>m/n</td><td>mean</td><td>m/n</td><td>mean</td></tr>
<tr><td>Response (at week 8)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>No-response (at week 8)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="5">Where; m is the number of records in the category, n is the number of unique patients in the category</td></tr>
</table>

Based on this table, the ERG understands that the utility values provided are the mean of the total records for each given category. For example, the mean utility value for SOT week-8 responders, is the mean of the [redacted] records (from [redacted] unique patients) in this category. As there were only 211 SOT patients enrolled in SOLSTICE, all [redacted] records must not have been measured at week 8, rather over</td>
</tr>
</table>

			multiple elicitation timepoints. The ERG has inferred that all measurements from week 0 to 20 were used (including those taken prior to the week-8 response assessment) as the sum of the number of records for week-8 responders and week-8 non-responders (■+■) equals the sum of the number of records for responders and non-responders, where response was assessed from weeks 0 to 20 (■+■). The ERG therefore does not consider there to be any factual inaccuracy in the quoted statement unless the data in Table 26 of the company's IPD analysis is incorrect or misleading. The ERG also notes that the quoted statement goes on to say, "Conversely, CMV health state utility values were estimated by averaging all utility measurements taken for patients who were non-responders at week 8." – acknowledging that the same approach was taken to estimate utility values for both nCMV and CMV health states, aside from the use of utility values taken from week 8 responders/non-responders.

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.

(Please add further lines to the table as necessary)

NICE National Institute for Health and Care Excellence

Technical engagement response form

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have Technical engagement response form

to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **16 May 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	Mark Robinson
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Takeda UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1: Impact of time since transplant on the clinical data and economic model	Yes	**Time since transplant has been extensively analysed from the SOLSTICE data and we have shown there is no statistical difference between the treatment arms. Analysis has demonstrated that time since transplant has no impact on the efficacy data from maribavir therapy.** ***Analysis of data shows no imbalance for time since transplant between treatment arms*** In addition to the breakdown of results by treatment arm based on time since transplant (TST) in the response provided 11 March 2022, we have provided additional analysis on the median and mean duration from transplant date to the start of antiviral treatment for refractory/resistant CMV by treatment arm in Table 1 below. Both analyses demonstrate no meaningful statistical difference between treatment arms in the mean or median time since transplant. It should be noted that the analysis of medians is the most reliable given that the data are not normally distributed. In addition to this analysis demonstrating that there is no significant difference between treatment groups, we further explored the impact of time since transplant on the outcomes of clearance and clinically significant recurrence in the SOLSTICE trial. This was done by using logistic regression models to assess the impact on the odds of each outcome, respectively.

The results of the logistic regression analysis are given in Table 2 for clearance at week 8, and Table 3 for recurrence requiring treatment after week 8.

The results show that time since transplant has no significant impact on either clearance or recurrence requiring treatment, with an odds ratio, representing the effect of each additional day since transplant, of [redacted] in both analyses. This indicates that the odds of each outcome are unchanged by increasing days since transplant, and it is the treatment effect of maribavir that is driving the efficacy. Since TST is not statistically different between the two arms, and since TST does not have any impact on the efficacy data, no adjustments on efficacy data used in the model were performed. Therefore, the estimates used in the economic model continue to be reliable.

For the clearance analysis, the only significant covariate was the treatment group, demonstrating that treatment with maribavir resulted in almost a four-fold increase in the odds of achieving clearance compared to treatment with existing standard of care treatments.

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 [redacted]), and despite not being statistically significant at the 5% threshold, the p-value was very small at [redacted] . 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 as per the company's base case analysis (see Issue 5).

Time since clearance showed a statistically significant impact on the odds of recurrence requiring treatment, showing that each additional day post-clearance lowers the odds by a factor of [redacted] . The additional flexibility in the revised model now allows for this dependence between the time spent in the non-clinically significant CMV state and the probability of a recurrence to be appropriately captured (see Issue 5).

Table 1: Mean and median time since transplant by treatment arm

Category	IAT (N=116)	Maribavir (N=234)
Time since solid organ transplant (days)		
N (%)	[redacted]	[redacted]

Mean (SD)	[redacted]	[redacted]		
Median	[redacted]	[redacted]		
95% CI	[redacted]	[redacted]		
p-value		[redacted]		
Mean	[redacted]	[redacted]		
SEM	[redacted]	[redacted]		
95% CI	[redacted]	[redacted]		
p-value		[redacted]		
Min, Max	[redacted]	[redacted]		
Time since haematopoietic stem cell transplant (days)				
N (%)	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Median	[redacted]	[redacted]		
95% CI	[redacted]	[redacted]		
p-value		[redacted]		
Mean	[redacted]	[redacted]		
SEM	[redacted]	[redacted]		
95% CI	[redacted]	[redacted]		
p-value		[redacted]		
Min, Max	[redacted]	[redacted]		
Overall time since transplant (days)				
N (%)	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]		
Median	[redacted]	[redacted]		
95% CI	[redacted]	[redacted]		
p-value		[redacted]		
Mean	[redacted]	[redacted]		

SEM	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value		[redacted]
Min, Max	[redacted]	[redacted]

Table 2. Logistic regression of confirmed CMV viraemia clearance response at week 8

Covariate	Adjusted OR (95% CI)	P-value
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Time since transplant (days)	[redacted]	[redacted]
Transplant type (HSCT vs SOT)	[redacted]	[redacted]
Prior use of CMV prophylaxis (Yes/No)	[redacted]	[redacted]

Table 3. Logistic regression of confirmed CMV viraemia recurrence requiring treatment after clearance at week 8

Covariate	Adjusted OR (95% CI)	P-value
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Time since transplant (days)	[redacted]	[redacted]
Transplant type (HSCT vs SOT)	[redacted]	[redacted]
Time since clearance (days)	[redacted]	[redacted]

Key Issue 2: Trial conduct and design leading to uncertainty and potential overestimates of maribavir efficacy	Yes	**We have provided further sensitivity analyses to demonstrate the robustness of the SOLSTICE data and the model has now been modified to use the primary endpoint of the clinical trial rather than the post-hoc IPD analysis** ***1. Patients assigned to anti-CMV treatment for which they had resistance*** The majority of [redacted] subjects who received an IAT agent to which their CMV has a mutation known to confer resistance at baseline had a medical history of acute or chronic renal dysfunction, and [redacted] were kidney transplant recipients. Given the renal toxicity of the other options, it is logical that investigators may have chosen to continue ganciclovir/valganciclovir even if the subject's CMV had a mutation known to confer resistance to these drugs.

Despite this, the conducted analysis shows that the benefit of maribavir over IAT is sustained when subjects who received IAT for which they had resistance mutation at baseline are excluded from the analysis (Table 4). In the UK it is possible that even more patients may receive treatment to which they are resistant since resistance testing is not part of current practice. Additionally, in clinical practice, patients may not require an alternative anti-CMV antiviral after a mutation is detected.

Table 4. Primary analysis of confirmed CMV viraemia clearance response at study Week 8 by treatment group

CMV Viraemia clearance response	Primary Resistance Set (PRS)		PRS excluding subjects who received IAT they were resistant to at baseline	
	IAT N (%) [95% CI]	Maribavir N (%) [95% CI]	IAT N (%) [95% CI]	Maribavir N (%) [95% CI]
Overall n				
Responders				
Adjusted Difference in proportion of responders (95% CI)				
p-value: Adjusted				

CI=confidence interval; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment; PRS=primary resistance set Primary Resistance Set includes subjects with baseline known (confirmed) resistance to GCV/VGCV/FOS/CDV. Subjects who received the same monotherapy for which a resistant mutation was detected were excluded from the analysis. Subjects who received combo therapy that included one agent for which a resistance mutation was not detected were not excluded from the analysis. Percentage of responders and non-responders are based on the number of subjects in the Randomized Set and the corresponding 95% CI is based on Wald confidence interval when all the cells are ≥5 and total is ≥30.

Clopper-Pearson estimation method is used when any cell is <5 or total is <30. Response within 8 weeks of study is defined as subjects who met the criteria of confirmed CMV viremia clearance defined as 2 consecutive post baseline assessments of CMV DNA target <LLOQ, separated by at least 5 days any time in treatment phase. Plasma CMV DNA assessments after starting alternative anti-CMV treatment or rescue treatment are not evaluable for the assessment of study assigned treatment effect. Randomized subjects with no efficacy data are treated as non-responders. a. Cochran-Mantel-Haenszel (CMH) weighted average approach is used for the adjusted difference in proportion (Maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration if homogeneity is met. The minimum risk weight method is used if the homogeneity is not met. Only those with both stratification factors are included in the computation if the p-value for homogeneity across strata is significant.

2. Outcomes data based on post-hoc analysis

To address the ERG's concern that post-hoc IPD data were used, the model has been modified to use the primary endpoint of the SOLSTICE study for clearance at week 8 and trial data for clinically relevant recurrence for weeks 8-20.

3. Assessment of clinically relevant recurrence

During the clarification stage, Takeda addressed this issue in response to clarification question A10. The protocol for requirement of initial therapy is as below:

- The participant must have a documented CMV infection in whole blood or plasma, with a screening value of greater than or equal to (>=) 2730 international units per milliliter (IU/mL) in whole blood or >= 910 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. 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

From a clinical perspective, CMV requiring treatment is associated with an impact on morbidity, quality of life and mortality therefore this outcome is more reflective of the key differences between patients who benefit from anti-CMV therapy. Having a strict limit on the lower limit of quantification and sample timepoints (as per the protocol definition) may not capture all clinically relevant patients that enter the csCMV health state.

The SOLSTICE protocol did not have a definition for when to start treatment for a recurrence event, but we would assume trialists would use the above definition. Note that we are not applying this definition above for recurrence within the model as recurrence is simply based on if a patient required treatment.

4. Increase Missing Data (CMV Clearance)

To allow for a robust comparison of maribavir vs IAT, the primary efficacy analysis was assessed at a fixed time point. The primary efficacy endpoint for the study is confirmed clearance of plasma CMV deoxyribonucleic acid (DNA) at the end of Study Week 8, regardless of whether a subject completed 8 weeks of assigned therapy. CMV DNA clearance is a precise, objective measure that has been validated as a surrogate marker in this indication. This conservative method of assessing the primary outcome required that the drug both clear the virus and maintain this clearance status until the end of Week 8 when the outcome was examined. This created the potential for subjects

		randomized to the IAT arm (comprised of standard of care with significant treatment-limiting toxicities), to have premature discontinuations leading to missing data at subsequent timepoints. Even though safety is a critical part of the effectiveness of any therapy for post-transplant CMV infections, to address the potential for bias arising from these premature discontinuations, several sensitivity analyses were performed controlling for the early discontinuations and missing data in both arms. Observed treatment effect Numerous sensitivity analyses of the primary endpoint were conducted per protocol to neutralize the impact of IAT toxicity on outcome and address the potential for bias in interpretation of the outcome. The results of these sensitivity analyses provide evidence of maribavir's true virologic benefit over IAT, independent of its favourable safety profile. A short overview of these sensitivity analyses demonstrating the robustness of maribavir's virologic benefit over IAT is described below: • A sensitivity analysis included subjects in both treatment groups who met the criteria of confirmed clearance at the time of study discontinuation as responders, (ie, last observed carried forward [LOCF]). This analysis eliminated any effect accruing from early study discontinuations due to drug toxicity, withdrawal of consent, or other reasons. The analysis included only subjects who met the criteria of confirmed CMV viremia clearance at the time of study discontinuation and did not receive alternative treatment. In this analysis, maribavir remained statistically significantly better at clearing CMV viremia compared to IAT ([redacted]], respectively; p-value: <0.001). Appropriateness of LOCF imputation The LOCF approach has limitations as it does not capture recurrences in viral load that may occur when antiviral pressure is removed in the face of ongoing immunosuppression. Since a greater proportion of subjects in the IAT group discontinued before Week 8, the LOCF results in this group may overestimate efficacy in a biased manner favouring the IAT group. Despite this, the results with LOCF imputation showed that maribavir achieved a more favourable outcome than did IAT treatment, further supporting the robustness of the primary analysis result. • Another sensitivity analysis counted subjects who had viremia clearance anytime within 8 weeks as responders. This analysis counted subjects as responders regardless of when in the treatment period they achieved CMV viremia clearance. In this sensitivity analysis, maribavir maintained its superior CMV viremia clearance compared to IAT ([redacted]], respectively; p-value: <0.001). • Finally, a sensitivity analysis examined CMV viremia clearance regardless of the use of alternative anti-CMV treatment (including rescue). This analysis assessed efficacy at Week 8, even if alternative anti-CMV treatment

		(including rescue) was utilized. In essence, the tolerability benefit of maribavir enabling better efficacy was eliminated in this analysis, as IAT subjects were not penalized for taking non-study anti-CMV agents after premature treatment discontinuation. The results of the analysis confirmed the true virologic effect of maribavir, which maintained its superior CMV clearance at Week 8 compared to the IAT group ([redacted]], respectively; p-value: 0.002). Responder definition To avoid misclassifying subjects who were missing viral load results at one or more visit, the responder definition used prespecified rules to determine whether the subject had achieved confirmed virological clearance. Subjects who started alternative anti-CMV or rescue treatment, withdrew from the study before these assessments could be made, or insufficient data for evaluation were considered non-responders. [redacted] Additional responder analysis Maribavir treatment provides a statistical and clinically meaningful superiority in efficacy of anti-CMV effect over IAT that is independent of its safety advantage. While the ability to remain on therapy enhances efficacy, even in numerous analyses that favour or strongly favour the IAT arm including last observation carried forward (LOCF), and multiple imputation analyses that impute data to remove the impact of IAT's treatment-limiting toxicity, maribavir is associated with superior efficacy to IAT. ***5. Using KM data (rather than response rates) for the primary outcome in the trial for clearance and the pre-specified analyses for recurrence (rather than post hoc analyses of other time points) in the economic model.*** The updated model now uses the 8-week primary endpoint instead of the 4-week probabilities based on the IPD analysis, as per the ERG's recommendation. Therefore, KM data for the primary outcome are not required to model time-dependent clearance. It should also be noted that the KM estimates for clearance are likely to be biased due to the censoring of patients who discontinue treatment due to lack of effect or toxicity, which happened more so in the IAT group. These censored patients are assumed to have the same risk of event (probability of achieving clearance)

as those who continue to be followed up. These patients, however, are not likely to have the same risk as they are no longer receiving a treatment to cause any further effect. The primary endpoint for clearance is therefore the most reliable to use in the model and this is applied in the revised base case.

For clinically significant recurrences, the issue of censoring is less so, as these patients are no longer receiving treatment and so censored patients can be considered to have a similar risk of future events as those who continue to be followed up. However, for consistency, we have also based the recurrence rates on the SOLSTICE exploratory end point for clinically significant recurrence rather than use KM data. Given that the recurrences for the trial period only apply for three model cycles, using the KM data instead would have a minimal impact on the results.

An exploratory analysis using the KM data presented in Table 5 to model recurrences for the trial period shows very little difference in the model results, with the ICER [redacted]. The net monetary benefit in fact shows [redacted] This demonstrates that the base case analysis is reliably applying the results from the SOLSTICE trial.

Table 5. Kaplan-Meier probabilities for clinically significant recurrence from SOLSTICE

Time since clearance	Maribavir		IAT	
	KM estimate[a]	Per-cycle probability[b]	KM estimate[a]	Per-cycle probability[b]
28 days	[redacted]	[redacted]	[redacted]	[redacted]
56 days	[redacted]	[redacted]	[redacted]	[redacted]
84 days	[redacted]	[redacted]	[redacted]	[redacted]

a. KM estimate represents proportion who are recurrence free.

b. Per-cycle probability of recurrence calculated from the KM estimate.

Key Issue 3:	Yes	**We have addressed the ERG's concerns about the Company's assumptions on mean time elapsed since transplant at baseline. The model has been adapted to include SOLSTICE-specific data for time since transplant**

Assumption of time elapsed since transplant at baseline in the model		**(TST). By using SOLSTICE data and SOLSTICE TST data, modelled outcomes are aligned with TST. Events that occur beyond the trial duration (20 weeks onwards) are estimated with real world evidence and/or published literature and are aligned with TST.** ***1. Patients entering SOLSTICE and the model starting cohort both reflect the cohort of R/R patients eligible for maribavir treatment*** R/R patients reside in the later portion of the CMV treatment pathway. Clinicians have indicated that the majority of patients (90% of HSCT, 75% of SOT) are initially administered prophylaxis after transplantation (approximately 100 days for HSCT and 100-200 days for SOT depending on donor/recipient serostatus), and those that develop CMV then go on to first line pre-emptive therapy. Patients would become eligible for Maribavir if they became refractory to treatment (with or without genotypic resistance). Therefore, there is an expectation that time will elapse after transplantation before patients are categorised as R/R. This reflects the patients included in SOLSTICE. Within SOLSTICE, the median time since transplant (TST) at baseline was [redacted] days for SOT patients and [redacted] days for HSCT patients. The model was constructed to align with the SOLSTICE trial and the anticipated labelled indication. The original model begins with R/R CMV and an assumed average time since transplant of 1 year in both SOT and HSCT population. The model has been modified to allow more precise TST inputs in days rather than integer years, with estimates specific to the SOT and HSCT populations, and better align with TST observed in the trial. We accept that mortality and graft loss might be impacted by TST and we have incorporated this into the model, in different degrees as explained below. Recurrence, however, is not dependent on TST as demonstrated by the logistic regression analyses presented in Issue 1. ***2. Model allows users to enter TST in days and adjust mortality risk accordingly*** In the Phase 2 Markov of the model, risk of mortality is estimated using data based on transplant type and TST. In the company submission model, TST could only be included as the nearest integer year, and this was then used to estimate mortality in the Phase 2 Markov. For example, for SOT patients, with a TST of [redacted] days, the user would have to assume '1' year as the TST. Then after 52 weeks of the Phase 1 Markov, patients enter the Phase 2 Markov two years from transplant (1-year TST on model entry plus a subsequent year for the Phase 1 Markov). When patients transition into the Phase 2 Markov, the model then applies the year 2 to year 3 mortality risks for a full 52 weeks. As noted by the ERG, this may inaccurately estimate mortality because patients who are [redacted] days since transplant

		should receive the year 1 to year 2 TST mortality risks for the first [redacted] days of the Phase 2 Markov (i.e., [redacted] days plus [redacted]) and then receive the year 2 to year 3 TST mortality risk from [redacted] days onwards in the Phase 2 Markov. In the updated model, TST is now entered in days taken from SOLSTICE with no rounding of TST data to the nearest integer year. Therefore, for SOT, the TST is set to [redacted] days and upon entry into the Phase 2 Markov, from a 78-week Phase 1 Markov, the model will apply [redacted] 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 [redacted] days onwards. The rationale for the extension of the Phase 1 Markov to 78 weeks is discussed further in the response to issue 4. ***3. The point estimates for risk of graft loss in the csCMV and n-csCMV state have been updated in the model to align with the baseline TST*** Hakimi et al., (2017)[1] provides evidence of changing rates of graft loss based on TST. The authors provide three different risks for graft loss: 1) E-CMV; 2) L-CMV-3M; 3) L-CMV-6M (Table 6). As the TST for SOT patients in SOLSTICE, and in the new model base case, is [redacted] days, the most appropriate source informing the risk of graft loss from Hakimi et al., (2017)[1] is the final L-CMV-6M category. The choice was informed by discussions with the author who explained: "*The Table 3 presents the outcomes measures 1 year post CMV infection, whether it being a early CMV infection (<3 months post transplant) or a late CMV infection (> 3 months post transplant, or >6 months post transplant). Of note the Late CMV infections had to occur within 2 years post transplant." (Hakimi 2022, personal communication)* Based on this learning, the alternative rates from Hakimi et al., (2017)[1] (and the E-CMV rates previously used) would not be appropriate and additional time-variable rates of graft loss have not been implemented. This is due to the CMV events occurring earlier and therefore not providing the longer-term risk of graft loss required for the new Phase 1 Markov which can extend to 798 days (2.19 years) post-transplant (258 days TST at baseline plus a 78-week Phase 1 Markov). The L-CMV-6M category theoretically can 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) and therefore was determined the most robust parameter to inform risk of graft loss in the model.

Table 6: Overall graft failure (Table 3, Hakimi et al., 2017)[1]

	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%

4. Evidence of no relationship between TST and recurrence

There is no evidence for the explicit relationship between TST and recurrence. In the follow-up response to the ERG questions on 11 March 2022, tables were provided to show rates of recurrence from SOLSTICE (by treatment arm) based on TST ranges (Table 6). On visual inspection, the data does not show a clear pattern or relationship between recurrence and TST. To verify this observation, a logistic regression was performed to assess the impact of treatment, transplant type, times since transplant, time since clearance and other covariates on clinically relevant recurrences.

The results show that time since transplant has no significant impact on either clearance or recurrence requiring treatment, with an odds ratio of 1.00 in both analyses. This indicates that the odds of each outcome are unchanged by differences in time since transplant, and it is the treatment effect of maribavir that is driving the efficacy. Since TST is balanced between the two arms, and since TST does not have any impact on the efficacy data, no adjustments on efficacy data used in the model were performed. Therefore, the estimates used in the economic model continue to be reliable.

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 0.062. 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 as per the company's base case analysis (see Issue 5).

		Time since clearance showed a statistically significant impact on the odds of recurrence requiring treatment, showing that each additional day post-clearance lowers the odds by a factor of 0.952. The additional flexibility in the revised model now allows for this dependence between the time spent in the non-clinically significant CMV state and the probability of a recurrence to be appropriately captured (see Issue 5). **Table 7: Recurrence requiring treatment by transplant type and TST** **Recurrence** / **IAT** (N, n, %) / **Maribavir** (N, n, %) <3 m 3-6 m 6-12 m 12+ Total
Key Issue 4: Structural assumptions in the company's model	Yes	**In alignment with the ERG recommendation, the model inputs and model structure have been modified. SOLSTICE data were used for weeks 0-20 and OTUS real-world data were used to estimate recurrence from week 20 in Phase 1 of the model. The regression analysis in Issue 1 demonstrated there was strong evidence to show a treatment related difference between recurrence rates, hence SOLSTICE data is used for the trial period.** 1. ***Evidence of multiple recurrences and the extension of the Phase 1 Markov from 52 weeks to 78 weeks*** Based on the ERG recommendation to validate the average frequency of "full cycles" of events, Takeda looked for data to inform this parameter in the model. Data from a RWE study commissioned by Takeda (OTUS) provides evidence that SOT and HSCT patients with R/R CMV may experience multiple recurrences with standard of care (Table 8 and

Table **9**). If a treatment cycle is assumed to be [redacted] days (time on treatment in the IAT arm of SOLSTICE), 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 [redacted] weeks for SOT (duration from the start of the CMV index episode to the start of the 4th recurrence (5th CMV episode)) and [redacted] weeks for HSCT (duration from the start of the CMV index episode to the start of the 6th recurrence (7th CMV episode). These data validate the updated duration of 78-week for the Phase 1 Markov, meaning CMV events are occurring [redacted] weeks after TST for SOT ([redacted] days TST plus a 78-week Phase 1 Markov) and after [redacted] weeks for HSCT ([redacted] days TST plus a 78-week Phase 1 Markov). The extension of the Phase 1 Markov from 52 weeks to 78 weeks was deemed appropriate based on findings from OTUS, and recent discussions with clinicians. While OTUS does provide additional support to extend the Phase 1 Markov beyond 78 weeks for SOT, following discussions with clinicians it was agreed that there was a likelihood for heterogeneity in the treatment pathway at longer time horizons. Therefore, 18 months (78 weeks) was deemed a sufficiently pragmatic timepoint to end the Phase 1 Markov for SOT and HSCT, as from this point there is more uncertainty in the modelling of care pathways and costings for patients which would be based on individual patient needs. Furthermore, it would be expected that extending the Phase 1 Markov would result in more CMV events in the IAT arm and therefore the extension of the Phase 1 Markov would only further favour maribavir and improve the ICER. Therefore, ending the Phase 1 Markov at 78 weeks is a more conservative approach.

Table 8: 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)	Cumulative duration since index episode (days)
1 (CMV index episode)	-	[redacted]	[redacted]	[redacted]
2	1	[redacted]	[redacted]	[redacted]
3	2	[redacted]	[redacted]	[redacted]
4	3	[redacted]	[redacted]	[redacted]
5	4	[redacted]	[redacted]	[redacted]

Table 9: 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)	Cumulative duration since index episode (days)
1 (CMV index episode)	-	[redacted]	[redacted]	[redacted]
2	1	[redacted]	[redacted]	[redacted]
3	2	[redacted]	[redacted]	[redacted]
4	3	[redacted]	[redacted]	[redacted]
5	4	[redacted]	[redacted]	[redacted]
6	5	[redacted]	[redacted]	[redacted]
7	6	[redacted]	[redacted]	[redacted]

2. **The ERG also raised issue with the recurrence assumptions in the model and proposed an alternative modelling approach using KM extrapolations.**

   These points are repeated in key issue 5 and thus the responses to these issues can be found in the text for key issue 5.

Key Issue 5: Overestimation of recurrences in the model	Yes	**The updated model uses SOLSTICE data to inform recurrence rates (up to week 20) then uses RWE from OTUS data to inform recurrence rates for the remainder of phase 1 of the model.** • **No clearance events (and therefore no recurrence event) occur before week 8 in the updated model; therefore, the model results can be validated as matching the SOLSTICE trial outcomes (primary endpoint for clearance and the exploratory endpoint for clinically significant recurrence)** • **Recurrences are only treatment specific for the first 12 weeks of clearance (i.e., from week 8 to 20) for patients who achieve clearance with maribavir or IAT at week 8 to align with the trial exploratory endpoint. All other recurrences in the model are treatment agnostic.**

- **For patients who achieve clearance at week 8, recurrences are informed by those observed in the trial for the first 12 weeks and then by data from the RWE study OTUS post week 12 (i.e. beyond 20 weeks in the model). For patients who have a second clearance event, the recurrence rates are all informed by data from OTUS.**

1. Updated model structure where declining risk of recurrence is based on duration of clearance

Based on the comments from the ERG around over estimation of recurrences in the model, findings from a logistic regression (see Issue 1) and data from a RWE study (OTUS) who are R/R (including intolerant) to anti-CMV therapy, Takeda has updated the model structure (see Figure 1) to include decreasing rates of recurrences based on time since clearance (i.e., duration of time patients occupy the n-csCMV health state). Fundamentally, the model still retains a 3-state Markov model structure (Figure 1), however the key improvement is that the transitions between the cs-CMV state and n-csCMV state have tunnel states to track time since clearance (

Figure 2). This approach is validated by findings from the logistic regression mentioned in the response to issue 1 (Tables 2 and 3) which showed a statistically significant relationship between recurrence and time since clearance. This finding can also be further validated by data from the OTUS study (Table 10 & 11) which 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 10a: 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]	[redacted]	[redacted]	[redacted]	[redacted]
Day 140 (week 20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 365 (week 52)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 730 (week 104)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 10b: 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]	[redacted]	[redacted]	[redacted]	[redacted]
Day 140 (week 20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 365 (week 52)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 730 (week 104)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11a: 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]	[redacted]	[redacted]	[redacted]	[redacted]
Day 140 (week 20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 365 (week 52)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 730 (week 104)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11b: KM estimates to second CMV recurrence from OTUS (HSCT)

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

To incorporate the data from OTUS (see Tables 10 and 11), the model now includes tunnel states to track the duration of time patients occupy the n-csCMV health state. The model, using data from OTUS, allows users to include different rates of recurrences based on duration of clearance (see Table 13 and Table 14). OTUS also provides further evidence of different rates of recurrences for patients who have their 1st clearance versus 2nd clearance. Therefore, the model also allows users to include alternative rates of recurrences (based on duration of clearance) for the 1st clearance and then all subsequent clearance events. Importantly, linking recurrences to number of clearance events and duration of clearance, addresses the issue raised by the ERG that the *'4-week probability of recurrence at*

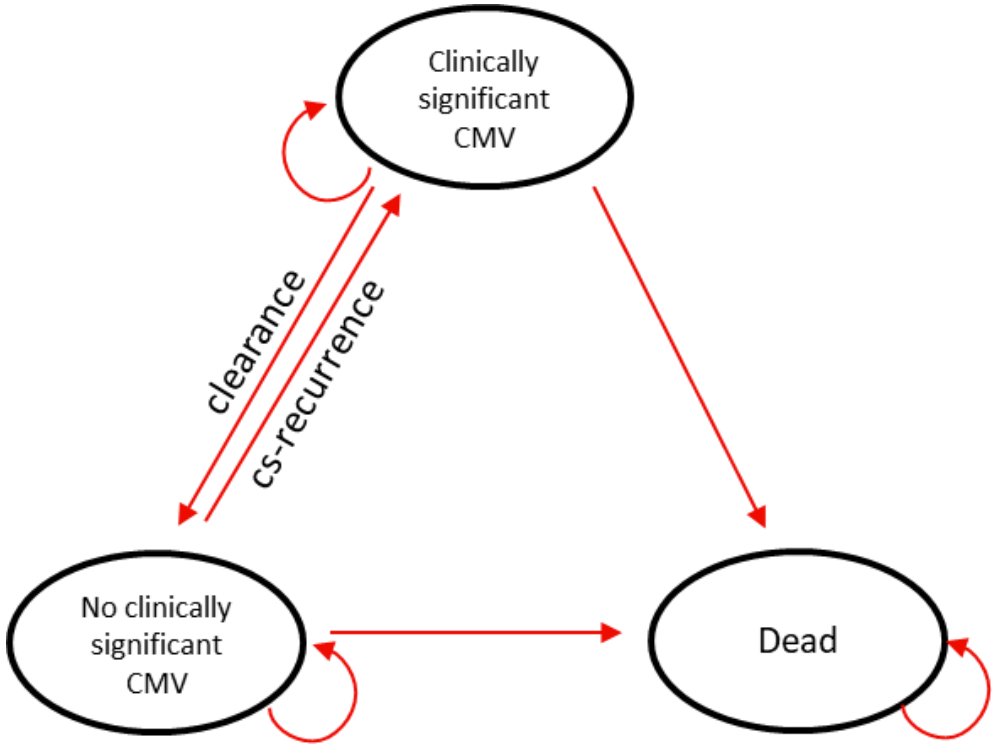
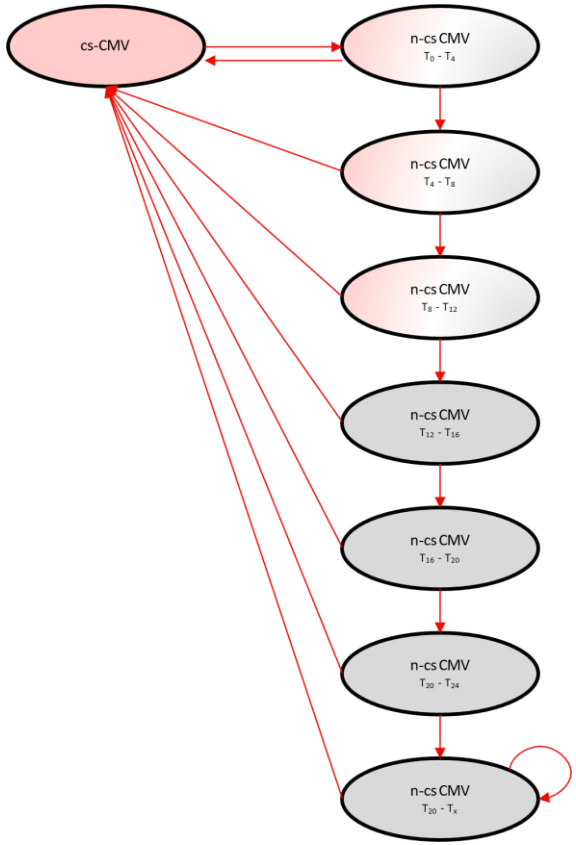
		the end of the trial period remains the same until week 52 in the model' and the critique that the model does not factor in *'how long they (patients) have been off treatment'.* **Figure 1: Base case model structure** 

Figure 2: Transitions between the csCMV and n-csCMV health states



		(1) Clearance from the cs-CMV (red) state to n-csCMV (T_0-T_4) is informed by data from SOLSTICE (2) Recurrence from a hybrid n-csCMV state (red and grey) to the red cs-CMV state is informed by transitions from SOLSTICE 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 T_n - T_{n+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 T_{24} - T_{24+} the model no longer tracks n-csCMV occupancy in 4-week increments (i.e., all patients in the health state have maintained clearance for a minimum of 24 weeks with no maximum time point known). ***2. Alignment of the model results with the SOLSTICE trial*** To enable more precise alignment with the primary endpoint of the trial, the model no longer includes clearance, recurrence or mortality events between week 0 to 8. Therefore, the ad-hoc IPD analyses for these treatment effects are no longer used, and data are directly sourced from the CSR, (i.e., primary endpoint for clearance at 8 weeks and exploratory endpoint for clinically significant recurrences). At week 8, the clearance numbers generated by the model ([redacted]% for maribavir and [redacted]% for IAT) are now in complete alignment with the primary endpoint of the SOLSTICE trial. For recurrence, in the trial 26% of patients had clinically relevant recurrence in the maribavir arm and 35.7% of patients had a clinically relevant recurrence in the IAT arm. The model results are very closely aligned with this exploratory endpoint where 25.23% have a recurrence with maribavir and 35.19% of patients have a recurrence with IAT. The model implements health state mortality from week 8 onwards. ***3. Adjustment of clinically relevant recurrence estimates to account for discontinuation and death*** The ERG suggested that the calculations for recurrences in the pre-technical engagement model may have included '*proportion of all patients who between week 8 and week 20 in the trial achieved a first clearance plus the proportion of patients who might have discontinued in the trial or died between the same period*'. To account for this, the patients who cleared at week 8 were followed until week 20 and the recurrence counts were adjusted for death and discontinuation (see Table 12). It should be noted there were no discontinuation events in the cohort of patients who cleared at week 8 who were then followed until week 20. Unadjusted results from the CSR of patients who cleared at week 8 that had a clinically significant recurrence between week 8 and 20 is 26% for maribavir and 35.7% for IAT. Adjusted results from the CSR of patients who cleared at week 8 that had a clinically significant recurrence between week 8 and 20 is 27% for maribavir and 37% for IAT. These adjusted values have been converted into 4-week probabilities and then incorporated into the model in cases where the SOLSTICE data is used to inform recurrences.

Table 12: Probability of recurrence between week 8 and week 20

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

Sources for longer-term risk of recurrence

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 of the first clearance event (through study week 20) and are taken directly from the recurrence rates observed in SOLSTICE. After 12 weeks of clearance (beyond week 20), the rates of recurrence are treatment agnostic and informed by the data from OTUS which provide risk of recurrence from week 0 through to day 730 (see Table 10). For the second clearance event, the rates of recurrences are informed exclusively by the data from OTUS. The rates and sources of recurrence used in the model in the IAT and maribavir arm are included in Table 13 and Table 14.

Table 13: 4-week probability of recurrence after 1st CMV clearance

Weeks since 1st clearance	IAT	Maribavir	Source
4	[redacted]	[redacted]	SOLSTICE
8	[redacted]	[redacted]	SOLSTICE
12	[redacted]	[redacted]	SOLSTICE
16	[redacted]	[redacted]	OTUS$^{\Omega}$ - Table 9 (SOT) and Table 11 (HSCT)

20	[redacted]	[redacted]	OTUS$^{\Omega}$ - Table 9 (SOT) and Table 11 (HSCT)
24 onwards	[redacted]	[redacted]	OTUS$^{\Omega}$ - Table 9 (SOT) and Table 11 (HSCT)

* 27.0% mortality-adjusted recurrence rate from SOLSTICE converted into a 4-week probability
† 35.0% mortality-adjusted recurrence rate from SOLSTICE converted into a 4-week probability
Ω Data from OTUS converted into a 4-week probability

Table 14: 4-week probability of recurrence after 2nd CMV clearance

Weeks since 2nd clearance	IAT	Maribavir	Source*
4	[redacted]	[redacted]	OTUS - Table 10 (SOT) and Table 12 (HSCT)
8	[redacted]	[redacted]	OTUS - Table 10 (SOT) and Table 12 (HSCT)
12	[redacted]	[redacted]	OTUS - Table 10 (SOT) and Table 12 (HSCT)
16	[redacted]	[redacted]	OTUS - Table 10 (SOT) and Table 12 (HSCT)
20	[redacted]	[redacted]	OTUS - Table 10 (SOT) and Table 12 (HSCT)
24 onwards	[redacted]	[redacted]	OTUS - Table 10 (SOT) and Table 12 (HSCT)

* Data from OTUS converted into a 4-week probability

Inclusion of time since clearance means that the model no longer applies a constant recurrence rate for the duration of the Phase 1 Markov. Now, recurrence rates decrease over time and reduce the number of patients with active CMV at the end of Phase I thereby improving the face validity of modelled results. Additionally, treatment specific rates of recurrence are only used between week 8 and 20 for patients who have their first clearance event with maribavir or IAT at week 8, all other recurrences in the model are agnostic to treatment. This change takes a pragmatic approach to align with the trial data while addressing the critique that '*the probability of recurrence is unlikely to depend on the type of treatment'*.

4. Exploration of ERG-proposed approach using KM data

Before proceeding with the new model structure in Figure 1, Takeda first explored the ERG's proposed approach of using KM data for clearance and recurrence, and then modelling a 'full cycle' of events. However, as proposed by the

		ERG, when the methods described in TSD 19 were implemented to extrapolate clearance and recurrence rates from the trial, the parametric curves did not have a good fit. In SOLSTICE, 26% of maribavir patients and 35.7% of IAT patients had a clinically significant recurrence (i.e., patients achieved a response at week 8 and had a recurrence requiring treatment between week 8 and week 20). The residual and cumulative hazard plots are presented in Figure 3. The Grambsch-Therneau test results in p=0.65 therefore the proportional hazard assumption can be accepted, and dependent models were fitted. The parametric model fits for IAT and maribavir for recurrence are presented in **Figure 4**. The goodness of fit is presented in **Table 15**. The analysis was also repeated for the pooled clinically significant recurrence rates. The parametric model fits are presented in Figure 5 and goodness of fit is presented in Table 16. The key issue with the recurrence extrapolations is that the sample size was inadequate and not mature enough to generate accurate extrapolations; for this reason, the extrapolations resulted in poor fits.

		Figure 3: The Schoenfeld residuals plot and cumulative hazard plot for recurrence  **Figure 4: Kaplan Meir and dependent parametric model fits for recurrence**

		[redacted]

Table 15: Goodness of fit for recurrence

Distribution	AIC	BIC
Gompertz	[redacted]	[redacted]
Lognormal		
Log-logistic		
Weibull		
Exponential		
Gamma		
Generalised Gamma		
Generalised		

Figure 5: Kaplan Meier and goodness of fits for pooled recurrence

The extrapolations were also completed for clearance, the residual and cumulative hazard plots are presented in Figure 6. The p-value from the Grambsch-Therneau test was [redacted], therefore the proportional hazard assumption can be accepted, and dependent models were fitted. The parametric model fits for IAT and maribavir for clearance are presented in Figure 7 and the goodness of fit is presented in Table 16. The clearance extrapolations resulted in poor fits. The extrapolation of clearance beyond week 8 did not result in a difference due to treatment effect in the long run. This is because the endpoint is only based on first clearance and does not consider recurrence after first clearance or second clearance.

Figure 6: The Schoenfeld residuals plot and cumulative hazard plot for clearance

		 **Figure 7 Kaplan Meier and dependent parametric model fits for recurrence**

[redacted]

Table 16 Goodness of fits for clearance

Distribution	AIC	BIC
Lognormal	[redacted]	[redacted]
Log-logistic		
Gamma		
Weibull		
Exponential		
Gompertz		

Based on the findings from the extrapolation, incorporating the KM approach into the economic model would have resulted in increased uncertainty due to the poor fits. In addition to this, the approach would require an assumed fixed number of CMV episodes, which would not adequately capture the treatment pathway of this heterogenous population.

		However, Takeda acknowledge the rationale for why the ERG have proposed this solution (i.e., due to the potential overestimation of recurrences in the previous model). For this reason, Takeda has implemented an alternative approach leveraging findings from a logistic regression and outputs from a RWE study which provides evidence for an association between duration of clearance and CMV recurrence (see response to issue 1). Specifically, new evidence from the OTUS study demonstrate a diminishing risk of recurrence based on duration of clearance. Therefore, the model structure has been updated to incorporate tunnel states to track the duration of time in the n-csCMV state and importantly, include a relationship in the model between duration of clearance and rates of recurrence.
Key Issue 6: Modelling of mortality in stage 1 Markov	Yes	**It has been acknowledged by both clinicians and the ERG that there is an association between CMV and mortality. Takeda believe the best source of data for health state mortality in R/R patients is the SOLSTICE trial. Mortality has been informed from the week 8-20 timepoint of SOLSTICE which only provides 12 weeks to inform the difference in mortality between treatment arms. This limited time period results in uncertainty in any relative treatment effects. However, analysis of the mortality by treatment arms adjusting for treatment switching to rescue arm demonstrates plausibility in the modelled treatment effect, with a clear albeit uncertain separation of the curves. This supports the mortality estimates used for the base case and validates the small incremental gain in life-years generated by the model.** ***1. Rationale for the use of health state mortality*** Clinicians provided advice on the choice of model structure and verified the model inputs during the model conceptualisation and development stages. A key driver for using a Markov model structure was the repeated input from clinicians that mortality was an important reason for treating patients with R/R CMV with urgency. Therefore, differential mortality outcomes between the csCMV and n-csCMV health states are important for the model to retain clinical validity. The committee should also be aware that an important limitation (as noted by the committee and ERG who reviewed the TA591 appraisal) of the model developed by the manufacturers for TA591 was the absence of a relationship between CMV and mortality in the decision tree structure. The Takeda model is an improvement on this approach, while maintaining conservativeness in implementation. ***2. Evidence of CMV related mortality from SOLSTICE (base case)*** The SOLSTICE trial was chosen as the preferred source of data to inform health state mortality. Specifically, patients in the trial were categorised at week 8 according to their transplant type and response status, and then followed for

		the remaining 12 weeks of the trial (week 8 to 20). The decision to establish categorisation of patients by response status at week 8 was to give the treatments (IAT or maribavir) sufficient time to have an impact on viraemia so that any consequential impact on mortality could be observed. Before week 8, as patients are fluctuating between health states, the inclusion of mortality data from this period in the model would not provide robust data to demonstrate the impact of CMV on mortality. The model is now aligned with the primary endpoint therefore these fluctuations before week 8 are no longer within the model. This can be observed in the Kaplan Meir plot of time to all-cause mortality regardless of anti-CMV treatment (and adjusted for treatment switch) between week 8 and week 20 in the trial (see Figure 8). In the KM plot, in the first 8 weeks (day 0 to day 56), there is overlap in the curve and thereafter (from week 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. **Figure 8 Kaplan Meier plot of time to all-cause mortality regardless of anti-CMV treatment use by treatment arm adjusted for treatment switch by IPCW method**

		 TRTPN=1 is IAT; TRTPN=2 is maribavir ***3. Evidence of CMV related mortality from external data (scenario analysis)***

		To support committee decision making, data on the risk of CMV related mortality for SOT and HSCT patients has been identified from published literature. The results from these analyses have been included in a scenario analysis resulting in improvements to the ICER. Camargo et al., (2018)[2] explored the impact of persistent viremia (patients who failed to clear CMV on treatment day 35) versus cleared viremia (patients who cleared within 35 days of treatment) on all-cause mortality in HSCT, and Hakimi et al., (2017)[1] 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)). While both sources provide evidence that mortality changes with respect to TST, it is only relevant and taken into considerations for HSCT patients in the scenario analysis. The baseline TST for SOT patients is [redacted] days, therefore the most appropriate data from Hakimi et al., (2017)[1] to inform the risk of mortality is the final L-CMV-6M category (Table 17). As explained in the response to issue 3, risks from the earlier TST time points from the study are not relevant. For HSCT, data from Camargo et al., (2018)[2] has been included to account for TST (Table 18). As the baseline TST for HSCT patients is [redacted] days, the model can use data from all three time points (100-, 200- and 300-days) post HSCT from Camargo et al., (2018).[2] It should be noted that the mortality risks from Hakimi et al., (2017)[1] represent a heterogenous population that does not necessarily represent the same population as the SOLSTICE trial. Hakimi et al., (2017)[1] has a greater proportion of kidney transplant patients (lower risk of death) and a lower proportion of lung transplant patients (higher risk of death). The overall risks from Hakimi et al., (2017)[1] are therefore lower than those estimated from SOLSTICE. As our model is based on the population of the SOLSTICE trial, our base case analysis more appropriately reflects the overall mortality rates. However, Hakimi et al., (2017)[1] provides further support that CMV has an impact on mortality and therefore the health-state specific mortality estimates used in our base case are reliable and appropriate.

Table 17: All-cause mortality – HSCT (Camargo et al., [2018][2])

	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%

Table 18: All-cause mortality – SOT (Table 3, Hakimi et al., [2017][1])

	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%

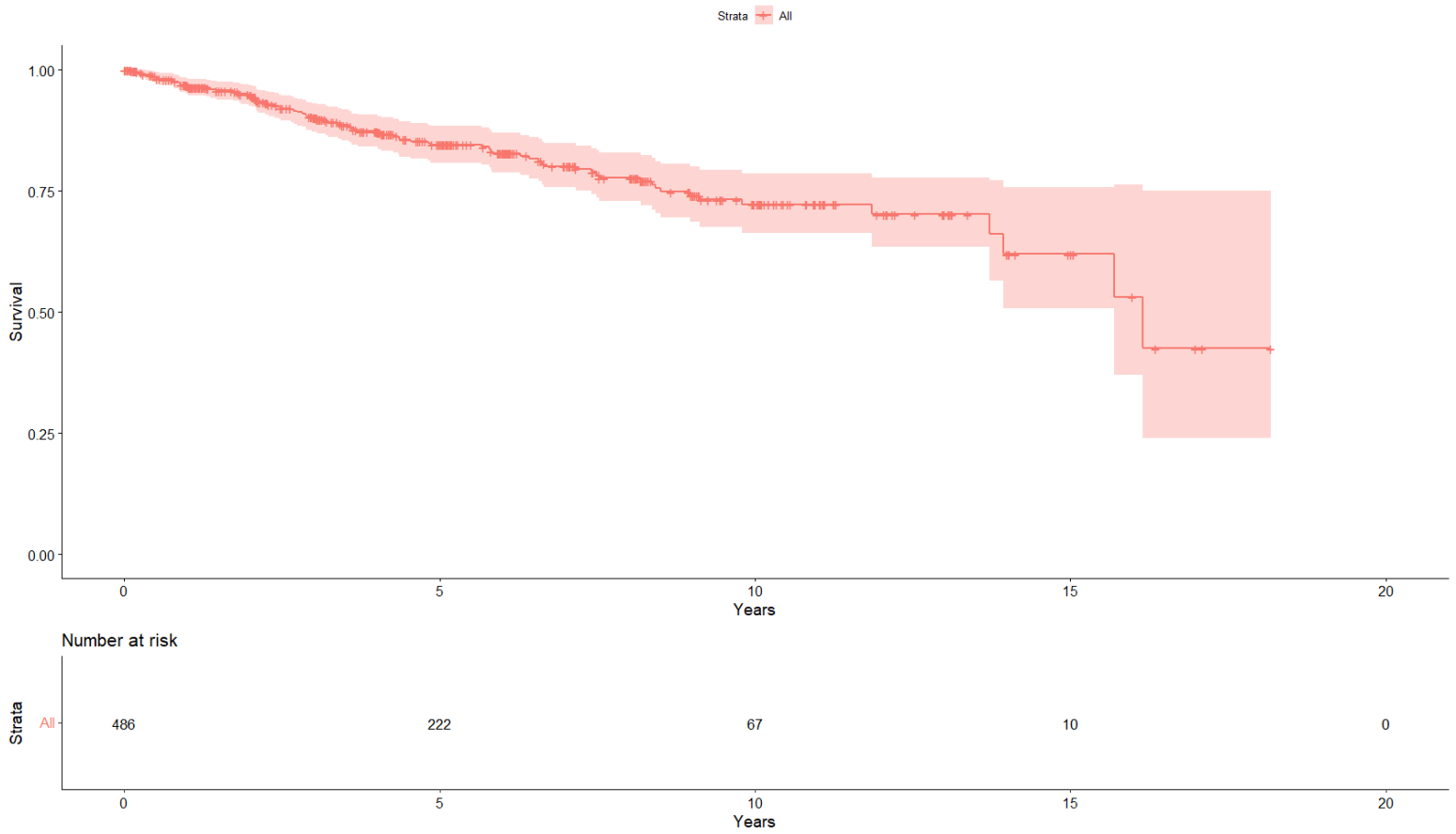
4. Removal of week 4 mortality outcomes

To allow the model to match the primary study endpoint in the 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 SOLSTICE.

		<table><tr><th rowspan="2">Time point</th><th colspan="2">Model output</th><th colspan="3">SOLSTICE CSR</th></tr><tr><th>Maribavir</th><th>IAT</th><th>Maribavir</th><th>IAT</th><th>Pooled IPD</th></tr><tr><td>Week 8</td><td>5.40%</td><td>5.40%</td><td>6.0%</td><td>4.3%</td><td>5.40%</td></tr></table> ***5. Removal of background mortality*** The ERG noted that it disagreed with the methodology of summing sex- and age-specific general population mortality rates to the mortality rates observed in SOLSTICE, as these were competing risks. The base case has been updated to remove the sex- and age-specific general population mortality rates from the Phase 1 Markov. ***6. Differences in mortality risk at the end of the Phase 1 Markov and start of Phase 2 Markov*** A scenario has been incorporated into the model where the background mortality that would be expected (based on TST) for SOT and HSCT, is applied as a proxy for the n-csCMV health state. The base case remains unchanged as the SOLSTICE trial estimates of mortality, which represents an R/R cohort, was preferred over external data for SOT (NHS) and HSCT (HMRN), which includes patients with and without CMV.
Key Issue 7: Modelling of mortality in stage 2 Markov	Yes	**As per the ERG suggestion, data from Martin *et al.* 2010[3] has been used to inform long-term HSCT mortality within the model. Takeda maintain the basecase approach for long-term SOT mortality as the ERG recognised this approach plausible** ***1. HSCT mortality in the stage 2 Markov*** To address the issue relating to HSCT mortality in the period beyond the 5 years of data available from the HMRN, we have made use of the data from Martin *et al.* 2010[3] highlighted by the ERG, which was also used to inform mortality in the letermovir NICE appraisal (TA591).[4] The ERG suggested the standardised mortality ratio (SMR) presented by Martin *et al.*[3] could be applied to general population survival to estimate mortality rates in the period after the 5 years of HMRN data. While we agree that Martin *et al.* 2010[3] provides a useful source of data to inform mortality rates for 5 years post HSCT, the application of an SMR potentially adds further uncertainty given the inherent assumption of a fixed relative risk between the HSCT data and the general population. The estimated SMR is only a reliable estimate for the period over which it was estimated. Therefore, we propose to use the data in a more reliable way.

		Martin *et al.* 2010[3] provides Kaplan-Meier (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 SOLSTICE population, and therefore, this data is the most relevant to use to inform the model. Our preferred method is to fit survival curves to this 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.* become lower than the general population. The author (Paul Martin) helpfully provided the individual event and censor times for the KM plots so that these could be used to fit the survival curves without the need for digitization. A recreation of the plot for the greater than 45 year age group is provided in Figure 9.

Figure 9. Kaplan-Meier recreated from Martin et al.[3] for the greater than 45 years age group



Parametric survival models were fitted to the data based on the methods recommended in NICE Technical Support Document 21. 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 10, and the goodness-of-fit statistics are given in Table 19.

Figure 10. Fitted survival curves for Martin et al.[3] for the greater than 45 years age group

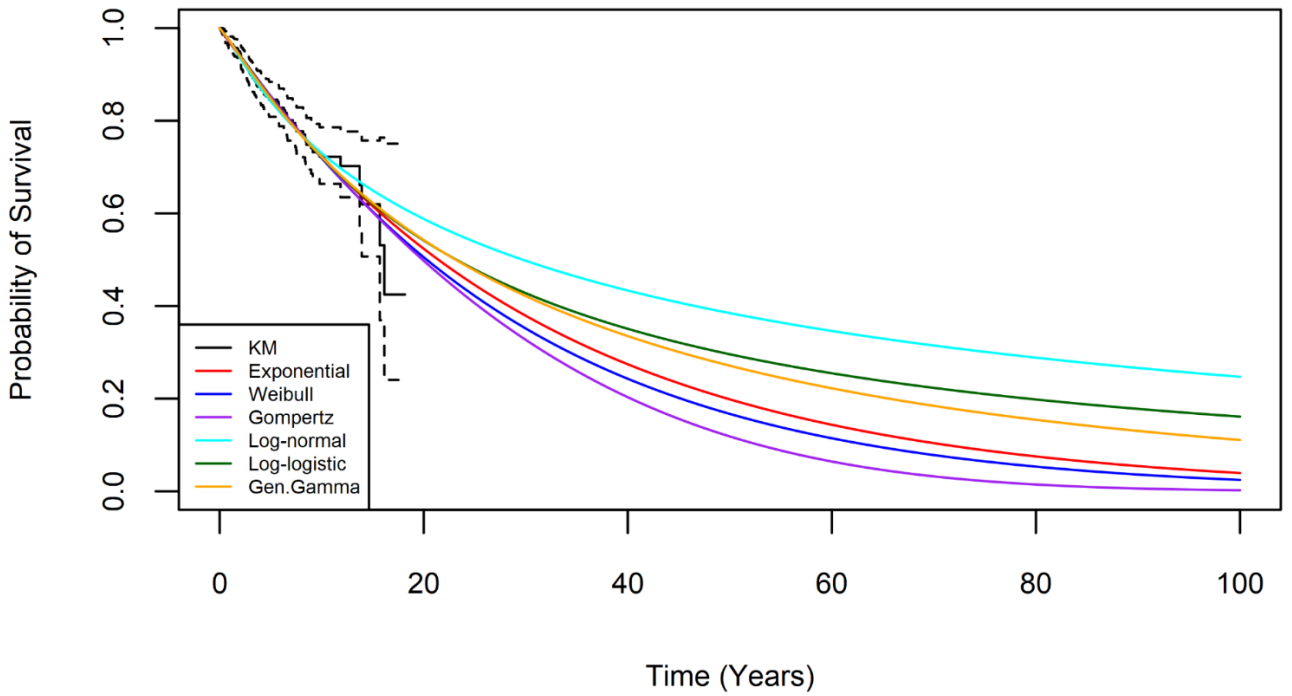


Table 19. Goodness-of-fit statistics for survival models fitted to Martin *et al.*[3]

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

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 model is also provided to demonstrate the impact of this similarly fitting but most extreme (highest overall mortality) model. The results are provided at the end of this document.

2. SOT mortality in the stage 2 Markov

For the SOT population, the mortality rates currently used in the model are based on 10 years of data and therefore, as the ERG noted, the extrapolation of mortality rates from this data is less problematic than the extrapolation in the HSCT population. Furthermore, there are no data available to inform the mortality rates from 10 years post SOT in order to apply the same approach as per the HSCT modelling discussed above. Therefore, the best approach for survival modelling for the SOT population is the same as the previous base case approach. This approach is a conservative as the mortality rates are expected to diminish over time. We are, therefore, limiting the modelled life expectancy and thus limiting the potential gain in quality-adjusted life-years. The ICER is therefore also likely to be overestimated based on this aspect of the model.

Key Issue 8: Modelling of graft failure	Yes	**Data from Hakimi *et al*[1] now aligns with the time since transplant of the SOLSTICE population. Takeda have provided real-world evidence for long-term graft loss to demonstrate graft loss events can occur beyond 12 months. The model has been updated to include graft loss utility decrements over a lifetime horizon but the mortality risk for retransplant maintains the current approach to not overestimate the benefits of maribavir.**

1. Health state related risk of graft loss has been updated

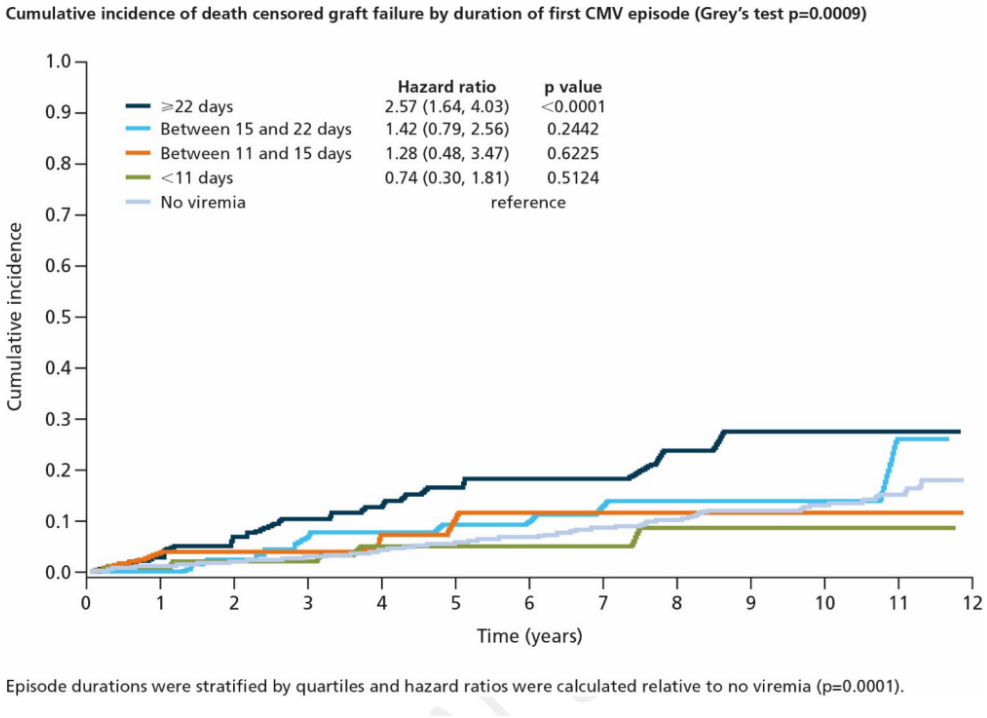
Following confirmation from the author, Takeda agrees that the data presented in Table 3 of Hakimi et al., (2017)[1] represent annual data. Takeda also accepts that the data previously used to model the risk of graft loss (overall graft rejection for E-CMV patients from Table 3) do not align with the TST of the population in SOLSTICE. Therefore, the probability of graft loss in the model is now calculated using the overall risk of graft loss for L-CMV-6M patients from Table 3 of Hakimi et al., (2017)[1] as explained in the text response to key issue 3.

2. Graft loss events can occur beyond 12 months

Hakimi et al., (2017)[1] show that patients may still experience graft loss events up to 3-years post-transplant. For example, if an L-CMV-6M 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, [redacted] of patients had a graft loss event by 365 days, while [redacted] 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.[5] 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 11 below).

Figure 11: Data from GENOME[5] on risk of graft loss



Episode durations were stratified by quartiles and hazard ratios were calculated relative to no viremia (p=0.0001).

3. ***A scenario where all patients do not receive retransplant***

   The ERG disagreed with the assumption that 100% of patients will have a second transplant, and thus requested scenarios to account for the patients who do not receive a second transplant. Following further conversations with clinicians, it was advised that if an assumption were to be made that patients with a heart, liver or lung transplant are not able to have a retransplant, then, the model should assume that these patients would be at risk of

immediate death. Therefore, a scenario was conducted where 100% of patients were not eligible for retransplant and at risk of immediate death (except for renal transplant patients who would receive lifetime dialysis). This scenario has only a small impact on the results, with a small increase in incremental QALYs but a slight decrease in the incremental costs. Overall there was a small reduction in the net monetary benefit of [redacted], demonstrating that the base case analysis is robust to this uncertainty.

4. Revised choice of utility estimates from vignette

Previously, the utility decrement for a graft loss event was sourced from data from the asymptomatic CMV (cs-aCMV) category in the vignette study. Now, graft loss utility decrement is informed by the asymptomatic csCMV (cs-aCMV), symptomatic csCMV (cs-sCMV) and n-csCMV categories in the vignette study. 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 decrements for each health state and transplant type are shown in Table 20.

Table 20: Graft loss disutility values for kidney and lung transplant patients (Vignette study)

Health state	Graft loss – kidney	Graft loss – lung
cs-sCMV	-0.166	-0.279
cs-aCMV	-0.079	-0.154
n-csCMV	-0.287	-0.450
Average	**-0.177**	**-0.294**

cs-sCMV: clinically significant – symptomatic cytomegalovirus; cs-aCMV: clinically significant – asymptomatic cytomegalovirus; n-csCMV: non-clinically significant cytomegalovirus

5. Application of utility decrements due to retransplant for a lifetime horizon

The ERG proposed that rather than applying utility decrement for retransplant as a one-off event in the cycle it occurs, the decrement should be assigned over a lifetime horizon. This approach has now been implemented in the model.

6. Mortality risk for patients who have a retransplant following a graft loss event

On entry into the model, patients are assumed to have had a transplant. Therefore, to calculate the elevated risk of mortality for patients who have a second transplant, the risk of mortality for patients who had their first transplant was compared with patients who have had a second transplant. The ERG noted that the model did not utilise data comparing patients who had a transplant versus no transplant. While these data may exist, the data already incorporated into the base case was deemed most appropriate. By taking the approach recommended by the ERG, maribavir would be further favoured as the standardised mortality rates would be greater than the current values in the model, therefore the current approach is conservative.

Transplant type	**Current values (first transplant vs retransplant)**			**Alternative values (no transplant vs transplant)**		
	HR	**Country**	**Author**	**SMR**	**Country**	**Author**
Heart transplant	1.79	United States	Miller et al. 2019[6]	2.84[a]	United States	Suarez-Pierre et al 2020[7]
Kidney transplant	1.25	United States	Panchal et al. 2015[8]	1.4[b]	United States	Gondos and Brenner 2011[9]
Lung transplant	1.30	United States	Kawut et al 2007[10]	5.39[c]	United States	Iguidbashian et al 2022[11]
Liver transplant	1.30	United States	Kim et al. 2010[12]	2.5[d]	Finland, Sweden, Norway, and Denmark (Nordic Liver Transplant Registry)	Aberg et al 2015[13]
Other	1.33	Assumption (weighted average of other transplants)		2.86	Assumption (weighted average of other transplants)	

SMR = Standardised mortatality rate
[a] 10-year survival

		[b] 5-year observed survival of 50–59 year-old renal transplant recipients (deceased donor) compared to the expected 5-year survival of 50-59 year old general population *[c] 10-year expected mortality of lung transplant recipients vs 10-year mortality of non-hospitalised general population* *[d] SMR based on transplant performed between 2000 and 2010*
Key Issue 9: Modelling of disease complications	Yes	**Takeda have implemented a scenario for underlying disease recurrence for HSCT patients in line with the ERG recommendation. Inclusion of GvHD is provided as a scenario; conservatively, it continues to be excluded from the basecase to retain clinical validity.** ***1. Scenario for relapse in underlying condition updated in line with the ERGs recommendations*** In a scenario analysis, 47% of HSCT patients are assumed to have a relapse in their underlying condition. The scenario has been updated to incorporate risk of mortality where all 47% of patients are assumed to die in the cycle the relapse occurs as well as given 6-months of costs and utility decrements. While a more accurate implementation of this approach would allow detailed tracking of patients in the Markov engine, the approach implemented overestimates utility, costs and mortality in the maribavir arm. Therefore, the scenario analysis is conservative and favours the comparator arm; given that the impact on the ICER is very small the approach taken was deemed pragmatic and sufficient to provide the committee with reassurance that relapse in underlying disease would not impact the decision on cost-effectiveness. ***2. Approach for inclusion of GvHD in a scenario analysis*** Takeda heard from clinicians that there is a weak link between the presence of CMV and the emergence of chronic or acute GvHD, and therefore to keep the model focussed on CMV, GvHD was excluded in the base case. GvHD is included in a scenario analysis where a relationship is established between CMV and GvHD based on a study from Hahn et al., (2008).[14] The study provided estimates to include a higher risk of GvHD in the csCMV health state compared with the n-csCMV health state. Cost and utility associated with a GvHD has also been identified from published literature (see Table 18). As patients in the maribavir arm are expected to have longer n-csCMV health state occupancy, the inclusion of GvHD in the base case would favour maribavir.

GvHD events have been excluded to ensure the model retains clinical validity. The committee should note that this is a conversative assumption and including GvHD would only further improve cost-effectiveness of maribavir.

Table 18: Input values for GvHD scenario

Input	Value	Source	Notes
4-week probability of GvHD (n-csCMV)	0.11	Hahn et. al (2008)[14]	100-day cumulative incidence of grade 2 to 4 GvHD of 35% converted into a 4-week probability
4-week probability of GvHD (csCMV)	0.24	Probability of GvHD: Hahn et. al (2008)[14] Hazard rate: Cantoni et al., (2010)[15]	4-week probability of GvHD in a general HSCT population multiplied by the hazard rate (2.18) for GvHD risk with active CMV (vs no CMV)
GvHD cost	£11,449.13	Average of acute and chronic GvHD from NICE TA591 (adjusted for inflation)	Acute GvHD cost from TA591 was £9,548 and the cost of chronic GvHD was £12,983. The average of these two was taken and then inflated by the NHS cost inflation index value of 1.63% (rate from 2018/19 to 2019/20) as published in the PSSRU Unit Costs of Health and Social Care 2020.
GvHD disutility (n-csCMV)	-0.09	TA591, Pidala et al., (2011)[16] and Ara and Brazier (2008)	Disutility value sourced from TA591, where "SF-36 QoL data from a study by Pidala et al (2011)[16] was converted into EQ-5D disutility using an algorithm by Ara and Brazier (2008)"
GvHD disutility (csCMV)	-0.09		

Key Issue 10: Estimation of utilities	Yes	**The utilities in the model have been revised to account for missing data. Overall, the impact to the utility data following reanalysis is a reduction in the incremental difference between health-state utility values.** **There is differential dropout between treatment arms with more data missing from the IAT arm. This is attributed to discontinuations and rescue treatment in this arm, and is expected due to the reduced efficacy vs. maribavir.**

		Takeda have performed some analysis to demonstrate there is no evidence that missing data impacts on the comparison between treatment within a mixed model repeated measures (MMRM) model.
		1. Methods implemented to account for missing data The ERG requested a re-analysis of utilities to investigate whether multiple imputations and pattern-mixture modelling methodologies can limit or overcome the potential for bias due to missing data. An initial assessment of the data shows that there is differential dropout but this is attributed largely to discontinuations and rescue treatment in the IAT arm. Missing not at random (MNAR) mechanism is appropriate when the missing scores are also reliant on unobserved factors. As we cannot declare the exact nature of the missing data 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 show 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, we have implemented estimates based on imputation assuming MAR to account for the missing data. Utility values were imputed using Multiple Imputation (MI) techniques including all randomized subjects; however, rescue subjects are omitted if imputed visit falls 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 being 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 (UN) 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 the investigator assigned treatment (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 missing at random (MAR), with models showing significant difference between health state at week 8 and transplant type and no differences between the 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 21 and the SOT or HSCT specific utilities have been used to update the inputs in the model.

Table 21: Utility imputation analysis

	SOT		HSCT		Overall / pooled	
	Without imputation	Imputation (only protocol visits and no rescue)	Without imputation	Imputation (only protocol visits and no rescue)	Without imputation	Imputation (only protocol visits and no rescue)
Response (week 0-20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No response (week 0-20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response (at week 8) utilities averaged out across visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No response (at week 8) utilities averaged out across visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response (at week 8), utilities at week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No response (at week 8), utilities at week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2. Use of week 8 utility values

The ERG noted that the economic model included values from week 0 to 20 based on response status at week 8. The model has been updated to ensure that the 8-week values are used to define the health state quality of life scores,

		which also aligns with the primary endpoint date. At 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. For this reason, the model was updated with the 8-week values from Table 21 with the multiple imputation method included. ***3. Ara et al., used to estimate age related utility decrements*** In the stage 2 Markov, utility decrements were estimated using data from Szende et al., (2014).[17] These values have now been updated with the ERG's preference for Ara et al., (2010).[18]
Key Issue 11: Estimation of costs	No	**Intravenous administration costs reflect the complex administration and handling of the IV drugs in the IAT arm and is in line with previous assumptions used in the letermovir NICE submission. Hospitalisation costs have been modified and use conservative assumptions. Hospitalisation costs reflect the differences in severity and intensity of care between csCMV and n-csCMV patients.**
		1. Intravenous administration costs The most suitable cost for the administration of intravenously (IV) administered drugs in the IAT arm is the NHS reference cost for complex chemotherapy. This is also in line with the previous letermovir NICE appraisal, as per base case approved by the appraisal committee. The use of this cost, as used in the precedent NICE appraisal, is the most appropriate as it reflects the complicated administrations of IV drugs in the IAT arm. Both cidofovir and ganciclovir require aseptic preparation; furthermore, the addition of concomitant medications and pre-hydration with IV fluids increase the hospital resource needed for the administration and have their own associated costs. As these associated cost and hospital resource would be difficult to model for the three combined, the use of NHS reference cost for complex chemotherapy, as used by letermovir in their NICE submission, is seen as most appropriate. The complex administration and handling of the IV drugs in the IAT arm is also represented in their respective SmPCs: **Foscarnet** <u>Administration</u> Foscarnet should be administered by the intravenous route only, either by a central venous line or in a peripheral vein.

		When peripheral veins are used, the solution of foscarnet 24 mg/ml must be diluted. Individually dispensed doses of foscarnet should be aseptically transferred and diluted ith equal parts of 0.9% sodium chloride (9 mg/ml) or 5% dextrose (50 mg/ml) by the hospital pharmacy. The diluted solutions should be used as soon as possible after preparation but can be stored for up to 24 hours if kept refrigerated. Hydration: Renal toxicity of Foscavir can be reduced by adequate hydration of the patient. It is recommended to establish diuresis by hydration with 0.5–1.0 litre of normal saline at each infusion. In compliant patients, oral hydration with similar hydration regimens has been used. Clinically dehydrated patients should have their condition corrected before initiating Foscavir therapy. **Cidofovir** Administration Adequate precautions including the use of appropriate safety equipment are recommended for the preparation, administration and disposal of cidofovir. The preparation of cidofovir reconstituted solution should be done in a laminar flow biological safety cabinet. Personnel preparing the reconstituted solution should wear surgical gloves, safety glasses and a closed front surgical-type gown with knit cuffs. If cidofovir contacts the skin, wash membranes and flush thoroughly with water. Cidofovir 75 mg/ml Concentrate for Solution for Infusion is for intravenous infusion only. The recommended dose, frequency, or infusion rate must not be exceeded. It must be diluted in 100 millilitres 0.9% (normal) saline prior to administration. The entire volume should be infused intravenously into the patient at a constant rate over a period of 1 hour by use of a standard infusion pump. To minimise potential nephrotoxicity, oral probenecid and intravenous saline prehydration must be administered with each Cidofovir 75 mg/ml Concentrate for Solution for Infusion Handling and disposal Adequate precautions including the use of appropriate safety equipment are recommended for the preparation, administration and disposal of cidofovir. The preparation of cidofovir reconstituted solution should be done in a laminar flow biological safety cabinet. Personnel preparing the reconstituted solution should wear surgical gloves, safety glasses and a closed front surgical-type gown with knit cuffs. If cidofovir contacts the skin, wash membranes and flush thoroughly with water. Excess cidofovir and all other materials used in the admixture preparation and administration should be placed in a leak-proof, puncture-proof container for disposal. Any unused product or waste material should be disposed of in accordance with local requirements. Obtaining probenecid

		Probenecid is not supplied with cidofovir and should be obtained via the Marketing Authorisation Holder of probenecid. However, in case of difficulty in obtaining probenecid the local representative of the Marketing Authorisation Holder of Cidofovir 75 mg/ml Concentrate for Solution for Infusion should be contacted for information **Ganciclovir** Caution should be exercised in the handling of ganciclovir. Since ganciclovir is considered a potential teratogen and carcinogen in humans, caution should be observed in its handling. Avoid inhalation or direct contact of the powder contained in the vials or direct contact of the reconstituted solution with the skin or mucous membranes. Ganciclovir solutions are alkaline (pH ~11). If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with plain water. Preparation of the reconstituted concentrate Aseptic technique should be used throughout to reconstitute lyophilised ganciclovir. 1. The flip-off cap should be removed to expose the central portions of the rubber stopper. Draw 10 mL of water for injection into a syringe, then slowly inject through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial. Do not use bacteriostatic water for injection containing parabens (para-hydroxybenzoates), since these are incompatible with ganciclovir. 2. The vial should be gently swirled in order to ensure complete wetting of the product. 3. The vial should be gently rotated/swirled for some minutes to obtain a clear reconstituted solution. 4. The reconstituted solution should be checked carefully to ensure that the product is in solution and practically free from visible particles prior to dilution with compatible solvent. Reconstituted solutions of ganciclovir range in colour from colourless to light yellow. ***2. Hospitalisation costs*** The ERG noted that the hospitalisation cost for csCMV patients may be too high. However, the ERG preference of applying the weighted average of WJ02C-WJ02E (non-elective long stay for infectious diseases) to csCMV and n-csCMV is inappropriate because csCMV patients would require additional care and incur greater costs compared with patients in the n-csCMV state.

		To incorporate the difference between csCMV and n-csCMV, the weighted average of WJ02C-WJ02E non-elective long stay (cost of £3,100.47) has been updated for the csCMV state while the weighted average of the total WJ02C-WJ02E codes remains for the n-csCMV state (£1,969.53). These costs reflect the differences in severity and intensity of care between csCMV and n-csCMV patients. It should be noted to the committee that the choice of input for hospitalisation reflects a conservative assumption. It would be expected that the hospitalisation costs in the absence of CMV would be more general and therefore, in the absence of CMV, codes for infectious diseases may be inappropriate and too high. If a more generic cost code was used for the n-csCMV health state, the differences in hospitalisation costs between the health states would be wider and thus the assumption would favour maribavir.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

No additional issues have been identified

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

<table>
<tr><th>Key issue(s) in the ERG report that the change relates to</th><th>Company's base case before technical engagement</th><th>Change(s) made in response to technical engagement</th><th>Impact on the company's base-case incremental cost-effectiveness ratio (ICER)</th></tr>
<tr><td>Insert key issue number and title as described in the ERG report</td><td>Briefly describe the company's original preferred assumption or analysis</td><td>Briefly describe the change(s) made in response to the ERG report</td><td>Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.</td></tr>
<tr><td>Issue 8. Modelling of graft failure</td><td>Graft loss: Identification of error for events
An error was identified where the risk of graft loss of n-csCMV patients was calculated incorrectly as it was referencing the wrong cells in the calculations</td><td>Graft loss: Identification of error for events
In the post-TE model the calculation for graft loss risk in the csCMV and n-csCMV states has been corrected</td><td>Please note that all subsequent changes will include the correction to the error.
<table><tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr><tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Inc LYs</td><td>0.160</td><td>0.152</td><td>-0.008</td></tr><tr><td>Inc QALYs</td><td>0.131</td><td>0.125</td><td>-0.006</td></tr><tr><td>ICER</td><td>£15,337</td><td>£17,966</td><td>£2,630</td></tr></table></td></tr>
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<tr><td>Inc QALYs</td><td>0.153</td><td>0.143</td><td>-0.010</td></tr>
<tr><td>ICER</td><td>£9,303</td><td>£12,726</td><td>£3,423</td></tr>
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<tr>
<td>Issue 4. Structural assumptions in the company’s model</td>
<td>Model structure
Before the technical engagement (pre-TE) the model utilises a 3-state Markov model</td>
<td>Model structure
At its core the model in response to the engagement model retains a 3-state Markov model structure, however, the transitions between the n-csCMV and csCMV state (i.e., the clinically significant recurrences) have been</td>
<td>Changes to the model structure in isolation has minimal impact on the model results. Only once the updated structure is informed by updated recurrence probabilities can the impact of the model structure be observed.
<table>
<tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
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updated in the response to the technical engagement (post-TE) so recurrence depends on time since clearance. (Figure 1 and Figure **2**)

Inc costs	[redacted]	[redacted]	[redacted]
Inc LYs	0.160	0.152	-0.008
Inc QALYs	0.131	0.125	-0.006
ICER	£15,337	£17,966	£2,630

SOT	Pre-TE base case	After change	Difference
Inc costs	[redacted]	[redacted]	[redacted]
Inc LYs	0.185	0.172	-0.013
Inc QALYs	0.153	0.143	-0.010
ICER	£9,303	£12,726	£3,423

HSCT	Pre-TE base case	After change	Difference
Inc costs	[redacted]	[redacted]	[redacted]
Inc LYs	0.123	0.123	0
Inc QALYs	0.097	0.097	0
ICER	£29,471	£29,471	0

<table>
<tr>
<td>Issue 4. Structural assumptions in the company's model</td>
<td>Duration of Phase 1 Markov
The duration of the Phase 1 Markov was set to 52 weeks in the pre-TE</td>
<td>Duration of Phase 1 Markov
Following discussions from clinicians, data from OTUS and discussions during the technical engagement call it was deemed plausible that CMV events can extend to 78 weeks (18 months) in the post-TE model</td>
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<tr><td>Section 4.2.5 – page 90</td><td>Half-Cycle Correction
The pre-TE model does not include a half-cycle correction</td><td>Half-Cycle Correction
The post-TE model incorporates a half cycle correction from week 12 onwards. The half-cycle correction is not included before week 12 to not compromise the observations of the trial data in the first 8 weeks. Earlier inclusion of a half-cycle correction will result in clearance events occurring at week 4 which was criticised by the ERG.</td><td>
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<tr><td>ICER</td><td>£29,471</td><td>£39,748</td><td>£10,277</td></tr>
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<tr><td>Issue 5. Overestimation of recurrence in the model</td><td>Treatment efficacy: clearance
The pre-TE model allowed the inclusion of early CMV clearance (at week 4) and thus the week 4 and week 8 clearance estimates were sourced from the IPD analysis</td><td>Treatment efficacy: clearance
The post-TE model only allows for the first clearance event at week 8 as per the primary endpoint of the SOLSTICE trial. The clearance estimate is taken directly from the CSR. The model adjusts the clearance value for mortality so that the proportion of patients that clear at week 8 is aligned with the SOLSTICE trial.</td><td>
<table>
<tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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<tr><td>Inc LYs</td><td>0.185</td><td>0.187</td><td>0.002</td></tr>
<tr><td>Inc QALYs</td><td>0.153</td><td>0.154</td><td>0.001</td></tr>
<tr><td>ICER</td><td>£9,303</td><td>£8,887</td><td>-£416</td></tr>
</table>
<table>
<tr><th>HSCT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.123</td><td>0.141</td><td>0.018</td></tr>
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<table>
<tr><td>Inc QALYs</td><td>0.097</td><td>0.110</td><td>0.012</td></tr>
<tr><td>ICER</td><td>£29,471</td><td>£16,241</td><td>-£13,231</td></tr>
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</td>
</tr>
<tr>
<td>Issue 5. Overestimation of recurrence in the model</td>
<td>Treatment effect: Long-term recurrence probability
A constant rate of recurrence was applied for the duration of the Phase 1 Markov in the pre-TE model. The choice of recurrence rate applied depended on the most recent treatment patients achieved clearance with (i.e., if patients achieved clearance with maribavir their risk of recurrence was maribavir specific, however, any patient who had a retreatment in the maribavir arm and achieved clearance with IAT would have IAT rates of recurrence).</td>
<td>Treatment effect: Long-term recurrence probability
In the post-TE model, the rates of recurrence are no longer constant and now depend on time since clearance (

Figure 2). The assumption that patients have recurrence rates based on the most recent treatment they have achieved treatment with has been updated to only allow this in the first 12 weeks for patients who achieve clearance at week 8 (i.e., the recurrences for these patients between week 8 and 20). All other patients who achieve clearance after week 8 in the model or who achieve clearance at week 8 but have a recurrence post week 20 in the model have treatment agnostic</td>
<td>The following three changes to the base case are conducted simultaneously. It should be noted that when implementing these scenarios, the updated model structure has been utilised.

<table>
<tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.160</td><td>0.192</td><td>0.031</td></tr>
<tr><td>Inc QALYs</td><td>0.131</td><td>0.155</td><td>0.024</td></tr>
<tr><td>ICER</td><td>£15,337</td><td>-£4,568 (Dominates)</td><td>-£19,905</td></tr>
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<td>rates of recurrences (i.e., same in both treatment arms).</td>
<td rowspan="3">
<table>
<tr><th>SOT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.185</td><td>0.213</td><td>0.027</td></tr>
<tr><td>Inc QALYs</td><td>0.153</td><td>0.175</td><td>0.022</td></tr>
<tr><td>ICER</td><td>£9,303</td><td>-£5,118 (Dominates)</td><td>-£14,421</td></tr>
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<table>
<tr><th>HSCT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.123</td><td>0.160</td><td>0.037</td></tr>
<tr><td>Inc QALYs</td><td>0.097</td><td>0.124</td><td>0.027</td></tr>
<tr><td>ICER</td><td>£29,471</td><td>-£3,412 (Dominates)</td><td>-£32,883</td></tr>
</table>
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</tr>
<tr>
<td>Issue 5. Overestimation of recurrence in the model</td>
<td>Treatment effect: Source of recurrence risk
In the pre-TE model, all recurrence rates were takin from SOLSTICE</td>
<td>Treatment effect: Source of recurrence risk
In the post-TE model, recurrences are based on time since clearance. The recurrence rates for the first 12 weeks in the n-csCMV health state are informed by the recurrences from the SOLSTICE trial between week 8 and 20. From week 12 onwards in the n-csCMV health state, the recurrences are informed by data from OTUS.</td>
</tr>
<tr>
<td>Section 4.2.6.2.1 – page 98</td>
<td>Treatment effect: Adjusting SOLSTICE recurrence for mortality
SOLSTICE recurrence rates were taken as reported in the SOLSTICE CSR and IPD analysis</td>
<td>Treatment effect: Adjusting SOLSTICE recurrence for mortality
As requested by the ERG the SOLSTICE recurrence rates are adjusted for mortality. Note, the ERG also requested to adjust for discontinuation however there were no discontinuation for the patients considered (i.e., proportion of patients who clear at week and follow-up until week 20)</td>
</tr>
</table>

<table>
<tr>
<td>Issue 3. Assumption of time elapsed since transplant at baseline in the model</td>
<td>Time since transplant
Time since transplant included in model as integer year</td>
<td>Time since transplant
Time since transplant now taken from SOLSTICE and can be entered in days</td>
<td>
<table>
<tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.160</td><td>0.146</td><td>-0.014</td></tr>
<tr><td>Inc QALYs</td><td>0.131</td><td>0.121</td><td>-0.010</td></tr>
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<tr><td>Inc LYs</td><td>0.185</td><td>0.166</td><td>-0.019</td></tr>
<tr><td>Inc QALYs</td><td>0.153</td><td>0.139</td><td>-0.014</td></tr>
<tr><td>ICER</td><td>£9,303</td><td>£13,109</td><td>£3,806</td></tr>
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			Inc costs [redacted] [redacted] [redacted] Inc LYs 0.123 0.116 -0.007 Inc QALYs 0.097 0.093 -0.004 ICER £29,471 £30,820 £1,348
Issue 6. Modelling of mortality in stage 1 Markov	**Mortality: Phase 1 Markov and background age- and sex- related mortality** In the Phase 1 Markov, background age-and sex related mortality was added to health state specific mortality	**Mortality: Phase 1 Markov and background age- and sex-related mortality** In the post-TE model, background age-and sex related mortality have been removed from the Phase 1 Markov	**ITT** Inc costs [redacted] [redacted] [redacted] Inc LYs 0.160 0.153 -0.007 Inc QALYs 0.131 0.125 -0.005 ICER £15,337 £17,763 £2,426 **SOT** Inc costs [redacted] [redacted] [redacted] Inc LYs 0.185 0.173 -0.013 Inc QALYs 0.153 0.144 -0.009

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<table>
<tr><td>ICER</td><td>£9,303</td><td>£12,553</td><td>£3,250</td></tr>
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<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.123</td><td>0.123</td><td>0.000</td></tr>
<tr><td>Inc QALYs</td><td>0.097</td><td>0.098</td><td>0.000</td></tr>
<tr><td>ICER</td><td>£29,471</td><td>£29,204</td><td>-£268</td></tr>
</table>
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<tr>
<td>Issue 6. Modelling of mortality in stage 1 Markov</td>
<td>Mortality: Phase 1 Markov initial transition to dead state
Mortality events taken from the IPD analysis and events can occur at week 4</td>
<td>Mortality: Phase 1 Markov initial transition to dead state
Mortality events taken from IPD analysis with first mortality events occurs at week 8</td>
<td>Please note that in this scenario, age- and sex-related mortality are excluded in the first cycle (week4) but included in all other cycles.
<table>
<tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.160</td><td>0.152</td><td>-0.008</td></tr>
<tr><td>Inc QALYs</td><td>0.131</td><td>0.125</td><td>-0.006</td></tr>
<tr><td>ICER</td><td>£15,337</td><td>£17,813</td><td>£2,477</td></tr>
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<table>
<tr><th>SOT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.185</td><td>0.172</td><td>-0.013</td></tr>
<tr><td>Inc QALYs</td><td>0.153</td><td>0.143</td><td>-0.010</td></tr>
<tr><td>ICER</td><td>£9,303</td><td>£12,605</td><td>£3,302</td></tr>
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<table>
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<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.123</td><td>0.123</td><td>0.000</td></tr>
<tr><td>Inc QALYs</td><td>0.097</td><td>0.098</td><td>0.000</td></tr>
<tr><td>ICER</td><td>£29,471</td><td>£29,247</td><td>-£225</td></tr>
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<tr>
<td>Issue 7. Modelling of mortality in stage 2 Markov</td>
<td>Mortality: Phase 2
Assumed 5-year HMRN mortality rate continued until general population mortality rates were higher.</td>
<td>Mortality: Phase 2
Revised base case uses mortality data from Martin et al. 2010[3] with fitted survival curves to extrapolate beyond the 5 years of HMRN data.</td>
<td>
<table>
<tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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</table>

Inc LYs	0.160	0.163	0.003
Inc QALYs	0.131	0.131	0.000
ICER	£15,337	£17,126	£1,789

SOT	Pre-TE base case	After change	Difference
Inc costs	[redacted]	[redacted]	[redacted]
Inc LYs	0.185	0.166	-0.019
Inc QALYs	0.153	0.139	-0.014
ICER	£9,303	£13,109	£3,806

HSCT	Pre-TE base case	After change	Difference
Inc costs	[redacted]	[redacted]	[redacted]
Inc LYs	0.123	0.158	0.035
Inc QALYs	0.097	0.119	0.022
ICER	£29,471	£24,138	-£5,333

<table>
<tr>
<td>Issue 10. Estimation of utilities</td>
<td>Health-related quality of life: Methods to account for missing data
The pre-TE model did not utilise any methods to account for missing data</td>
<td>Health-related quality of life: Methods to account for missing data
Utility values were imputed using Multiple Imputation techniques including all randomised subject and adjusting for patients in the rescue arm (see response 10)</td>
<td>
<table>
<tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.160</td><td>0.152</td><td>-0.008</td></tr>
<tr><td>Inc QALYs</td><td>0.131</td><td>0.123</td><td>-0.008</td></tr>
<tr><td>ICER</td><td>£15,337</td><td>£18,311</td><td>£2,975</td></tr>
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<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.185</td><td>0.172</td><td>-0.013</td></tr>
<tr><td>Inc QALYs</td><td>0.153</td><td>0.147</td><td>-0.006</td></tr>
<tr><td>ICER</td><td>£9,303</td><td>£12,425</td><td>£3,122</td></tr>
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<table>
<tr><th>HSCT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.123</td><td>0.123</td><td>0.000</td></tr>
<tr><td>Inc QALYs</td><td>0.097</td><td>0.086</td><td>-0.011</td></tr>
<tr><td>ICER</td><td>£29,471</td><td>£33,242</td><td>£3,771</td></tr>
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<table>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Issue 10. Estimation of utilities</td><td>Health-related quality of life: Source for age general population utility
Age related utility decrement taken from Szende et al., (2014)</td><td>Health-related quality of life: Source for age general population utility
Age related utility decrement taken from Ara et al., (2010)</td><td>
<table>
<tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.160</td><td>0.152</td><td>-0.008</td></tr>
<tr><td>Inc QALYs</td><td>0.131</td><td>0.130</td><td>-0.001</td></tr>
<tr><td>ICER</td><td>£15,337</td><td>£17,329</td><td>£1,992</td></tr>
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<table>
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<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.185</td><td>0.172</td><td>-0.013</td></tr>
<tr><td>Inc QALYs</td><td>0.153</td><td>0.148</td><td>-0.004</td></tr>
<tr><td>ICER</td><td>£9,303</td><td>£12,282</td><td>£2,980</td></tr>
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<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.123</td><td>0.123</td><td>0.000</td></tr>
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Inc QALYs</td><td>0.097</td><td>0.101</td><td>0.004</td></tr>
<tr><td>ICER</td><td>£29,471</td><td>£28,386</td><td>-£1,086</td></tr>
</table>
</td></tr>
<tr><td>Issue 11. Estimation of costs</td><td>Costs: Hospitalisation costs
In the pre-TE model, csCMV hospitalisation costs were taken from the weighted average of WJ02A and WJ02B, while the n- state used the weighted average of WJ02C-WJ02.</td><td>Costs: Hospitalisation costs
The csCMV health state cost has been reduced (weighted average of non-elective long-stay WJ02C-WJ02E) so that the differences between the csCMV and n-csCMV health state is now lower.</td><td>
<table>
<tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.160</td><td>0.152</td><td>-0.008</td></tr>
<tr><td>Inc QALYs</td><td>0.131</td><td>0.125</td><td>-0.006</td></tr>
<tr><td>ICER</td><td>£15,337</td><td>£30,395</td><td>£15,058</td></tr>
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<table>
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<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.185</td><td>0.172</td><td>-0.013</td></tr>
<tr><td>Inc QALYs</td><td>0.153</td><td>0.143</td><td>-0.010</td></tr>
<tr><td>ICER</td><td>£9,303</td><td>£24,081</td><td>£14,778</td></tr>
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<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.123</td><td>0.123</td><td>0.000</td></tr>
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<tr><td></td><td></td><td></td><td>
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<tr><td>Inc QALYs</td><td>0.097</td><td>0.097</td><td>0.000</td></tr>
<tr><td>ICER</td><td>£29,471</td><td>£44,257</td><td>£14,786</td></tr>
</table>
</td></tr>
<tr><td>Issue 8. Modelling of graft failure</td><td>Graft loss: Risk of event
In the pre-TE model, risk of graft loss was estimated from the E-CMV category from Hakimi et al (2017)[1]</td><td>Graft loss: Risk of event
After discussions with the author, in the post-TE model, risk of graft loss was estimated from the L-CMV-6M category from Hakimi et al (2017)[1] which best aligns with the 258 days TST at baseline (Table 6)</td><td rowspan="2">These two changes were conducted simultaneously

<table>
<tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.160</td><td>0.157</td><td>-0.003</td></tr>
<tr><td>Inc QALYs</td><td>0.131</td><td>0.128</td><td>-0.002</td></tr>
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<tr><td>Inc LYs</td><td>0.185</td><td>0.180</td><td>-0.006</td></tr>
<tr><td>Inc QALYs</td><td>0.153</td><td>0.149</td><td>-0.004</td></tr>
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</table>
</td></tr>
<tr><td>Issue 8. Modelling of graft failure</td><td>Graft loss: Calculation of 4-week probabilities
It was assumed the risk of graft loss reported in Hakimi et al., (2017)[1] were reporting 2-year risks

The 4-week probability after converting the E-CMV category into 4-week probability is included below
csCMV: 0.44%
n-csCMV: 0.38%</td><td>Graft loss: Calculation of 4-week probabilities
After contacting the author, it was confirmed that the Hakimi et al., (2017)[1] study was reporting annual risk

The 4-week probability after converting the L-CMV-6M category into 4-week probability is included below
csCMV: 0.40%
n-csCMV: 0.13%</td></tr>
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<table>
<tr><td>Inc LYs</td><td>0.123</td><td>0.123</td><td>0.000</td></tr>
<tr><td>Inc QALYs</td><td>0.097</td><td>0.097</td><td>0.000</td></tr>
<tr><td>ICER</td><td>£29,471</td><td>£29,471</td><td>£0</td></tr>
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<tr>
<td>Issue 8. Modelling of graft failure</td>
<td>Graft loss: Duration of utility decrement
Utility decrement for graft loss applied as a one-off event</td>
<td>Graft loss: Duration of utility decrement
Utility decrement for graft loss applied every cycle for a lifetime horizon</td>
<td>
Please note that in this change, graft lost events only occur during the Phase 1 Markov
<table>
<tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.160</td><td>0.154</td><td>-0.006</td></tr>
<tr><td>Inc QALYs</td><td>0.131</td><td>0.126</td><td>-0.005</td></tr>
<tr><td>ICER</td><td>£15,337</td><td>£17,854</td><td>£2,518</td></tr>
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<tr><td>Inc LYs</td><td>0.185</td><td>0.174</td><td>-0.011</td></tr>
<tr><td>Inc QALYs</td><td>0.153</td><td>0.145</td><td>-0.008</td></tr>
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<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.123</td><td>0.123</td><td>0.000</td></tr>
<tr><td>Inc QALYs</td><td>0.097</td><td>0.097</td><td>0.000</td></tr>
<tr><td>ICER</td><td>£29,471</td><td>£29,471</td><td>£0</td></tr>
</table>
</td>
</tr>
<tr>
<td>Issue 8. Modelling of graft failure</td>
<td>Graft loss: Utility decrements from Vignette
Previously, the utility decrement for a graft loss event was sourced from data from the asymptomatic CMV category in the vignette study</td>
<td>Graft loss: Utility decrements from Vignette
Graft loss utility decrement is informed by the asymptomatic csCMV (cs-aCMV), symptomatic csCMV (cs-sCMV) and n-csCMV category in the vignette study</td>
<td>This change was run simultaneously with the above change to duration of graft loss utility decrement
<table>
<tr><th>ITT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.160</td><td>0.154</td><td>-0.006</td></tr>
<tr><td>Inc QALYs</td><td>0.131</td><td>0.126</td><td>-0.005</td></tr>
<tr><td>ICER</td><td>£15,337</td><td>£17,856</td><td>£2,519</td></tr>
</table>
<table>
<tr><th>SOT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr>
<tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Inc LYs</td><td>0.185</td><td>0.174</td><td>-0.011</td></tr>
<tr><td>Inc QALYs</td><td>0.153</td><td>0.145</td><td>-0.008</td></tr>
<tr><td>ICER</td><td>£9,303</td><td>£12,612</td><td>£3,310</td></tr>
</table>
</td>
</tr>
</table>

			<table><tr><th>HSCT</th><th>Pre-TE base case</th><th>After change</th><th>Difference</th></tr><tr><td>Inc costs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Inc LYs</td><td>0.123</td><td>0.123</td><td>0.000</td></tr><tr><td>Inc QALYs</td><td>0.097</td><td>0.097</td><td>0.000</td></tr><tr><td>ICER</td><td>£29,471</td><td>£29,471</td><td>£0</td></tr></table>
Company's base case following technical engagement (or revised base case)	Incremental QALYs: 0.203	Incremental costs: [redacted]	Maribavir dominates IAT (£-3,358)

Sensitivity analyses around revised base case

Summary of updated results

1. ITT population

1.1 Pre-technical engagement deterministic results (discounted)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Maribavir	[redacted]	8.39	6.02	2,004	0.160	0.131	15,337

IAT	[redacted]	8.23	5.89				

1.2 Post-technical engagement deterministic results (discounted)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Maribavir	[redacted]	8.72	6.35	-£682	0.248	0.203	Maribavir dominates IAT (-3,358)
IAT		8.48	6.15				

1.3 Pre-technical engagement Markov trace (Phase 1)

1.4 Post-technical engagement Markov trace (Phase 1)

[redacted]

1.5 Pre-technical engagement csCMV health state occupancy

1.6 Post-technical engagement csCMV health state occupancy

1.7 Pre-technical engagement DSA tornado

1.8 Post-technical engagement DSA tornado

Technical engagement response form

[redacted]

1.9 Pre-technical engagement PSA results

Technical engagement response form

	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER (£/QALY)	Probability cost-effective at £20,000 (%)	Probability cost-effective at £30,000 (%)
Maribavir	[redacted]	6.03	2,176	0.127	17,156	[redacted]	[redacted]
IAT		5.91					

1.10 Post-technical engagement PSA results

	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER (£/QALY)	Probability cost-effective at £20,000 (%)	Probability cost-effective at £30,000 (%)
Maribavir	[redacted]	6.39	-391	0.201	Maribavir dominates IAT (-£1947)	[redacted]	[redacted]
IAT		6.19					

1.11 Pre-technical engagement PSA (ICER scatterplot)

1.12 Post-technical engagement PSA (ICER scatterplot)

1.13 Pre-technical engagement PSA (CEAC)

1.14 Post-technical engagement PSA (CEAC)

2. SOT population

Pre-technical engagement deterministic results (discounted)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Maribavir	[redacted]	9.41	7.05	1,422	0.185	0.153	£9,303
IAT	[redacted]	9.23	6.90				

Post-technical engagement deterministic results (discounted)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Maribavir	[redacted]	8.76	6.722	-£951	0.248	0.222	Maribavir dominates IAT (-£4,281)
IAT		8.51	6.499				

3. HSCT population

Pre-technical engagement deterministic results (discounted)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Maribavir	[redacted]	6.85	4.48	2,873	0.123	0.097	29,471
IAT		6.73	4.38				

Post-technical engagement deterministic results (discounted)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Maribavir	[redacted]	8.68	5.806	-281	0.249	0.175	Maribavir dominates IAT (£-1,608)
IAT		8.43	5.631				

4. Scenario Analysis

	Scenario; Description	Incremental costs (£)	Incremental LYs	Incremental QALYs	Incremental Net Monetary Benefit	ICER (£/QALY) gained	Additional Notes
Base-case		[redacted]	**0.248**	**0.203**	**£4,746**	**Dominates**	
1	Comparator: Foscarnet only with IAT ToT	[redacted]	**0.248**	**0.203**	**£20,527**	**Dominates**	
2	Intervention: Retreatment with maribavir in the intervention (maribavir) arm	[redacted]	**0.516**	**0.424**	**£24,937**	**Dominates**	
3	Costs: No discontinuation after retreatment	[redacted]	**0.248**	**0.203**	**£11,535**	**Dominates**	
4	Study 303 with imputation (week 0 - 20)	[redacted]	**0.248**	**0.199**	**£4,665**	**Dominates**	
5	Risk of GvHD	[redacted]	**0.248**	**0.151**	**£3,415**	**Dominates**	
6	Graft loss - disutility values from literature	[redacted]	**0.248**	**0.202**	**£4,721**	**Dominates**	
7	Exclude adverse events	[redacted]	**0.248**	**0.198**	**£3,462**	**£2,536**	
8	Exclude duration of adverse events	[redacted]	**0.248**	**0.294**	**£6,561**	**Dominates**	
9	Societal perspective	[redacted]	**0.248**	**0.203**	**£4,909**	**Dominates**	
10	Retransplant mortality: Off	[redacted]	**0.243**	**0.201**	**£4,713**	**Dominates**	
11	Survival curves: Gompertz	[redacted]	**0.248**	**0.203**	**£4,742**	**Dominates**	[redacted]
12	Risk of leukaemia relapse	[redacted]	**0.203**	**0.173**	**£3,433**	**£123**	
13	Recurrence - Study 303 (pooled recurrence) and OTUS	[redacted]	**0.210**	**0.172**	**£1,355**	**£12,120**	
14	Half cycle correction	[redacted]	**0.252**	**0.207**	**£5,781**	**Dominates**	
15	Mortality: Phase 1 - Literature	[redacted]	**0.017**	**0.043**	**£3,766**	**Dominates**	
16	Mortality: Phase 2 - Pre-TE method	[redacted]	**0.221**	**0.185**	**£4,392**	**Dominates**	

17	No immediate retransplant	[redacted]	**0.259**	**0.208**	**£4,753**	**Dominates**	[redacted]
18	Adjusting n-csCMV mortality risk between Phase 1 and Phase 2	[redacted]	**0.302**	**0.247**	**£5,583**	**Dominates**	
19	Phase 2 Markov starts at week 52	[redacted]	**0.253**	**0.207**	**£5,072**	**£9,724**	

5. Other summaries in the model

- In the deterministic sheet, breakdown of costs, QALYs and health state occupancy are provided for the SOT and HSCT population
- In the PSA sheet, the PSA results sheet summaries can be found for the SOT and HSCT populations. The sheet also includes convergence plots.

References

1. Hakimi, Z., et al., *Burden of cytomegalovirus disease in solid organ transplant recipients: a national matched cohort study in an inpatient setting.* Transpl Infect Dis, 2017. **19**(5).
2. Camargo, J.F., 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, 2018. **24**(4): p. 806-814.
3. Martin, P.J., et al., *Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation.* J Clin Oncol, 2010. **28**(6): p. 1011-6.
4. NICE, *Letermovir for preventing cytomegalovirus disease after a stem cell transplant (TA591).* 2019.
5. Dobrer S, e.a. *Impact of Magnitude and Duration of Cytomegalovirus Viremia on Graft and Mortality Outcomes in Transplant Recipients: Genome Canada Precision Medicine Analysis*. in *8th International Congenital CMV Conference & 18th International CMV Workshop. March 28 – April 1, 2022. Virtual*. 2022.
6. Miller, R.J.H., et al., *Outcomes in patients undergoing cardiac retransplantation: A propensity matched cohort analysis of the UNOS Registry.* J Heart Lung Transplant, 2019. **38**(10): p. 1067-1074.
7. Suarez-Pierre, A., et al., *Long-term Survival After Heart Transplantation: A Population-based Nested Case-Control Study.* Ann Thorac Surg, 2021. **111**(3): p. 889-898.
8. Panchal, H., et al., *Expanded criteria donor kidneys for retransplantation United Network for Organ Sharing update: proceed with caution.* Transpl Int, 2015. **28**(8): p. 990-9.
9. Gondos, A. and H. Brenner, *Relative survival of transplant patients: quantifying surplus mortality among renal transplant recipients compared with the general population.* Transplantation, 2011. **92**(8): p. 913-7.
10. Kawut, S.M., et al., *Outcomes after lung retransplantation in the modern era.* Am J Respir Crit Care Med, 2008. **177**(1): p. 114-20.
11. Iguidbashian, J., et al., *Survival following lung transplantation: A population-based nested case-control study.* J Card Surg, 2022. **37**(5): p. 1153-1160.
12. Kim, H.J., et al., *Impact of MELD on waitlist outcome of retransplant candidates.* Am J Transplant, 2010. **10**(12): p. 2652-7.
13. Aberg, F., et al., *Differences in long-term survival among liver transplant recipients and the general population: a population-based Nordic study.* Hepatology, 2015. **61**(2): p. 668-77.
14. Hahn, T., 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. **26**(35): p. 5728-34.
15. Cantoni, N., et al., *Evidence for a bidirectional relationship between cytomegalovirus replication and acute graft-versus-host disease.* Biol Blood Marrow Transplant, 2010. **16**(9): p. 1309-14.
16. Pidala, J., et al., *The global severity of chronic graft-versus-host disease, determined by National Institutes of Health consensus criteria, is associated with overall survival and non-relapse mortality.* Haematologica, 2011. **96**(11): p. 1678-84.
17. Szende, A., in *Self-Reported Population Health: An International Perspective based on EQ-5D*, A. Szende, B. Janssen, and J. Cabases, Editors. 2014: Dordrecht (NL).
18. Ara, R. and J.E. Brazier, *Populating an economic model with health state utility values: moving toward better practice.* Value Health, 2010. **13**(5): p. 509-18.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in section 1.3 and 1.4 of the executive summary at the beginning of the ERG report. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm on 16 May 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating refractory or resistant cytomegalovirus infection and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Sophie Gillett
2. Name of organisation	Clinical Virology Network
3. Job title or position	Virology consultant
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with refractory or resistant cytomegalovirus infection? ☐ A specialist in the clinical evidence base for refractory or resistant cytomegalovirus infection or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

8. What is the main aim of treatment for refractory or resistant cytomegalovirus infection ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To prevent CMV disease, ill health and death.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Clearance or reduction to non-significant levels of CMV DNA in blood, or resolution of CMV associated symptoms/disease.
10. In your view, is there an unmet need for patients and healthcare professionals in refractory or resistant cytomegalovirus infection?	Yes
11. How is refractory or resistant cytomegalovirus infection currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Depends on the type of antiviral resistance. Current options available following the most common form of resistance to first line treatment (Ganciclovir/valganciclovir) are limited to foscarnet and cidofovir, both of which are renal toxic and myelosuppressive. National guidelines are available for management of CMV following SOT (British Transplantation society guidelines) which includes the treatment of resistant CMV. Otherwise, professional opinion predominates. This technology would add a further treatment option in patients with difficult to treat CMV infection.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	Currently unavailable as not licensed. Maribavir would be used as a second or third-line option in R/R CMV infections, on specialist advice. Could be used for inpatient or outpatient care, but on specialist advice only.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Minimal investment required to introduce technology as no specific infrastructure or equipment needed to administer.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes – as an option for a specific group of patients with R/R CMV, particularly where the side effects of current second-line antiviral options make them unfavourable in certain patient groups with co-morbidities. Yes – in the group described above Yes – in the group described above
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not to my knowledge.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	In cases where an oral option is preferable e.g. outpatient care or difficult IV access, maribavir may be preferable to current second line IV antiviral therapies.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes – resistance testing will be required to continue therapy and monitoring of CMV viral load. No additional testing to that currently required for managing R/R CMV infection.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Oral option, so benefits from not requiring IV treatment.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes – as different mode of action. Reduction in renal toxicity associated with current second-line therapies.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Main side effect of dysgeusia unlikely to have significant impact on quality of life. Other common side effects of nausea, vomiting and diarrhoea may impact minimally on quality of life in the short term whilst on treatment, and appear to occur at a similar rate to other anti-CMV drugs. Side effects of bone marrow suppression and renal impairment appear less common with maribavir than with other anti-CMV drugs.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	High proportion of patients with R/R CMV in SOLSTICE trial in the IAT arm continued on ganciclovir/valganciclovir – in clinical practice this proportion may be lower. CMV DNA clearance and symptom control are most important outcomes and these were measured.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Not enough data from real-world experience to compare.
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	HIV positive patients Paediatric patients

• lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. **Find more general information about the Equality Act and equalities issues here.**	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1: **Impact of time since transplant on the clinical data and economic model**	Dependent on the difference in mean time since transplant for both arms, but as mortality rates decrease over time following both HSCT and SOT transplants, agree that ICER may be underestimated and this needs correcting for. However, unable to comment on the extent to which this may impact on the ICER without knowing the difference in mean time since transplant in both arms.
Key Issue 2: **Trial conduct and design leading to uncertainty and potential overestimates of maribavir efficacy**	No additional comments.

Key Issue 3: Assumption of time elapsed since transplant at baseline in the model	Agree that type of treatment is less likely to impact on probability of recurrence, rather it is affected by factors such as level of immunosuppression, time since transplant, type of transplant.
Key Issue 4: Structural assumptions in the company's model	No additional comments.
Key Issue 5: Overestimation of recurrences in the model	No additional comments.
Key Issue 6: Modelling of mortality in stage 1 Markov	No additional comments.
Key issue 7: Modelling of mortality in stage 2 Markov	No additional comments.
Key Issue 8: Modelling of graft failure	No additional comments.
Key Issue 9: Modelling of disease complications	No additional comments.

Key Issue 10: Estimation of utilities	No additional comments.
Key Issue 11: Estimation of costs	No additional comments.
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Treatment options for refractory or resistant CMV infection following transplant are currently limited and involve drugs with significant side effects. A further option with less significant side effects could improve the outcome of many of these patients.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

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We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm on 16 May 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating refractory or resistant cytomegalovirus infection and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Joanna Moore
2. Name of organisation	British Association for the Study of the Liver (BASL) and British Liver Transplant Group (BLTG)
3. Job title or position	Consultant Hepatologist and Honorary Senior Clinical Lecturer
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with refractory or resistant cytomegalovirus infection? ☐ A specialist in the clinical evidence base for refractory or resistant cytomegalovirus infection or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ I wrote the draft submission for BASL but this was prior to receiving the full documents therefore as discussed on the call yesterday I would prefer this updated version to be used instead please.

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
8. What is the main aim of treatment for refractory or resistant cytomegalovirus infection ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Cytomegalovirus (CMV) is a herpesvirus which can cause infection and tissue-invasive disease in immunocompromised patients after solid-organ transplantation. The aim of treatment would be to prevent CMV disease and improve end organ damage should it have progressed to that extent.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Serial CMV PCR is an objective measure of the degree of viraemia and response. In patients with CMV disease, I would consider titres having fallen below 10% of the initial titre at diagnosis (one Log10 drop) and if end-organ damage is clinically and biochemically improving to be indicators of treatment response
10. In your view, is there an unmet need for patients and healthcare professionals in refractory or resistant cytomegalovirus infection?	There is an unmet need if there is resistance to ganciclovir, foscarnet and cidofovir but in my view, in liver transplant patients, such a need for Maribavir would be rare.
11. How is refractory or resistant cytomegalovirus infection currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The treatment will vary slightly on the solid organ transplant (SOT). For liver transplant recipients, management involves reducing immunosuppression where possible and giving oral (eg valganciclovir) or intravenous antiviral drugs (eg ganciclovir) depending on the severity of illness. • Are any clinical guidelines used in the treatment of the condition, and if so, which? Many liver transplant units in the UK will have local guidance. Other guidance; Razonable R, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019

	Kotton CN, Kumar D, Caliendo AM et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation. 2018 Jun;102(6):900-931 British Transplantation Society. The Prevention and Management of CMV Disease after Solid Organ Transplantation. July 2015. Available from https://bts.org.uk/wp-content/uploads/2016/09/14_BTS_CMV_3RDE-1.pdf • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) Pathways of care are not well defined and will vary between centres in the UK and also with the organ transplanted. • What impact would the technology have on the current pathway of care? It is proposed that Maribavir would be used to treat refractory or resistant CMV infection after transplant so could be an additional option in this scenario.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	It is a proposed new anti-CMV agent but could be incorporated in current treatment strategies. • How does healthcare resource use differ between the technology and current care? I can't comment fully on this but I would not expect healthcare resource use to differ greatly from current care. I also note that Maribavir is an oral preparation so if patients were well, it could be administered as an outpatient. • In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.) This would be used in specialist care eg transplant teams.

	• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) I can't comment fully on this but I would think very little and would revolve more about dissemination of product characteristics and when it should be used.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Do you expect the technology to provide clinically meaningful benefits compared with current care? Possibly. I note the recently completed phase III trial on ClinicalTrials.Gov (NCT02931539) and the FDA Briefing Document October 2021. The phase III trial demonstrated that maribavir was statistically superior to Investigator Assigned Treatment (IAT) for the primary endpoint which was clearance of CMV DNA from plasma in a population which had refractory CMV and some who had CMV resistance. In a subgroup analysis in patients who had 'refractory' disease' there was no statistical significance however over IAT. • Do you expect the technology to increase length of life more than current care? Possibly - assuming currently used treatments for refractory disease eg Foscarnet are not tolerated/don't work • Do you expect the technology to increase health-related quality of life more than current care? Only potentially in the small number of patients who would require its use
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I can't comment fully on this but not for a liver transplant cohort. It would be expected it could be used in patients with resistance/refractory disease to current treatments. I am aware of the subgroup analysis referred to in the FDA briefing report above.

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It is an oral preparation which would negate the need for inpatient care if the patient was well yet had resistant/refractory disease. Maribavir targets the UL97 kinase which phosphorylates ganciclovir and aciclovir so these drugs should not be used in combination.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	CMV viral loads (often PCR) are used to guide when to start and stop treatment. This would continue and not be different to current practice.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Unable to comment on this.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Assuming the results of the SOLSTICE trial are borne out in clinical practice, this could have a significant impact as options are currently limited for this group. • Is the technology a 'step-change' in the management of the condition? See previous comment. • Does the use of the technology address any particular unmet need of the patient population? Again, please see comment above.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Reading the briefing documents it would appear the technology is well tolerated with taste disturbance being the main side effect reported.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Do the clinical trials on the technology reflect current UK clinical practice? Having reviewed the briefing documents, it would seem similar to current UK practice with the choice of antivirals given. Treatment duration was for 8 weeks which is often longer than needed but is the same for both arms. • What, in your view, are the most important outcomes, and were they measured in the trials? The most important outcomes should be reduction in viral load and/or improvement in clinical symptoms and biochemistry as relevant. The primary outcome in the trial seems reasonable; 'Confirmed CMV viremia clearance was defined as plasma CMV DNA concentration less than (<) lower limit of quantification (LLOQ) that is, <137 International Units per milliliter (IU/mL) when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive post baseline samples, separated by at least 5 days. ' • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? N/A • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? I can't comment fully on this. Not that I am aware of from the briefing documents.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Similar.

	The majority of liver transplant patients would be expected to respond to valganciclovir/ganciclovir however.
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	No issues any different to current care

Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1: **Impact of time since transplant on the clinical data and economic model**	I would agree with the ERG report that time since transplant is relevant and there is decreasing risk of CMV infection with increasing time since transplant. Symptoms are rare more than 50 days post transplant assuming the patient has not received antiviral drugs.
Key Issue 2: **Trial conduct and design leading to uncertainty and potential overestimates of maribavir efficacy**	A large proportion of patients in the IAT arm were assigned to a CMV treatment for which they were resistant. I acknowledge the comment in the ERG report that this could lead to an overestimate of the relative efficacy of maribavir. If it is anticipated maribavir will be used for patients with refractory/resistant disease (where in clinical practice foscarnet is often then tried) I think it is important to identify its efficacy in this cohort. In clinical practice in the UK, resistance testing is often prompted by persistent or increasing viral load after a therapeutic dosage and compliance with ganciclovir or valganciclovir eg 2-4 weeks. In SOT, resistance to ganciclovir/valganciclovir may occur in up to 3% of recipients.

Clinical expert statement

Key Issue 3: Assumption of time elapsed since transplant at baseline in the model	I agree with the ERG report that estimating the cost effectiveness when given immediately after surgery is flawed. As above, clinical outcome varies as time from transplant elapses. Symptoms due to primary disease may occur as early as 20 days and are rare more than 50 days post transplant. Prophylaxis is offered in SOT for at least 3 months after transplant in vulnerable groups.
Key Issue 4: Structural assumptions in the company's model	The frequency of CMV disease varies for example, based on the intensity of immunosuppression and definition. The ERG report comments about the stage 1 and 2 Markov (dead/alive) model are acknowledged.. There is a risk of late onset CMV disease and recurrences throughout a patients life.
Key Issue 5: Overestimation of recurrences in the model	I would agree that the company's assumption that the 4 weekly probability of recurrence at the end of the trial period is the same until week 52 is flawed. Factors impacting on recurrence include for example the degree of immunosuppression and time after transplant.
Key Issue 6: Modelling of mortality in stage 1 Markov	No additional comments to the ERG report.
Key issue 7: Modelling of mortality in stage 2 Markov	No additional comments to the ERG report.
Key Issue 8: Modelling of graft failure	I would agree with the ERG report that it would be unusual for graft failure within 4 weeks . I also agree that the company's assumption that 100% of patients with graft failure get a second transplant is not correct. These patients are often sick and a second transplant may not be possible. Graft failure can occur over 12 months after transplant.

	There are conflicting reports about the impact of CMV on graft outcomes. Graft failure is usually only seen when rejection is also present in the context of persistent CMV viraemia.
Key Issue 9: Modelling of disease complications	These comments are largely around HSCT patients which is outside my area of expertise.
Key Issue 10: Estimation of utilities	This is outside my area of expertise.
Key Issue 11: Estimation of costs	See below my comment that ganciclovir can be administered via a peripheral cannula and central access is not required. I would agree with the comment that foscarnet would be the most relevant comparator to maribavir and a scenario analysis is performed where the first line IAT treatment consists of the cost of foscarnet.
Are there any important issues that have been missed in ERG report?	In the 'care pathway', cidofovir is not mentioned as an option for treatment though it is added in the body of the text. It is an option for treatment. Comments were made about central line access being needed/cost of ICU time. For ganciclovir this is very simply given on any ward via a peripheral cannula.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Maribavir is an oral preparation and therefore has ease of administration
- There is a need in the small numbers of patients with resistant or refractory disease who have had a solid organ transplant provided Maribavir is demonstrated to be effective

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with the condition or caring for a patient with the condition. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.; section 1.1 and 1.4.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **16 May 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with refractory or resistant cytomegalovirus infection

Table 1 About you, refractory or resistant cytomegalovirus infection, current treatments and equality

1. Your name	**Steve Rothberg**
2. Are you (please tick all that apply)	☒ A patient who had cytomegalovirus infection? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with refractory or resistant cytomegalovirus infection ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Anthony Nolan
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing a patient expert statement

Patient expert statement

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience. Please specify what other experience: I am drawing on others' experiences ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with refractory or resistant cytomegalovirus infection? **If you are a carer (for someone with refractory or resistant cytomegalovirus infection) please share your experience of caring for them**	I was diagnosed with AML on 12 March 2009. I completed four cycles of chemotherapy over the next 5 months and was discharged in August 2009. In March 2010, my relapse was diagnosed and I was advised that a transplant was needed to save my life. I had my transplant (matched unrelated donor) on 17 September 2010. I was discharged on 6 October 2010, by which time I had spent 150 nights in hospital since my original diagnosis 17 months earlier. A week later ,I was advised that my CMV had reactivated. My CMV reactivated 25 days after my transplant. Unlike many who suffer CMV reactivation, I did not experience any additional physical symptoms from CMV (or side-effects of the medicines) beyond those symptoms associated with being just 4 weeks since transplant. In terms of mental wellbeing, however, the CMV reactivation was a terrible setback for me, my wife (my carer) and my daughters (at that point aged 13 and 11). I had been progressing well since transplant but after so much treatment over such a long period, any negative news comes as a bitter blow.

	Ten days later (35 days after transplant) my CMV level was back under control but 5 days after that (40 days after transplant) the levels were really high again, even higher than during the initial reactivation. Practically, this meant readmission to hospital for IV treatment. Emotionally, my family and I started to feel as though my CMV might prove to be an insurmountable problem. After the failure of my first round of AML treatment, the fear that the transplant would also not succeed was inescapable.
7a. What do you think of the current treatments and care available for refractory or resistant cytomegalovirus infection on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	For my first reactivation, I took a course of Valganciclovir tablets at home. When this treatment failed to control my CMV, I was prescribed a one-week course of IV Ganciclovir, which also meant readmission to hospital. I was also extremely distressed about the prospect of a return to hospital. With my immunity so compromised by transplant, I had decided to isolate myself from everybody except my wife and daughters. I lived this way for 6 months because the risk of catching an infection was something that terrified me but this risk was also something that I felt I could mitigate by self-imposed isolation. Clinic trips terrified me. I wore a mask and avoided touching any surfaces. Because my CMV reactivated so soon after transplant, my immunity was still extremely compromised, even more so by my initial course of valganciclovir. The need to return to hospital, without the special isolation arrangement in the transplant unit, was therefore very stressful for me. The reality was even worse than I feared. The familiar pressure on beds meant that there was no haematology bed for me and I was an ‘outlier’ on a ward that was not specialist in my condition. I went all day without my regular medicines. Staff are so busy and the consequence for me was this chaotic readmission. To make matters worse, I initially had to share toilet facilities. It’s hard to convey just how frightening this was for a vulnerable immuno-suppressed patient.

	After a couple of days, I was moved to a side-room which was an immense relief to me but it meant that a precious side room was now occupied by an immuno-compromised patient whose active treatment was for just 3 hours a day. Then, 7 days after readmission, I was told that I had to move out of my side-room and into a bay because seasonal flu had caused even greater pressure on beds than normal. I point-blank refused to go into a shared bay and, after some difficult discussion, I was discharged. In the end, my CMV levels dropped and, though the harm to my mental wellbeing (and that of my carer and daughters) was significant, I was lucky enough not to contract the infection that could have severely complicated my recovery or even cost me my life.
8. If there are disadvantages for patients of current NHS treatments for refractory or resistant cytomegalovirus infection (for example, how maribavir is given or taken, side effects of treatment, and any others) please describe these	If IV Ganciclovir had failed to control my CMV, I would have been prescribed foscarnet which commonly has very severe side-effects. A fellow patient told me that associated sickness and diarrhoea made it by far the worst part of his treatment, including chemotherapy and conditioning pre-transplant. His resistant CMV and the after-effects of taking foscarnet caused him to have to give up work and several years later his fatigue is still overwhelming.
9a. If there are advantages of maribavir over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	The treatments that transplant patients endure – 150 nights in hospital in my case – are extremely prolonged but a successful transplant gives us a realistic chance of a return to normal life, in my case to be a parent and a husband again and to return to work to be economically active and to pursue professional ambitions. Current treatments for resistant CMV steal that prospect from transplant patients just as we dare to raise our hopes that a return to normal life is within reach. We need treatments that do not require hospitalisation, which harms mental wellbeing and carries a life-threatening risk of infection, and that are more effective than current options and less toxic. As

9c. Does maribavir help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	an oral therapy that can be taken at home and with greater efficacy, maribavir represents a significant step forward for transplant patients in the treatment of resistant CMV.
10. If there are disadvantages of maribavir over current treatments on the NHS please describe these. For example, are there any risks with maribavir? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from maribavir or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	CMV positive stem cell transplant patients, whose CMV reactivation is not prevented by the prophylactic (letermovir) and not then controlled by the only oral medicine available (valganciclovir), will benefit the most. It is possible that maribavir, had it been available, may have offered an alternative to my hospital readmission.
12. Are there any potential equality issues that should be taken into account when considering cytomegalovirus infection and maribavir? Please explain if you think any groups of people with this condition are particularly disadvantaged	

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Key Issue 1: **We consider patient perspectives may particularly help to address this issue** **Impact of time since transplant on the clinical data and economic model** The ERG consider mean time since transplant was imbalanced in the main clinical trial which might bias the results. The ERG suggests the data is adjusted to correct the imbalance.	My CMV reactivated 25 days after my transplant. I took a course of Valganciclovir tablets at home. Ten days later (35 days after transplant) my CMV level was back under control but 5 days after that (40 days after transplant) the levels were really high again, even higher than during the initial reactivation. I was prescribed a one-week course of IV Ganciclovir, which also meant readmission to hospital. I wish to highlight how the clinical trial reports ignore the chaotic reality of readmitting a recent transplant patient, who is still severely immune-compromised and psychologically extremely vulnerable, into a hospital that is stretched to its limits and desperately short of beds.

Key Issue 2: **Trial conduct and design leading to uncertainty and potential overestimates of maribavir efficacy** The trial was an open label design and some outcomes were subjectively assessed. The ERG suggests using Kaplan Meier data (rather than response rates) and using the prespecified analysis (rather than a post hoc analysis) will provide more robust estimates.	
Key Issue 3: Assumption of time since transplant at baseline in the model is unclear The ERG is unclear about the company's assumption of mean time since transplant at baseline in the model. It suggests the company's model is adjusted to be in line with the assumptions around time since transplant.	
Key Issue 4: Structural assumptions in the company's model The ERG note the company model assumes the infection can recur many times, but this is in contrast to the way recurrence is reported in the trial. The ERG suggest alternatives of how data could be used in the model to correct this uncertainty.	
Key Issue 5: Recurrences in the model have been overestimated The ERG believe the way the company have used recurrence data from the trial will bias the results. It suggests an alternative approach.	
Key Issue 6: Modelling of mortality in stage 1 Markov The ERG does not agree with the company's approach to modelling survival and suggests an alternative approach.	

Patient expert statement

Key Issue 7: Modelling of mortality in stage 2 Markov The ERG does not agree with the company's long term assumptions of survival and suggests an alternative approach.	
Key Issue 8: **Modelling of graft failure** **We consider patient perspectives may particularly help to address this issue** The ERG does not agree with the company's assumptions on graft failure and suggests an alternative approach.	I do not have experience of graft failure
Key Issue 9: **Modelling of disease complications** **We consider patient perspectives may particularly help to address this issue** The ERG does not agree with the company's approach to estimate the impact of underlying diseases and suggests an alternative approach.	I do not have appropriate experience to offer
Key Issue 10: **Estimation of utilities** The ERG does not agree with the company's approach for estimating health-state utility values and suggests an alternative approach.	
Key Issue 11: **Estimation of costs** The ERG considers the costs of IAT retreatment are overestimated in the company's model and suggests an alternative approach.	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Current treatments for CMV reactivation have serious side effects which cause severe problems for patients.
- Resistant post-transplant CMV infection affects quality of life and causes immuno-compromised patients to return to hospital without the protections against infection associated with a transplant unit
- The experience of post-transplant CMV reactivation and especially resistant infection has a significant impact on mental wellbeing for both patients and their families.
- High pressure on beds means hospital readmission with resistant post-transplant CMV infection is difficult to manage and expensive for the hospital.
- Patients, their families and the hospital itself would therefore benefit significantly from a more effective treatment which patients can take orally at home.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with the condition or caring for a patient with the condition. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.; section 1.1 and 1.4.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

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- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **16 May 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with refractory or resistant cytomegalovirus infection

Table 1 About you, refractory or resistant cytomegalovirus infection, current treatments and equality

1. Your name	Tim Wright
2. Are you (please tick all that apply)	☐X A patient with refractory or resistant cytomegalovirus infection? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with refractory or resistant cytomegalovirus infection ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐X Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐X I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ X I have not completed part 2 of the statement

6. What is your experience of living with refractory or resistant cytomegalovirus infection ? **If you are a carer (for someone with refractory or resistant cytomegalovirus infection) please share your experience of caring for them**	I received a Bone marrow transplant in Oct 2014, which did not engraft, requiring me to have a rescue stem cell transplant in Nov 2014. I was able to go home in Dec 2014, however I became unwell and as re-admitted 4 days later, where it was found that my CMV had reactivated. I had a fever, was very tired and had bowel problems. As a result of the CMV after my transplant, I remained in hospital for a total of five and a half months, which psychologically was extremely difficult. I had very little social interaction, other than 2 visits per day and not everyday was there someone to visit. The treatment also left me very weak and I lost a lot of muscle mass, which resulted in difficulty in walking. With the CMV on top of my transplant it took me a lot longer to recover and I didn't get back to an independent life for over a year. it took a further 3 years before I could return to any physical social activities (I play 6-a-side football and used to belong to a golf club, playing twice a week) I was very lucky, in a way, as I was divorced and had moved back in with my parents, which meant i had no financial worries about a house, mortgage and bills, but other patients will. However, I still had other financial concerns and children at university. I wasn't able to return to my previous field of work as a qualified Warehouse and Transport Manager and ultimately it took me another 4 years, before I was able to return to work. I now work in the NHS as a Cancer Information and Support Officer at Queen Elizabeth Birmingham. As part of my research for this submission, I have been able to speak with other patients and they have reported similar experiences.

7a. What do you think of the current treatments and care available for refractory or resistant cytomegalovirus infection on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	For my initial treatment, I was commenced on Foscarnet treatment due to my high viral load, which required me to have 3 x IV doses per day at 8 hour intervals. Foscarnet is a particularly unpleasant drug to receive, as in my case in burned as it passed through my veins and had some vomiting. Receiving Foscarnet is also time-consuming as you require large amounts of fluids afterwards. This meant that treatment consumed most of my day. My CMV was very resistant and I was unable to leave the hospital for an extra 7 weeks. At that point my CMV had improved enough to allow me to drop to 2 doses per day and the hospital allowed me out on day release to travel and stay at home, which was a 20 mile round journey, during the day, However, I left at 9:30am to return for my second dose at 6pm, spending the night back in the hospital. The whole period was psychologically difficult and caused a great deal of time and cost to my family and friends. Having spoken to other patients, who have also experienced refactory or resistant CMV infection, many of the treatment seem to be quite time consuming and require you to be a hospital inpatient, not to mention very expensive and then you add the cost of being a prolonged inpatient in an isolation ward (not a regular one)
8. If there are disadvantages for patients of current NHS treatments for refractory or resistant cytomegalovirus infection (for example, how maribavir is given or taken, side effects of treatment, and any others) please describe these	One significant disadvantage of treatment options that I have experienced is the need to spend prolonged periods of time in hospital receiving treatment. Not being at home in your own bed, surrounded by your family and friends and eating your own food, has a significant impact. The uncomfortable admission of the current drugs and associated side effects on your body, coupled with monotonous inpatient periods.

9a. If there are advantages of maribavir over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does maribavir help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**Being able to receive the treatment at home would be a great advantage to a patient and the psychological and social burden would be removed, as well as some of the unpleasant side effects.** **Psychological benefits would greatly improve the recovery process from both the CMV and transplant.** **Seems to be more effective at disease clearance**
10. If there are disadvantages of maribavir over current treatments on the NHS please describe these. For example, are there any risks with maribavir? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Not available to under 12's, which may be something to consider if it is shown to be safe and with fewer side effects than current treatment options.
11. Are there any groups of patients who might benefit more from maribavir or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	There are some patients who are resistant to some current treatments and their side effects and quality of life impacts must be taken into consideration.

12. Are there any potential equality issues that should be taken into account when considering cytomegalovirus infection and maribavir? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	None that I can see
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Key Issue 1: **We consider patient perspectives may particularly help to address this issue** **Impact of time since transplant on the clinical data and economic model** The ERG consider mean time since transplant was imbalanced in the main clinical trial which might bias the results. The ERG suggests the data is adjusted to correct the imbalance.	

Patient expert statement

Key Issue 2: **Trial conduct and design leading to uncertainty and potential overestimates of maribavir efficacy** The trial was an open label design and some outcomes were subjectively assessed. The ERG suggests using Kaplan Meier data (rather than response rates) and using the prespecified analysis (rather than a post hoc analysis) will provide more robust estimates.	

Key Issue 3: Assumption of time since transplant at baseline in the model is unclear The ERG is unclear about the company's assumption of mean time since transplant at baseline in the model. It suggests the company's model is adjusted to be in line with the assumptions around time since transplant.	
Key Issue 4: Structural assumptions in the company's model The ERG note the company model assumes the infection can recur many times, but this is in contrast to the way recurrence is reported in the trial. The ERG suggest alternatives of how data could be used in the model to correct this uncertainty.	

Patient expert statement

Key Issue 5: Recurrences in the model have been overestimated The ERG believe the way the company have used recurrence data from the trial will bias the results. It suggests an alternative approach.	
Key Issue 6: Modelling of mortality in stage 1 Markov The ERG does not agree with the company's approach to modelling survival and suggests an alternative approach.	
Key Issue 7: Modelling of mortality in stage 2 Markov The ERG does not agree with the company's long term assumptions of survival and suggests an alternative approach.	

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Key Issue 8: **Modelling of graft failure** **We consider patient perspectives may particularly help to address this issue** The ERG does not agree with the company's assumptions on graft failure and suggests an alternative approach.	
Key Issue 9: **Modelling of disease complications** **We consider patient perspectives may particularly help to address this issue** The ERG does not agree with the company's approach to estimate the impact of underlying diseases and suggests an alternative approach.	

Key Issue 10: **Estimation of utilities** The ERG does not agree with the company's approach for estimating health-state utility values and suggests an alternative approach.	
Key Issue 11: **Estimation of costs** The ERG considers the costs of IAT retreatment are overestimated in the company's model and suggests an alternative approach..	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- All treatments available come with significant side effects.
- Psychological impact cannot be understated on patients and their families.
- Significant impact on the patients quality of life.
- Cost of current treatment, coupled with the cost of in-patient stay.
- Oral treatment at home would be so much better and improve overall patient recovery.

Thank you for your time.

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Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

ERG review of company's response to the TE

May 2022

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This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135439.

1 Introduction

This document provides the evidence review group's (ERG's) response in relation to the company's comments and additional data presented as a response to the technical engagement document (TE).

2 ERG review of comments

2.1 Issue 1: Numerical imbalance in time since transplant in SOLSTICE

There was a numerical difference in time since transplant (TST), a key prognostic factor according to the ERG's clinical experts, between treatment arms in SOLSTICE. The company has provided an analysis showing that neither the difference in mean or median in TST were statistically significant between the treatment arms in the full trial population or in the solid organ transplant (SOT) and haematopoietic stem cell transplant (HSCT) subgroups (Table 1). The ERG notes that two different sets of data for the mean TST for the SOT subgroup are presented. It is unclear why the data sets differ and if the statistical test is based on the correct set of data.

Table 1. Mean and median time since transplant by treatment arm

Category	IAT (N=116)	Maribavir (N=234)
Time since solid organ transplant (days)		
N (%)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median 95% CI p-value	[redacted]	[redacted]
Mean SEM 95% CI p-value	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Time since haematopoietic stem cell transplant (days)		
N (%)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

Median 95% CI p-value	[redacted]	[redacted]
Mean SEM 95% CI p-value	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Overall time since transplant (days)		
N (%)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median 95% CI p-value	[redacted]	[redacted]
Mean SEM 95% CI p-value	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Abbreviations: CI, confidence interval; IAT, investigator-assigned anti-CMV treatment; SEM, standard error of the mean

The company considers that the analysis of medians may be more reliable as the data for TST are not normally distributed. The ERG acknowledges that the underlying data does not seem to be normally distributed but considers a mean-based approach provides a better reflection of the whole population. The ERG also notes that the difference between the mean and the median TST is not based on a small number of "outliers" with very long TST. Data in Table A (see appendix), provided by the company at the clarification stage, show a substantial difference in TST between maribavir and IAT. For SOT, a quarter of the patients responding to maribavir had a TST of [redacted] days, whereas a quarter of the patients responding to IAT had a TST of [redacted] days. The impact of this substantial difference in TST longer than the median are not represented when using the median TST.

The ERG notes that subgroup analyses like the one provided by the company based on TST, are very rarely powered to detect a statistically significant difference. Although no significant difference was

identified in the company's analysis, it does not follow that the observed difference in TST isn't different and won't have an effect on the outcome of recurrence. The ERG, therefore, suggests that the company explores the effect on recurrence of adjusting for the numerical imbalance in TST at baseline between the treatment arms.

In order to address the ERG's concerns about the imbalance in TST between the treatment arms in SOLSTICE, the company also performed a logistic regression assessing the impact of TST on clearance and clinically significant recurrence. The company also assessed the impact of treatment (maribavir vs IAT), transplant type (HSCT vs SOT), prior use of CMV prophylaxis (yes vs no, only assessed for clearance) and time since clearance (days, only assessed for recurrence).

The company clarified that these additional factors were included as they may also have a clinically relevant effect on the outcomes of clearance and clinically relevant recurrence. The company did not explain what the selection of factors was based on. No other factors were included in the analyses and no variable selection procedures were performed to determine a final reduced model, with the exclusion of any non-significant covariates. The company also states that correlation was not explicitly tested for the included variables.

The ERG notes that predictors in a logistic regression need to be independent of each other and that it is very likely that, at least, time since clearance is strongly correlated with TST in the company's analysis. If there is a strong correlation between these two variables, this may lead to multicollinearity. This can produce spurious results such as an apparent correlation between one of the variables and the outcome but a lack of correlation with the other variable and the outcome despite the expectation that the correlation with the outcome would be similar for the two.[1] Due to the lack of testing for correlation between variables included in the analysis when correlation is highly likely to be present, the ERG considers the company's regression analysis to be fundamentally flawed. The ERG considers it important to explore the potential correlation between the variables included in the model, with results of the regression analysis presented separately for each variable. The company may want to consider using log TST as the data for this variable are not normally distributed, at least on the linear scale. The ERG also recommends that the company presents the results of the regression analysis for TST as the odds ratio of recurrence for each additional month (or even additional 3 or 6 months) from transplant rather than for each additional day as the current scale is likely to obscure any clinically meaningful difference.

The results of the regression analysis for clearance show a statistically significant correlation between clearance and the treatment received but no statistically significant correlation between clearance and TST, transplant type or prior use of CMV prophylaxis (Table 2).

Table 2. Logistic regression of confirmed CMV viraemia clearance response at week 8

Covariate	Adjusted OR (95% CI)	p-value
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Time since transplant (days)	[redacted]	[redacted]
Transplant type (HSCT vs SOT)	[redacted]	[redacted]
Prior use of CMV prophylaxis (Yes/No)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; HSCT, haematopoietic stem cell transplant; IAT, investigator-assigned anti-CMV treatment; OR, odds ratio; SOT, solid organ transplant

For clinically relevant recurrence the correlation with time since clearance was statistically significant but treatment, TST and transplant type did not reach statistical significance (Table 3).

Table 3. Logistic regression of confirmed CMV viraemia recurrence requiring treatment after clearance at week 8

Covariate	Adjusted OR (95% CI)	p-value
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Time since transplant (days)	[redacted]	[redacted]
Transplant type (HSCT vs SOT)	[redacted]	[redacted]
Time since clearance (days)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; HSCT, haematopoietic stem cell transplant; IAT, investigator-assigned anti-CMV treatment; OR, odds ratio; SOT, solid organ transplant

Since TST at baseline was not found to be statistically significantly different between the two treatment arms for the HSCT or SOT subgroups, and the regression analysis showed that TST does not have a statistically significant effect on recurrence, no adjustments on the effectiveness data used in the model were performed. However, based on the statistically significant result for the correlation between time since clearance and recurrence, the company revised their model to allow for a dependence between the time spent in the non-clinically significant CMV state and the probability of a recurrence (see Issue 5).

The ERG reiterates its concerns around the regression analysis due to the highly likely correlation between different variables, in particular those relating to time (i.e. TST and time since clearance). However, there is a strong clinical rationale for recurrence to be related to time (both time since clearance and TST). As such, the ERG considers that time should be incorporated in the model and consider the way the company has implemented this to be acceptable (see Issue 5).

Similar to the analysis comparing TST at baseline, a regression analysis only including independent variables may show no statistically significant difference in recurrence based on TST as there may not be enough data in SOLSTICE to establish such a relationship. The clinical experts advising the ERG consider TST to be an important prognostic factor with a strong clinical rationale for its likely effect on recurrence and later outcomes for patients eligible for maribavir. If the difference between treatment arms in TST is large enough to impact on the risk of recurrence, then this is likely to benefit maribavir as the mean TST was longer in the maribavir arm than in the IAT arm in the full trial population as well as in the HSCT and SOT subgroups. The ERG, therefore, suggests the company present a scenario analysis where the difference in TST at baseline has been appropriately adjusted for.

The company also highlights that the results of the regression analysis show that first recurrence is impacted by treatment received, although the result did not reach statistical significance. The ERG disputes the company's conclusion that the results show a strong relationship between the treatment received and the likelihood of recurrence. The issues with the regression analysis apply to all variables assessed, including the effect of treatment. The ERG acknowledges the trial results showing a numerical difference in the rates of clinically relevant recurrence between maribavir and IAT but reiterates that there is no clinical rationale for treatment received affecting the risk of or time to recurrence. The ERG's clinical expert informed that anti-CMV treatment, including maribavir, only supresses the virus and there is no rationale for why the suppression would be sustained or have a lingering effect once treatment is stopped. However, time since clearance and treatment effect are intrinsically linked in the model. The ERG, therefore, suggests the company provide a scenario analysis exploring the impact of assuming no treatment specific effect on recurrence by removing the non-statistically significant difference in recurrence between the treatment arms. This is discussed in detail in Issue 5.

2.2 Issue 2: Trial conduct and design leading to uncertainty

Patients assigned to anti-CMV treatment for which they had resistance

A large proportion of patients in the IAT arm were assigned to an anti-CMV treatment for which they had confirmed resistance. The ERG considers that this is likely to lead to an underestimate of clearance in the IAT arm and therefore an overestimate of the relative efficacy of maribavir compared to what would be expected in clinical practice. The company explains that the majority of patients who received an IAT agent to which their CMV has a mutation known to confer resistance at baseline had a medical history of acute or chronic renal dysfunction. Given the renal toxicity of the other treatment options, investigators may have chosen to continue ganciclovir/valganciclovir even if the patient's CMV had a mutation known to confer resistance to these drugs. The company provided the results of a sensitivity analysis excluding patients who received an IAT for which they had resistance at baseline (TE response Table 4), which showed a statistically significant improvement in clearance with maribavir, although the effect was less pronounced than the primary analysis. Clinical opinion is needed to determine if this level of renal impairment among patients resistant to ganciclovir and valganciclovir is reflective of the patient population in clinical practice.

Outcome data based on *post-hoc* analysis

In the updated model, the company is using data for the primary outcome of clearance at week 8 rather than the *post hoc* outcomes of clearance at week 4 and clearance at week 8 for those without clearance at week 4, which are likely to be associated with a higher risk of bias.

Assessment of clinically relevant recurrence

The ERG considers the assessment of clinically relevant recurrence to be highly subjective and at a high risk of bias due to the open label trial design and the need for alternative anti-CMV treatment at the discretion of the investigator. In their TE response, the company has confirmed that the SOLSTICE protocol did not have a definition for when to start treatment for a recurrence event, and that the company assumes that trialists would use the protocol definition for requirement of initial therapy. The ERG reiterates that this is subjective and contributes to uncertainty due to potential bias. No additional data or analysis can resolve this uncertainty, however, the uncertainty around the recurrence outcome data should be borne in mind when considering the cost effectiveness results.

Missing Data – CMV clearance and clinically relevant recurrence

Study discontinuations led to missing CMV measurements and thus missing data for both clearance and recurrence in SOLSTICE.

The company has provided results of several sensitivity analyses of the primary outcome of clearance at week 8 in order to validate the robustness of the primary result by applying different assumptions for missing data. The sensitivity analyses include:

- Including all patients with clearance at the time of study discontinuation ([redacted], respectively; p-value: <0.001).
- Last observation carried forward (LOCF), that is, including patients with clearance at any timepoint up to 8 weeks ([redacted], respectively; p-value: <0.001).
- Including clearance regardless of use of alternative anti-CMV therapy, that is, not censoring patients who received rescue therapy with maribavir or who changed to an alternative anti-CMV treatment ([redacted], respectively; p-value: 0.002).

Comparing the results of these analyses with the results of the primary outcome (55.7% [131/235] vs 23.9% [28/117], for maribavir and IAT, respectively) show that all three analyses are likely to overestimate the clearance rates in both treatment arms, but the effect will be more pronounced in the IAT arm as more patients randomised to IAT discontinued from the study, had missing data at week 8 and received alternative anti-CMV treatments.

The company has not commented on how they have dealt with missing data for recurrence in their Technical Engagement response. The ERG notes that it is unclear what the proportions of missing data were for the subset of patients informing the analysis of clinically relevant recurrence. However, comparing the rates of clinically relevant recurrence at week 20 among responders at week 8 (ERG report Table 22), with the cumulative probability of having a clinically relevant recurrence at week 20 after clearance at week 8 (ERG report Figure 5) and KM probabilities for clinically relevant recurrence (Company TE response, Table 5), there seems to be limited amount of missing data for recurrence at this timepoint.

Using KM data, rather than response rates, in the economic model.

The ERG is reasonably happy with the company's approach to use the primary outcome to inform clearance in the model and as there seems to be little missing data for clinically relevant recurrence, while the ERG would prefer the use of KM estimates, the two give very similar results.

Cost-effectiveness issues

In light of the OTUS study, a new real-world evidence retrospective analysis of patients with r/r CMV presented by the company in response to TE, the ERG considers that the company's economic analysis should be changed to be based on OTUS, with the maribavir relative treatment effect being taken from SOLSTICE. OTUS provided a larger sample size and a much longer follow up period for IAT patients than SOLSTICE, and as a real-world data source, the outcome data captured in OTUS are likely to be more generalisable to UK clinical practice

The ERG considers the company's current methodology for using OTUS data inappropriate for decision making. By using OTUS data to model subsequent CMV events after first events modelled with SOLSTICE data (and particularly by assuming that the probability of second clearance can be estimated from SOLTICE while the probability of remaining in the second clearance state is estimated from OTUS), the company has assumed that not only the populations, but also clearance and recurrence in both studies are directly comparable and interchangeable.

However, these two studies differ from each other both in terms of study design (randomised controlled trial vs retrospective observational study) and patient characteristics, which are likely to lead to differences in outcomes. Notable differences in baseline characteristics included a larger proportion of patients with a liver transplant in the OTUS SOT cohort (18.8%) compared with the SOT subgroup of SOLSTICE ([redacted]). Additionally, mean TST in SOLSTICE was around [redacted] months for SOT patients and [redacted] months for HSCT patients, which compares to 7 months for SOT patients and 1.7 months for HSCT patients in OTUS. Therefore, it could be argued that patients in OTUS were at higher risk of recurrences than patients in SOLSTICE.

Furthermore, as discussed in the ERG's original report, SOLSTICE only captured patients' first clearance and first recurrence events. The probability of clearance in both studies at week 8 was starkly different, with 49% of OTUS patients achieving clearance, compared to 24% of IAT patients in SOLSTICE.

The ERG is therefore concerned that the populations in OTUS and SOLSTICE are not comparable, which renders the company's methodology for using OTUS data not appropriate.

The ERG considers that a more robust approach would have been to use the OTUS data to model the probability of clearance and recurrence for IAT in the stage 1 Markov model, which would have provided a larger sample size and a much longer follow up period for IAT patients than SOLSTICE. The company could then have applied the relative risk of recurrence and clearance observed for maribavir compared to IAT from SOLSTICE to the IAT OTUS "baseline".

In order to maintain consistency in the clinical outcomes used in the model, the company could use OTUS to model clinical outcomes such as mortality and mean time since transplant (TST) and, if available, data on graft failures and GvHD events. This would align all of the parameter estimates relating to treatment with IAT from a single data source as opposed to relying on multiple different data sets as with the company's current approach.

The following sections of the ERG report provide a critique for the company's current approach and discuss recommendations to overcome issues identified by the ERG for the scenarios where the company uses the OTUS data as suggested by the ERG; and also in case the company maintains the use of SOLSTICE data as the primary source of IAT data in the model.

2.3 Issue 3: Assumption of time elapsed since transplant at baseline in the model

The company clarified its intention to capture mean TST in the model according to the median TST in the SOLSTICE trial. To this end, the company reported that at baseline, the model assumed a TST of [redacted] days for SOT patients and [redacted] days for HSCT patients. The implementation of this is discussed in the next sections of this report.

As originally stated in the ERG report, there is a marked difference between mean and median times since transplant at baseline in SOLSTICE, with overall mean TST for SOT patients of [redacted] days and [redacted] days for HSCT patients. As discussed in Section 2.1, the ERG maintains its view that a mean-based approach would have been a better reflection of the whole population under consideration rather than focusing on median values, particularly when dealing with a therapeutic area where there is a wide range of outcomes as is the case here with CMV infection occurring after transplant.

Therefore, the ERG replaced the company's assumption in the model, and used mean TST instead of median TST at baseline.

If the company changes its modelling approach to include OTUS as the main source of data for the IAT arm of the model, then the mean TST in OTUS should be used at baseline.

2.4 Issue 4: Structural assumptions in the company's model

The ERG was concerned that the stage 1 Markov model (first 52 weeks of the model) allowed for multiple clearance and recurrence episodes per patient at various time points, when the outcomes reported in SOLSTICE were clearance at week 8; and recurrence after first clearance (i.e., only one episode of recurrence after one episode of clearance). The company had not presented any evidence to substantiate why patients could have multiple recurrences in the model between 8 and 52 weeks. The company also used 20-week data from SOLSTICE on first recurrences to model multiple recurrences outcomes up to week 52 based on the assumption that the same rate of recurrence observed during the 20-week follow-up of SOLSTICE would be observed until week 52. The ERG noted that having the stage 1 Markov model extended to 52 weeks did not add any methodological or conceptual benefit to the economic analysis, and only introduced bias in favour of maribavir as the estimates of treatment effectiveness used by the company at week 20 were in favour of maribavir.

Finally, the ERG also noted that the company's assumption that no CMV events occurred after 12 months in the model was in contradiction of the SOLSTICE data for SOT patients, and of clinical expert opinion.

Therefore, the ERG recommended that the company used SOLSTICE KM trial data to model patients' pathway through a "full cycle" of events (i.e., first clearance, first recurrence and second clearance) in the model without compromising data integrity (see Issue 5 for more details on this). The ERG also recommended that the company obtained clinical expert opinion and/or external data to validate the average frequency of subsequent "full cycles" of events in order to capture the likelihood of SOT patients having multiple episodes of CMV recurrences throughout their lives. The ERG concluded that the duration of the stage 1 Markov model should be determined by the duration of these cycles and that the company could then repeat these cycles as appropriate in the model.

2.4.1 Company's response to technical engagement

The company's updated model used tunnel states to estimate transitions between the CMV and the nCMV states, according to duration of clearance in the model, and according to recurrence being the

first or second event. The company based these changes in the model on data from OTUS, a real-world evidence retrospective study of patients with r/r CMV.

The primary objective of OTUS was to evaluate and describe the clinical outcomes with current management patterns of CMV. Results were reported separately for the SOT and HSCT cohorts; OTUS SOT included 115 patients, of whom 58 were European patients who had undergone an SOT between January 2014 and September 2021, and OTUS HSCT included 121 patients, of whom 39 were European patients who had undergone an allogeneic HSCT from January 2017 to October 2021.

The company also concluded that the OTUS data provided evidence that SOT and HSCT patients may experience multiple recurrences with IATs throughout their lives and reported to have used these data to update the duration of the stage 1 Markov from 52 to 78 weeks.

The company reported that if a treatment cycle is assumed to be 5.14 weeks (time on treatment in the IAT arm of SOLSTICE), and the time between each recurrent episode in OTUS reflects the duration of clearance, it could be estimated that CMV events can still reoccur after 150.2 weeks for SOT (duration from the start of the CMV index episode to the start of the 4th recurrence, excluding the 4th recurrence treatment period) and 77.1 weeks for HSCT (duration from the start of the CMV index episode to the start of the 6th recurrence, excluding the treatment period of the 6th recurrence), as per Table 4. The company added that while OTUS provided additional support to extend the stage 1 Markov beyond 78 weeks for SOT, clinical expert opinion was that the heterogeneity in the treatment pathway at longer time horizons meant that 78 weeks was a, "*sufficiently pragmatic timepoint to end the Phase 1 Markov for SOT and HSCT*", as from this point there is more uncertainty in the modelling of care pathways and costings for patients which would be based on individual patient needs.

Table 4. Time since index CMV event to last recurrence and time since transplant to last CMV event (in weeks) in OTUS

CMV episode	Recurrence	Time since end of previous CMV episode to start of new episode	Number of patients with event	Cumulative duration since index episode (time since end of previous CMV + duration of 5.14 weeks of treatment)	Cumulative duration since index episode in years	Cumulative duration since transplant (mean TST) in years
SOT patients (N=202)						
1 (CMV index episode)	-	-	-	5.1	0.10	4.2
2	1	16.8	47 (23.3%)	27.1	0.52	4.6
3	2	14.2	10 (5.0%)	46.5	0.89	5.0
4	3	93.4	4 (2.0%)	144.9	2.79	6.9
5	4	5.3	1 (0.5%)	**150.2**	2.89	7.0
HSCT patients (N=213)						
1 (CMV index episode)	-	-	-	5.1	0.10	1.1
2	1	6.8	88 (41.3%)	17.1	0.33	1.3
3	2	6.4	34 (16.0%)	28.6	0.55	1.5
4	3	3.1	15 (7.0%)	36.9	0.71	1.7
5	4	4.6	10 (4.7%)	46.6	0.90	1.9
6	5	18.6	4 (1.9%)	70.4	1.35	2.3
7	6	6.8	2 (0.9%)	**77.1**	1.48	2.5

Weighted by SOT and HSCT distribution in the model						
1 (CMV index episode)	-	-	-	5.1	0.10	3.0
2	1	12.8	63 (30.5%)	23.1	0.44	3.3
3	2	11.1	20 (9.4%)	39.3	0.76	3.6
4	3	57.3	8 (4.0%)	101.7	1.96	4.8
5	4	5.0	5 (2.2%)	108.8	2.09	5.0

2.4.2 ERG's critique of company's approach after technical engagement

The ERG agrees with the company that the OTUS data is a valuable source of evidence to inform further recurrence in the model. However, the company's methodology for using OTUS data is inappropriate for decision making as the company has assumed that not only the populations, but also clearance and recurrence in both studies are directly comparable and interchangeable. This issue is discussed in further detail in Section 2.5.

Furthermore, the ERG notes that some of its original concerns remain fully (or partially) unaddressed by the company's updated modelling approach:

1. The company's use of 20-week data from SOLSTICE on first recurrences to model multiple recurrences outcomes up to week 52 based on the assumption that the same rate of recurrence observed during the 20-week follow-up of SOLSTICE would be observed until week 52.

   The company's updated model uses different rates of recurrences for patients depending on how long they have been in the nCMV (i.e., clearance) state and based on the event being a first versus a second recurrence. This improves on the company's previous assumption of a constant rate of recurrence. Nonetheless, the company's updated model still includes multiple recurrences beyond a second event and assumes that the rate of third and further recurrences is the same as that observed for second recurrences in OTUS. As can be seen from the data in Table 4 (and as discussed in Section 2.5), the rates of subsequent recurrences in OTUS were much lower after second recurrence, thus, the company's approach is still overestimating the recurrences in the model and, therefore, the benefit associated with maribavir.

2. The ERG noted that having the stage 1 Markov model extended to 52 weeks did not add any methodological or conceptual benefit to the economic analysis, and only introduced bias in favour of maribavir as the estimates of treatment effectiveness used by the company at week 20 were in favour of maribavir.

   The ERG is unclear on the company's justification for choosing 78 weeks. The company's assumption implies that patients can experience CMV events 1.5 years after becoming eligible for treatment with maribavir, when the OTUS data show that SOT patients were still experiencing events 2.89 years after their CMV index event. Even though the company provides a clinical rationale for why events beyond 1.5 years (78 weeks) should not be considered in the analysis, it

does not provide a justification for extending the stage 1 Markov from 52 to (specifically) 78 weeks.

Furthermore, the company's rationale for looking into the occurrence of CMV events up to the start of the 4th recurrence and the start of the 6th recurrence, for SOT and HSCT patients, respectively, is highly inconsistent with the company's use of the OTUS data in the model, given that only the probability of second recurrences (and no further) from the study were used (as discussed in Section 2.5). Therefore, the ERG's view remains that having the stage 1 Markov model extended to an even longer time horizon of 78 weeks does not add any methodological or conceptual benefit to the economic analysis, and only introduces bias in favour of maribavir.

Given the number of patients with third (or further) recurrences in OTUS is very low (see Table 4) and the fact that OTUS patients were likely to be at a higher risk of recurrence events (due to the discrepancy between TST in SOLSTICE and OTUS - around [redacted] months for SOT patients and [redacted] months for HSCT patients in SOLSTICE, compared to 7 months for SOT patients and 1.7 months for HSCT patients in OTUS), the ERG concludes that the OTUS data does not provide sufficiently robust evidence to model recurrence events beyond second recurrences after transplant.

Crucially, the ERG disagrees with the company's chosen duration of a "full cycle" of events and considers that:

- If the company changes its modelling approach to include OTUS as the main source of data for the IAT arm of the model, then the duration of the stage 1 Markov should match the time to second events in OTUS, which is 39.3 weeks (34.1 weeks of cumulative duration since index episode to second episode plus the duration of 5.14 weeks of treatment for the second episode).
- If the company does not change its current modelling approach, then the duration of the stage 1 Markov should be limited to 20 weeks, to reflect the duration of events captured in SOLSTICE. This issue is further discussed in Section 2.5.

3. Finally, the ERG also raised the issue that the company's assumption that no CMV events could occur after 12 months in the model was in contradiction of the SOLSTICE data for SOT patients, and of clinical expert opinion.

The updated model relies on new clinical expert opinion provided to the company that CMV events after 78 weeks should be considered sporadic and therefore, not relevant for this modelling exercise.

Having analysed the data from OTUS, the ERG agrees that events become more sporadic as time from transplant elapses, for example, time to first recurrence (and time between first and second recurrence) for the overall population in OTUS was approximately 4 months, while time between second and third recurrence was over 1 year (Table 4). Therefore, the ERG is satisfied that the stage 2 Markov model does not include CMV events, even though the ERG disagrees with the company's assumption for the duration of the stage 1 Markov, as discussed in the previous section.

2.5 Issue 5: Overestimation of recurrence in the model

The ERG was originally concerned that the use of recurrence data from SOLSTICE was fundamentally flawed and introduced bias in favour of maribavir. One of the ERG's key concerns was the company's assumption that patients could have multiple episodes of recurrences in the model when SOLSTICE only captured first clearance and first recurrence episodes.

The ERG also noted that there were two additional assumptions contributing to the overestimation of recurrences in the model as well as the benefit associated with maribavir:

1. The company's assumption that the 4-weekly probability of recurrence at the end of SOLSTICE (week 20) remained the same until week 52 in the model.
2. The assumption that patients who achieved clearance with maribavir had a lower probability of recurrence (regardless of how long they had been off treatment) compared to IAT patients.

Clinical expert opinion provided to the ERG was that the probability of recurrence is unlikely to depend on the type of treatment on which patient achieved clearance, but instead to be dependent on time since transplant and on the level of lifelong immunosuppression needed by the patient. The ERG's clinical experts explained that the initial 3 months after transplant represented the highest period of risk, followed by the next 3 months of lower, but still considerable risk.

Furthermore, the ERG also noted that KM data on time to recurrence after first clearance at week 8 from the SOLSTICE CSR suggested no statistically significant difference between recurrence for maribavir and IAT patients. The ERG reported

Figure 1, and noted that when the difference in baseline numbers for the two groups was considered, it was likely that the separation of the curves after week 4 was due to the small number of patients at risk in the IAT arm compared to the number of patients at risk in the maribavir arm. Thus, a single event in the IAT arm had a much larger impact than a single event in the maribavir arm.

The ERG also hypothesised that the difference in curves was likely to be cofounded by the difference in time since transplant across treatment arms at baseline as patients in the maribavir arm entered the trial considerably later (on average) after transplant than IAT patients.

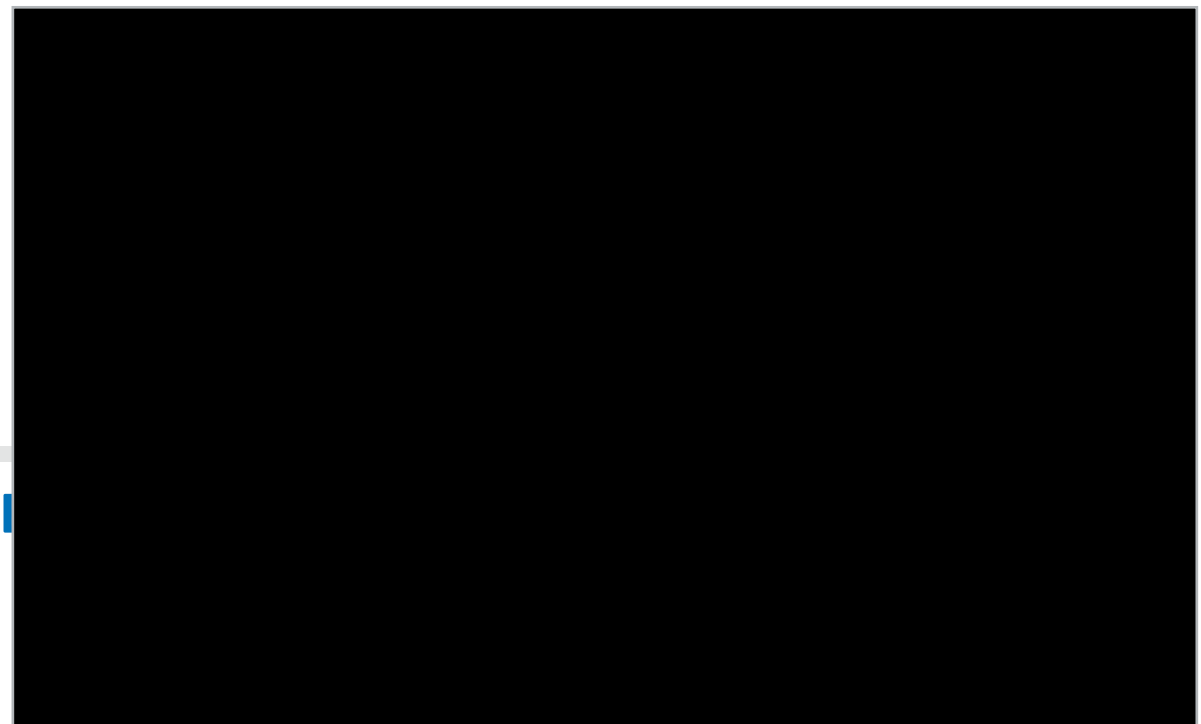


Figure 1. KM data on time to recurrence requiring alternative treatment after clearance at week 8 (shaded areas represent the confidence interval around the curves)

The ERG advised the company to use the SOLSTICE KM to estimate a "full cycle" of events consisting of a maximum of 2 episodes of clearances and one episode of recurrence per patient in the stage 1 Markov model. Patients entering the model with CMV could therefore experience one clearance; followed by one potential recurrence; followed by another clearance (associated with subsequent IAT treatment).

2.5.1 Company's response to technical engagement

The company updated their model structure to include decreasing rates of recurrences based on time since clearance (i.e., the longer patients stay in the clearance state of the model, the lower is the probability of experiencing a recurrence). The company used data from OTUS in combination with data from SOLSTICE to inform this in the model.

The company has maintained the assumption that patients could have multiple recurrences during the stage 1 Markov; however, used the OTUS data to model the probability of patients experiencing a third (or further) recurrence. The company also used the OTUS data to model the probability of patients remaining in the clearance state after a second (or further) recurrence. However, the company used the IAT SOLSTICE data to inform the probability of patients achieving a second clearance in the model.

Furthermore, the company has maintained the assumption that patients have recurrence rates based on the most recent treatment they have achieved clearance with, however, limited this to the first 12 weeks after clearance at week 8. All other patients who achieved clearance after week 8 in the model, or who achieve clearance at week 8 but have a recurrence post week 20 in the model, have the same probability of recurrence in both treatment arms.

2.5.2 ERG's critique of company's approach after technical engagement

Use of OTUS data to estimate multiple recurrences in the model

The ERG considers the company's methodology for using OTUS data inappropriate for decision making. By using OTUS data to model subsequent CMV events after first events modelled with SOLSTICE data (and particularly by assuming that the probability of second clearance can be estimated from SOLTICE while the probability of remaining in the second clearance state is estimated from OTUS), the company has assumed that not only the populations, but also clearance and recurrence in both studies are directly comparable and interchangeable. As discussed at the beginning of the cost-effectiveness section of this report, the ERG does not consider that these populations are comparable.

Given the lack of evidence (or justification given by the company) to substantiate the underlying assumption that SOLSTICE and OTUS populations are comparable, the ERG considers that a more robust approach would have been to use the OTUS data to model the probability of clearance and recurrence for IAT in the stage 1 Markov model, which would have provided a larger sample size and a much longer follow up period for IAT patients than SOLSTICE. The company could have then applied the relative risk of recurrence and clearance observed for maribavir compared to IAT from SOLSTICE to the IAT OTUS data.

Therefore, the company's updated approach does not mitigate the ERG's original concern that the probability of recurrence in the model is not appropriately estimated. The ERG maintains its opinion that the number of recurrences in the model should be based on the number of recurrences in the underlying clinical data used in the analysis and that KM data should be used to model time to clearance and time to recurrence. Given the newly presented OTUS data, the ERG considers that the available KM OTUS data should be used to estimate time to first clearance; time to first recurrence and second clearance; and time to and second recurrence and third clearance in the IAT arm of the stage 1 Markov model, with the duration of 39 weeks (as discussed in Section 2.4). The relative effect of maribavir vs IAT would then be taken from the SOLTICE trial.

As discussed in Section 2.4, the company's updated approach improves on the company's previous assumption of a constant rate of recurrence. Nonetheless, the company's updated model still includes multiple recurrences beyond a second event and assumes that the rate of third and further recurrences is the same as that observed for second recurrences in OTUS. As discussed in Section 2.4, the rates of subsequent recurrences in OTUS were much lower after second recurrence, thus,

the company's approach is still overestimating the recurrences in the model and, therefore, the benefit associated with maribavir.

If the company does not change its current modelling approach, then the ERG maintains its original view that SOLSTICE data should be used to estimate a "full cycle" of events consisting of a maximum of 2 episodes of clearances and one episode of recurrence per patient in the stage 1 Markov model. Patients entering the model with CMV could therefore experience one clearance; followed by one potential recurrence; followed by another clearance (associated with subsequent IAT treatment).

The lower probability of recurrence associated with maribavir (regardless of how long patients have been off treatment)

The company has maintained the assumption that maribavir patients who achieve clearance at week 8 have a lower probability of recurrence than IAT patients, however, limited this to the first 12 weeks after clearance. The company has not provided any justification for why the benefit associated with maribavir would only be observed for the first 12 weeks after clearance. The justification for assuming a benefit associated with maribavir was also not clearly stated. Instead, the company implies that the impact of maribavir on the probability of recurrence works through the impact of maribavir on the duration of clearance and its impact on recurrence. More specifically, the company concluded from its logistic regression that a longer clearance was associated with a lower probability of recurrence. Therefore, by assuming that maribavir keeps patients in the clearance state for longer, it indirectly keeps patients at a lower probability of recurrence.

Nonetheless, the company failed to explain (or acknowledge) why maribavir patients on clearance for the same duration of time as IAT patients (during the first 12 weeks of clearance achieved at week 8) have an added benefit of having a lower probability of recurrence (14% vs 10% as per Table 5), despite being in the clearance state for the same period of time. As reported in Table 5, the probability of patients remaining in the clearance state increases with time spent in clearance - the probability of remaining in clearance for the first 12 weeks of the model is 86% and 90% for IAT and maribavir patients, respectively; which then increases to 97.88% for the 4 subsequent weeks (and becomes the same in both treatment arms), which then finally increases to 99.69% until the end of the stage 1 Markov (same in both treatment arms).

The clinical benefit associated with maribavir works through two ways in the model: 1) the higher probability of clearance for maribavir patients at week 8 (56% vs 24% for IAT); and 2) the lower

probability of recurrence for maribavir patients in the 12 weeks following clearance, which means that a higher proportion of maribavir patients are in the clearance state at week 24 in the model, when the rates of recurrence become independent of treatment.

As discussed in Section 2.1, the ERG acknowledges the clinical plausibility that patients who maintain a sustained clearance (and therefore are also clear of CMV for longer since transplant) might have a lower probability of recurrence than patients who are in a higher risk period (closer to transplant and at the beginning of their clearance). Therefore, the ERG agrees with the company's introduction of tunnel states in the model, where duration of clearance is linked to a lower probability of recurrence.

However, as also discussed in Section 2.2, the ERG cannot be sure that SOLSTICE data are robust enough to confirm that patients are likely to maintain clearance with maribavir for longer than with IATs. If the rate of recurrence during the initial 12 weeks after clearance was assumed to be the same across treatment arms (but still decreasing with time since clearance), the benefit associated with maribavir in the model would be the 8-week differential observed in clearance rates in the model, propagated until the end of the stage 1 Markov, or until the same proportion of patients had cleared their CMV in both arms.

Therefore, the ERG conducted a scenario analysis whereby the probability of maintaining clearance in the model was independent of the treatment received by patients, and only dependent on time spent in clearance (i.e., the probability of maintaining clearance in the model was the same in both treatment arms). Results of this scenario analysis are reported in Section 2.14.

Table 5. Clearance and recurrence rates used in the company's updated model

Outcome	Used in the company's base case model	
	IAT	Maribavir
Probability of clearance at week 8	24.7%	57.6%
Probability of clearance at week 12 (and onwards) for patients not achieving clearance in the previous model cycle*	28/117 (23.9%) converted into a 4-week probability of 13%	Same as IAT arm
Probability of remaining in the first clearance state when first clearance was achieved at week 8 (i.e., clearance achieved with maribavir or first round of IAT)		

Probability of remaining in the clearance state for 4; 8; 16; and 20 weeks after achieving clearance at week 8	86% • Estimated as 100% minus 14% • 14% was estimated as the number of recurrences in SOLSTICE at week 20 divided by the total number of patients who cleared CMV at week 8 (37% converted to 4-weekly probabilities).	90% • Estimated as 100% minus 10% • 10% was estimated as the number of recurrences in SOLSTICE at week 20 divided by the total number of patients who cleared CMV at week 8 (27% converted to 4-weekly probabilities).
Probability of remaining in the clearance state at week 24 (from week 20) with continuous clearance achieved at week 8 Probability of remaining in the clearance state at week 28 (from week 24) with continuous clearance achieved at week 8	97.88% • Estimated as 100% minus 2.11% • 2.11% was estimated as the probability of a first recurrence between week 8 and week 20 in OTUS, converted to 4-weekly cycles, and weighted by the proportion of SOT and HSCTs in SOLSTICE.	Same as IAT arm
Probability of remaining in the clearance state at week 32 onwards with continuous clearance achieved at week 8	99.69% • Estimated as 100% minus 0.31% • 0.31% is the probability of having a recurrence event from week 20 to week 52 in OTUS, converted to 4-weekly cycles, and weighted by the proportion of SOT and HSCTs in SOLSTICE.	Same as IAT arm
Second clearances		
Probability of achieving second clearance	28/117 (23.9%) converted into a 4-week probability of 13% Probability of clearance in SOLSTICE at week 8 with IATs.	Same as IAT arm
Probability of remaining in the second (and further) clearance state for 4 and 8 weeks after achieving second (and further) clearance	89.6% • Estimated as 100% minus 10.4% • 0.41% is the probability of having a second recurrence event at week 8 in OTUS, converted to 4-weekly cycles, and weighted by the proportion of SOT and HSCTs in SOLSTICE.	Same as IAT arm
Probability of remaining in the second (and further)	96%	Same as IAT arm

clearance state for 12; 16; and 20 weeks after achieving second (and further) clearance	• Estimated as 100% minus 4.13% • 4.13% is the probability of having a second recurrence event at between week 8 and week 20 in OTUS, converted to 4-weekly cycles, and weighted by the proportion of SOT and HSCTs in SOLSTICE.	
Probability of remaining in the second (and further) clearance state for 24 weeks or longer	99.3% • Estimated as 100% minus 4.13% • 0.7% is the probability of having a second recurrence event at between week 20 and 1 year in OTUS, converted to 4-weekly cycles, and weighted by the proportion of SOT and HSCTs in SOLSTICE.	Same as IAT arm
Abbreviations: IAT, investigator-assigned antiviral therapy *taken from the probability of clearance observed from week 0 to 8 in the trial for the IAT arm		

2.6 Issue 6: Modelling of mortality in stage 1 Markov

The ERG had several issues with the company's estimation of mortality in the original stage 1 Markov model. These consisted of:

1. The company's approach of using SOLSTICE data to model a differential in survival related to CMV status. The trial data (which, by default, incorporated the difference in CMV events across treatment arms) showed no significant difference in overall mortality for maribavir and IAT patients (ITT population), thus suggesting that the CMV-related mortality in the trial was also not significantly different (and was also numerically similar) across treatment arms.

2. The ERG acknowledged that CMV occurrence is a key prognostic factor of mortality, however, noted that this is likely to be dependent on how long after transplant the CMV event occurs:
    a. For SOT patients, additional literature sources (Hakimi *et al*. 2017) showed that the annual probability of death during the first year after transplant depended on: type of organ transplanted; presence or absence of CMV; and time of CMV event. A trend was also noted where having CMV events later after transplant was associated with a lower risk of death vs having CMV events earlier after transplant (7.12% if CMV occurs within 3 months after transplant vs 4.10% if CMV occurs 6 months after transplant). The same trend was observed for patients without CMV (2.84% vs 0.96%), suggesting that the risk of mortality (when CMV is not present) also decreases over the first-year post-transplant.

b. For HSCT patients, the data on survival post-transplant provided in TA591 also showed that the rate of mortality decreased over the first-year post HSCT.

Therefore, the ERG recommended using SOLSTICE KM data to model survival for the stage 1 Markov model, where the KM data should be separated only by type of transplant (i.e., SOT vs HSCT). The ERG suggested that the company fitted survival curves and extrapolated the KM data in order to estimate the SOLSTICE survival until the end of the stage 1 Markov model. Subsequently, the ERG recommended that the company used existent data available in literature to estimate a differential in mortality according to CMV in the SOT and HSCT populations, separately, and according to mean TST in SOLSTICE (approximately over [redacted]).

3. The company assumed that after week 8, the 4-weekly probability of death was 2.5% for SOT patients with CMV and 1.3% for patients without CMV. This represented an increase in the probability of death from week 4-8 (of 0.97%) for both patients with and without CMV. This increase was not clinically plausible in light of the data observed in Hakimi *et al*. 2017; the NHS blood and transplant report and clinical expert opinion and overestimated the benefit associated with maribavir on survival in the model.

4. Finally, the ERG disagreed with the company's methodological approach of summing sex- and age-specific general population mortality rates to the mortality rates observed in SOLSTICE given these are competing risks.

2.6.1 Company's response to technical engagement

The company reiterated that SOLSTICE data provides evidence that mortality for maribavir patients was lower than for IAT patients. The company provided a KM plot of time to all-cause mortality (adjusted for treatment crossover) between week 8 and week 20 in the trial (Figure 2). The company reported that the overlap in the curves for the first 8 weeks is due to patients still being on treatment and therefore, fluctuating between the CMV and nCMV states within each treatment group. The company added that thereafter (from day 56 to 140) there is a separation between the maribavir and IAT curves with higher mortality observed in the IAT arm at day 140.

Figure 2. Kaplan Meier plot of time to all-cause mortality by treatment arm adjusted for treatment switch by Inverse Probability of Censoring Weights method (TRTPN=1 is IAT; TRTPN=2 is maribavir)

The company concluded that the use of CMV-related mortality from SOLSTICE in the model was appropriate, the company replaced the 4-week outcomes used in the original model by 8-week outcomes and assumed that no deaths occurred in the first 4 weeks. The company did not report the updated mortality rates used in their response to TE.

The ERG investigated the company's updated model and reported the mortality rates used for week 8 in the model, by type of transplant (Table 6), and from week 8 to week 78, by CMV status (Table 7). The latter remained unchanged from the company's original model. The company also updated their base case to remove the sex- and age-specific general population mortality rates from the stage 1 Markov, as per the ERG's request before TE.

Table 6. Mortality rates in first 8 weeks of the model

Time period	Solid organ transplant (SE)	Haematopoietic stem transplantation (SE)
Week 0 to week 8	[redacted]	[redacted]

Table 7. Mortality rates in week 8 to week 78 in the model

Time period	CMV state (SE)	nCMV state (SE)
Week 8 to week 78	[redacted]	[redacted]

The company also undertook scenario analysis where the impact of CMV on mortality was modelled with external literature. The company used the Hakimi *et al*. 2017 study to explore the differences in all-cause mortality depending on patients having an early CMV infection (CMV within 3-months post-

transplant); CMV beyond 3-months post-transplant; or CMV beyond 6-months but less than 2-years post-transplant. The company chose the annual mortality rates for the CMV events occurring beyond 6-months but less than 2-years post-transplant, as these were the more closely aligned to TST in SOLSTICE for SOT patients. Finally, the company added that the mortality risks from Hakimi *et al*. 2017 represent a heterogenous population which the company considered did not represent the same population as the SOLSTICE trial. The company considered that the Hakimi *et al*. 2017 study included a higher proportion of kidney transplant patients (associated with a lower risk of death) and a lower proportion of lung transplant patients (associated with a higher risk of death), which the company considered explained why the mortality in the study was lower than that observed in SOLSTICE.

For HSCT patients, the company used the Camargo *et al.* 2018 study, which explored the impact of persistent viremia (patients who failed to clear CMV on treatment day 35) versus cleared viremia (patients who cleared within 35 days of treatment) on all-cause mortality in HSCT patients 100; 200; and 365 days post-HSCT.

2.6.2 ERG's critique of company's approach after technical engagement

The ERG acknowledges that the original KM data provided by the company (Figure 2), showing that there [redacted] included IAT patients who had crossed to maribavir after failing treatment with IAT, which might have overestimated survival in the IAT arm.

Figure 2. KM data on all-cause mortality by treatment group, randomised set (reproduced from the CSR Figure 6)

[redacted]

Even though the company provided the survival data from SOLSTICE adjusted for crossover, no details on the method used to adjust the curves was provided, other than reporting that the Inverse Probability of Censoring Weights (IPCW) method had been used. The ERG notes that the choice of method used to adjust trial outcomes for crossover, "*often drastically alters the estimated incremental cost effectiveness ratio*" (NICE DSU TSD 16). The company provided no justification for why the IPCW method was used, as opposed to, for example, the Rank Preserving Structural Failure Time Model (RPSFTM) method. NICE DSU TSD 16 also notes that the IPCW method will be prone to bias if out of those patients who switched, there is a high proportion (around 90%) of patients who experienced disease progression (and thus became eligible to switch).

In conclusion, the ERG cannot validate the use of the adjusted survival data without understanding how the adjustment was carried out. Crucially, the 95% confidence intervals reported in Figure 1 suggest that there is no statistically significant difference between survival in both treatment arms (even when survival is adjusted for crossover).

Furthermore, the company did not provide KM data separated by type of transplant (i.e., SOT vs HSCT) and by CMV status as recommended by the ERG before TE, which would have allowed the committee to understand the difference in survival by type of transplant.

The ERG remains concerned that the mortality data from SOLTICE have only been presented by CMV status or type of transplant (i.e. SOT vs HSCT), and not by CMV status and type of transplant:

- The overall mortality observed in the SOT SOLSTICE arm was [redacted] over 20 weeks compared to 2.08% in the Hakimi *et al*. 2017 for all patients (CMV and nCMV) with mortality events occurring between 6 months and 2 years after SOT (so for 1 and a half years). For HSCT patients, [redacted] of patients died in the SOLSTICE trial over 20 weeks, while the Camargo *et al.* 2018 study reported 22% of deaths for CMV patients and 7% for nCMV patients over 14 weeks.
- For the CMV vs nCMV mortality – the mortality in the aggregated population from SOLSTICE (i.e., SOT and HSCT) is considerably higher than the mortality observed in the

Hakimi *et al*. 2017 and the NHS Organ Donation Annual Activity Report for 1-;2-;5-; and 10-years after SOT. Given that some of the estimates in these sources, for example the annual mortality rates for the CMV events occurring beyond 6-months but less than 2-years post-transplant in Hakimi *et al*. 2017, are in theory reflective of a period of higher risk for CMV-related death than SOLSTICE (on average), the ERG remains concerned that these populations might not be comparable. The mortality rates for HSCT patients seem more aligned between SOLSTICE and Camargo *et al.* 2018, which could be explained by the first set of mortality data from the study being for 100 days after HSCT, and the mean TST in SOLSTICE being [redacted] days for HSCT patients (Table 8).

Nonetheless, the ERG notes that the effect of CMV events on mortality (vs no CMV) is higher in the external literature sources than that estimated in SOLSTICE for SOT patients (Table 8). The relative risk associated with CMV (vs nCMV) deaths for SOT patients in Hakimi *et al*. 2017 is 3.61, whereas the relative risk in SOLSTICE is 1.95 (for the SOT and HSCT populations combined).

Given the discrepancy in the overall mortality rates between SOLSTICE and the external literature sources, and the discrepancy in these sources between the impact of CMV events on mortality, the ERG disagrees with using the literature mortality estimates directly in the model, even as a scenario analysis. To do so generates an inconsistency in the overall mortality in the model (which also affects the stage 2 Markov), and crucially is not an accurate representation of the SOLSTICE trial, given that absolute mortality in SOLSTICE was much higher than in external literature.

Instead, the ERG recommends that:

- The OTUS KM mortality data are used to estimate mortality in the IAT arm of the model, separated by HSCT and SOT. The ERG recommends that the company then investigates if mortality by CMV status (within each population) is statistically significantly different for CMV and nCMV IAT patients. If this is the case, then the company would not have to use external literature to estimate CMV-related mortality, and the maribavir treatment effect derived from SOLSTICE leading to the difference in CMV events in the maribavir and IAT arms would generate any potential survival benefit associated with maribavir.

  If mortality by CMV status (within each population) is not statistically significantly different for CMV and nCMV IAT patients in OTUS, then CMV-related mortality from literature sources from Hakimi *et al*. 2017 and Camargo *et al.* 2018 should be applied to the OTUS KM data.

- If the company does not change its current modelling approach, then the ERG reiterates the importance of having SOLSTICE data (particularly KM data) by type of transplant and by CMV status, to try to further understand the differences in mortality between these populations in SOLSTICE. Given the much higher mortality rates observed in the HSCT population compared with SOT patients, it is likely that the former is driving the latter. Once KM data are available by type of transplant and by CMV status, the ERG recommends that the effect of CMV on mortality from Hakimi *et al*. 2017 and Camargo *et al.* 2018 is applied to the SOLSTICE KM data as a scenario analysis.

The ERG also disagrees with the company's assessment that the mortality risk from Hakimi *et al*. is lower than that observed in SOLSTICE due to the former including a higher proportion of kidney transplants (associated with a low risk of death) and a lower proportion of lung transplant patients (associated a higher risk of death). Whereas it is true that kidney transplants are higher in Hakimi *et al*., the mortality risks in the study for 6 months after SOT show that the highest risk of mortality is associated with liver transplants, which made up 13% of transplants in Hakimi *et al*. but only 3% of transplants in SOLSTICE (Table 8). In fact, the second lowest risk of mortality (following kidney transplant) was that associated with lung transplant. Re-weighting the mortality risks from Hakimi *et al*. 2017 (provided for every type of transplant) by the distribution of transplants in SOLSTICE, decreased the CMV-related mortality rate of 0.322% (for 4 weeks) to 0.268%. The rate decreased, as expected, given the lower percentage of patients with liver transplants in SOLSTICE. For the nCMV state, the weighted rate remained the same at 0.074%.

Table 8. Probability of death over 12 months for patients with or without CMV

Organ	Probability of death			Distribution of patients	
	CMV	No CMV	p-value	Hakimi *et al*. 2017	SOLSTICE
Probability of death by CMV status and organ transplanted in Hakimi *et al.* 2017					
Overall	24/586 (4.10)	12/1245 (0.96)	<.0001	100%	100%
Kidney	10/383 (2.61)	3/812 (0.37)	.0005	65%	50%
Liver	9/75 (12.00)	5/160 (3.13)	.01	13%	3%
Lung	2/68 (2.94)	2/148 (1.35)	NS	12%	29%
Other*	3/60 (5.00)	2/125 (1.60)	NS	10%	17%

Total 4-weekly probability in Hakimi *et al*. 2017	0.322%	0.074%	-	-	-
Total 4-weekly probability from Hakimi et al. 2017 weighted to reflect SOLSTICE	0.268%	0.074%	-	-	-
Relative risk of death (CMV vs nCMV) from Hakimi et al. 2017	3.61	-	-	-	-
Probability of death by CMV status in Camargo *et al.* 2018					
100 days post-HCT	6.72%	2.01%	-	-	-
200 days post-HCT	2.22%	1.39%	-	-	-
365 days post-HCT	3.17%	1.68%	-	-	-
Relative risk of death (CMV vs nCMV) from Camargo *et al.* 2018					
100 days post-HCT	3.34	-	-	-	-
200 days post-HCT	1.60	-	-	-	-
365 days post-HCT	1.89	-	-	-	-
Probability of death by CMV status in SOLSTICE					
Probability of death in SOLSTICE by CMV status	2.5%	1.3%	-	-	-
Relative risk of death (CMV vs nCMV) from SOLSTICE	1.95	-	-	-	-

Abbreviations: NS, not statistically significant

* Heart, pancreas, double organ, and intestine.

2.7 Issue 7: Modelling of mortality in stage 2 Markov

The ERG originally agreed with the sources of data used to estimate the mortality parameters in the stage 2 Markov model (the NHS Organ Donation Annual Activity Report and the Haematological Malignancy Research Network - HMRN). Nonetheless, the ERG noted that the company needed to ensure consistency between the data used and when patients were assumed to enter the economic model after transplant.

The ERG disagreed with the long-term assumption made for both the SOT and the HSCT populations that the mortality estimate observed for the last year of data available in the NHS Organ Donation Annual Activity Report (year 10) and in the HMRN data (year 5), respectively, would be observed for

the remainder of the model (or until general mortality background rates were higher than the transplant-specific rates). Given that the data available indicated that transplant-specific mortality decreased with time since transplant, the company's approach was likely to overestimate the mortality of transplanted patients.

It was also noted that the ERG for TA591 reported that the life expectancy of patients in the long-term Markov phase of the model was a key driver of incremental QALYs and hence cost-effectiveness. The ERG for TA591 used the same HMRN data to estimate mortality in the first 5 years post-HSCT, however, after 5 years the ERG ran a scenario using the RR applied to general population mortality from Martin *et al.* (RR 4.5).[34]

Finally, the ERG also noted that the transition from the mortality in the stage 1 Markov to the stage 2 Markov model for HSCT patients implied an increase in mortality rates from 1.3% to 1.5%, which did not reflect a clinically plausible scenario (given that data suggested the opposite trend).

Therefore, before TE, the ERG recommended that the company changed its approach to estimating mortality in the stage 2 Markov model to ensure:

1. That the cost-effectiveness of maribavir in the trial population was captured and that mortality in the phase 2 Markov model reflected the appropriate population and time since transplant.
2. That overall mortality was not overestimated after 5 years for HSCT patients and after 10 years for SOT patients. In order to do this the ERG recommended that the company investigated the possibility of using a RR to adjust background survival for HSCT patients in the long term (similar to what has been done by the ERG in TA591).
3. A clinically plausible transition between mortality rates from the stage 1 to the stage 2 Markov models.

2.7.1 Company's response to technical engagement

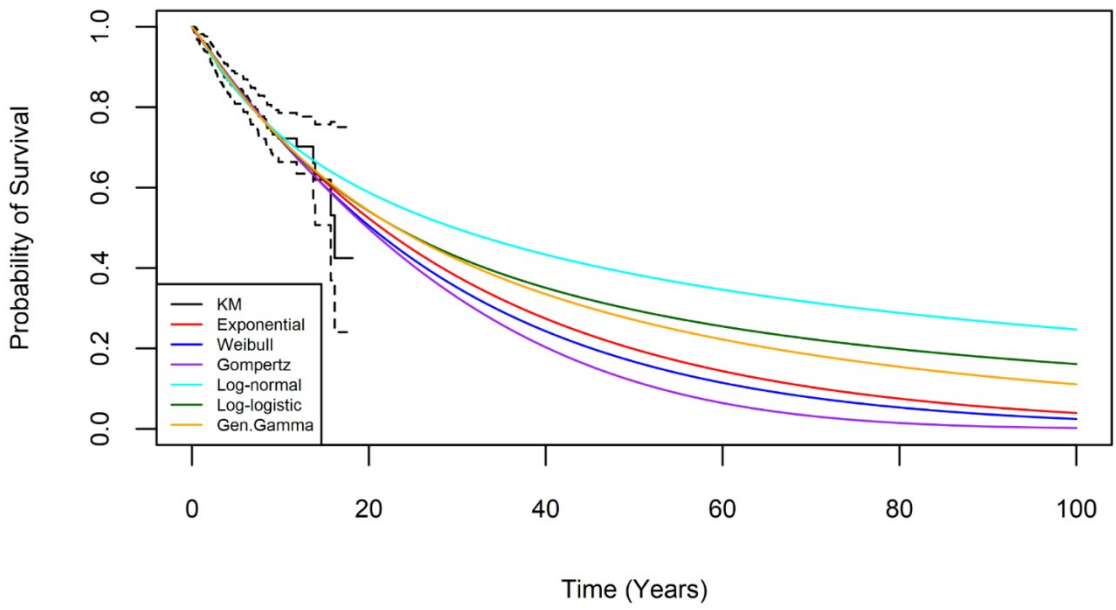
The company's updated model assumed a TST of [redacted] days for SOT patients and [redacted] days for HSCT patients. Therefore, the company reflected this in the associated mortality experienced by patients transitioning to the stage 2 Markov.

To address the issue of overestimation of long-term mortality for HSCT patients, the company used the data from Martin *et al.* 2013 highlighted by the ERG, which was also used to inform mortality in

the letermovir NICE appraisal (TA591). The company obtained KM data from the author of the study 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 company considerer that the latter subgroup represented the closest age match to the SOLSTICE population, and therefore, used it to inform the model. The company then fitted survival curves to these 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 became lower than the general population.

Parametric survival models were fitted to the data based on the methods recommended in NICE DSU Technical Support Document 21. The company chose the exponential model as it considered it provided a good visual fit (Figure 3), as well as having the lowest Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). A scenario using the Gompertz model was also provided.

Figure 3. Survival curves fitted to the Martin *et al.* 2013 HSCT survival data



The company did not change their approach to estimating long-term mortality for SOT patients as these were based on 10 years of data.

2.7.2 ERG's critique of company's approach after technical engagement

As discussed in Section 2.3, the ERG considers that a mean-based approach for TST would have been a better reflection of the whole population under consideration rather than focusing on median

values. Therefore, the ERG replaced median TST by mean TST in the model, which automatically updated the impact of TST on mortality.

The ERG is uncertain if the company's choice of the exponential model is appropriate as it seems to considerably overestimate survival after year 20 (Figure 3). The scenario using the Gompertz model had a negligible impact on the company's base case ICER; however, Figure 3 would suggest that the Gompertz curve also overestimates survival after year 20. Given that at year 27 in the model (20 years of the KM data from Martin *et al.* plus 5 years of HMRN data plus 1.5 years of stage 1 Markov) there were 31% of patients alive in the maribavir HSCT arm and 30% of patients alive in the IAT HSCT arm, the extrapolated portion of the curve will have a considerable impact on mortality after that period.

Therefore, the ERG has conducted a scenario analysis where the RR from Martin *et al.* of RR 4.5 was applied to the general population mortality, as suggested in TA591. The impact of the final ICER was negligible.

2.8 Issue 8: Modelling of graft failure

The ERG disagreed with the company's assumption that the rates of graft loss reported in Hakimi *et al.* (used in the model), were biannual, but instead noted that the estimates provided in the study were annual. Importantly, the ERG noted that the estimates from Hakimi *et al.* used by the company in their base case were only applicable to patients within their first-year post-transplant (as the rates chosen by the company were for patients who had a CMV event within 3 months after transplant), thus, the rates were not reflective of the risk of graft failure for the SOT SOLSTICE population.

The ERG disagreed with the company's assumption that 100% of patients with graft failure get a second transplant in the model. The ERG's clinical experts advised that less than 5% of patients get a re-transplant after first graft failure.

The ERG also had several concerns regarding the company approach to incorporating the quality-of-life impact of graft loss into the model. Firstly, the disutilities were applied only in the 4-week model cycle in which patients experienced graft failure, implicitly assuming that graft loss impacted quality of life for only 4 weeks. The ERG considered this assumption inappropriate as graft loss is non-reversible and expected to have a long-lasting effect a patient's quality of life. As the ERG's clinical experts indicated that only a small minority of patients would receive a second transplant, the ERG considered that the disutility associated with graft failure should be applied until death (accounting

for additional age-related reduction in quality of life). Furthermore, as patients who experience graft loss are unlikely to receive a second transplant, those with kidney graft loss are expected to receive lifelong dialysis and therefore the disutility associated with dialysis should be estimated for these patients.

Additionally, the ERG was uncertain of why the company estimated graft loss disutilities based on utility estimates (with and without graft loss) for health state vignettes of only asymptomatic clinically significant CMV patients, rather than also including estimates for symptomatic clinically significant CMV patients and patients without clinically significant CMV.

2.8.1 Company's response to technical engagement

The company agreed with the ERG that the data from Hakimi *et al.*, 2017 provides annual data and that the data originally used to model the risk of graft loss did not align with the TST of the population in SOLSTICE. Therefore, the company updated the probability of graft loss in the model to reflect the graft loss reported in the study for patients experiencing CMV events beyond 6 months (and up to 2 years) after SOT. Furthermore, even though this was not specifically stated in the company's response to TE, the ERG assumes that the company maintained its original assumption that graft loss could occur during the entire duration of the stage 1 Markov.

The company added that data from OTUS provided evidence that patients may still experience graft loss events up to 2-years post-transplant. The company also mentioned evidence for longer-term risk of graft loss from the retrospective GENOME Canada study, which was designed to define the impact of viremia on graft and patient outcomes. The company considered that data from GENOME Canada provided further evidence that patients with CMV may still experience graft loss at approximately 9-years post-transplant.

Regarding the ERG's concern that 100% of patients with graft failure were assumed to get a second transplant in the model, the company reported that if an assumption were to be made that patients with a heart, liver or lung transplant are not able to have a retransplant, then, the model should assume that these patients would be at risk of immediate death. Therefore, the company conducted a scenario where 100% of patients were not eligible for retransplant and were at risk of immediate death (except for renal transplant patients who would receive lifetime dialysis). The company reported that this scenario had a small impact on the ICER. The company also reported assigning a utility decrement associated with graft loss over patients' lifetime, as per the ERG's suggestion.

Finally, the company updated their utility analysis to include asymptomatic CMV; symptomatic CMV; and nCMV patients in the estimation of the disutility associated with graft loss. The disutility value has been updated 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. A simple average was then taken of the decrements from the three CMV categories. Due to limited data on heart, lung and other graft loss, the average disutility of a lung graft loss was used as a proxy to inform the utility decrement for these graft losses. The utility decrements for a kidney graft loss was 0.177 while other graft losses were associated with 0.294.

2.8.2 ERG's critique of company's approach after technical engagement

The company should investigate if graft failure events occurred in OTUS and use these data in the model if these are available.

If the company does not change its current modelling approach, or graft failure data from OTUS are not available, then the ERG is satisfied with the company's updated approach to modelling graft failure in the model.

The ERG agrees with the changes made by the company, however, notes that the utility decrements for a kidney graft loss (0.177) and a lung graft loss (0.294) estimated by the company are quite high. The company's assumption that the 0.294 disutility observed for lung loss was applicable to the other graft losses is not a conservative one, as the benefit associated with maribavir increases with the assumption that graft loss has a higher burned on patients' quality of life. Therefore, the ERG conducted a scenario analysis where the disutility for kidney loss was used to estimate the impact of a liver, heart, and other organs transplants. Due to the very low number of graft losses occurring the model, the impact on the final ICER was negligible.

2.9 Issue 9: Modelling of disease complications

The company's base case did not originally include graft versus host disease (GvHD) events or any leukaemia recurrences in the base case model.

The ERG's clinical experts indicated that HSCT patients with chronic GvHD (i.e., unresolved GvHD at 100 days post-transplant) have a higher probability of CMV recurrence due to intense immunosuppressant treatment and are expected to not survive beyond 2 years after transplant. Out of the 141 HSCT patients in SOLSTICE, new GvHD was reported during the study for 25 (26.9%)

maribavir patients and for 10 (20.8%) HSCT recipients in the IAT group. Furthermore, 6 (6%) patients and 5 (10%) patients had chronic GvHD at baseline, in the maribavir and the IAT arms, respectively, while 23 (25%) patients and 8 (17%) patients had acute GvHD at baseline, in the in the maribavir and the IAT arms, respectively. It was not possible for the ERG to identify which of the new cases of GvHD occurring during SOLSTICE became chronic cases; or which baseline acute cases also became chronic; however, given that HSCT patients entered the trial, on average, over 100 days after transplant (maribavir: mean 149 days, IAT: mean 113 days) it would be clinically plausible that most new/acute GvHD cases during the trial became chronic.

Therefore, in order to estimate the impact of GvHD in the economic results, the ERG recommended that the company run a scenario analysis where the pooled percentage (i.e., not differentiating by CMV or nCMV) of patients with chronic GvHD at baseline in SOLTICE was used to estimate disease in the model; and another scenario where all acute and new cases in SOLSTICE (in addition to the chronic cases at baseline) were assumed to become chronic during the trial. These scenarios should assume that patients with chronic do not survive beyond 2 years after transplant.

The ERG also noted that in TA591, the ERG-preferred scenario included the assumption that 47% of patients have leukaemia relapse; and that during the 6-month survival period of these patients, a per cycle cost of £6,460 was also applied, together with a per-cycle disutility of 0.0114.

Therefore, in order to estimate the impact of underlying disease recurrence for HSCT patients, the ERG also recommended that the company run a scenario analysis which:

- Assumed that 47% of patients with a recurrence live for 6 months from recurrence of leukaemia;
- Assumed that patients with disease recurrence experience a per-cycle disutility of 0.0114;
- Updated the per-cycle cost of £6,460 (2015/2016 prices) to the correct price year and applies it in every cycle of the model for 6 months.

2.9.1 Company's response to technical engagement

The company conducted a scenario analysis where 47% of HSCT patients were assumed to have a relapse in their underlying condition. The scenario incorporated a risk of mortality where all 47% of patients were assumed to die in the same cycle as the relapse occurred, as well as producing 6-months of costs and utility decrements. The company noted that while a more accurate

implementation of this approach would have allowed detailed tracking of patients in the Markov engine, the approach implemented overestimated utility, costs, and mortality in the maribavir arm. Therefore, the scenario analysis was considered conservative. The company added that given that the impact on the ICER was small, the approach taken was deemed pragmatic and sufficient to provide the committee with reassurance that relapse in underlying disease would not impact the decision on cost-effectiveness.

With regards to GvHD, the company reported that there is a weak link between the presence of CMV and the emergence of chronic or acute GvHD, and therefore, the base case analysis excluded GvHD events. Instead, GvHD was included in a scenario analysis where a relationship was established between CMV and GvHD based on a study from Hahn *et al*. 2008. The study provided estimates to include a higher risk of GvHD in the CMV health state compared with the nCMV health state. Cost and utility associated with a GvHD were identified from published literature. The company concluded that excluding GvHD events from the base case analysis is a conversative assumption and including GvHD would only further improve cost-effectiveness of maribavir.

2.9.2 ERG's critique of company's approach after technical engagement

The company reports that the scenario analysis incorporating the risk of leukaemia recurrence considered 6-months of costs associated with occurrence, however, the company estimated 2 years of costs and 1 year of a utility decrement of 0.0114. The £6,460 cost of recurrence was a 3-monthly cost (which the company multiplied by 8 to estimate 2-year costs). The ERG is unclear why the company was trying to estimate 2-year costs. To estimate 6-months of costs £6,460 should have been multiplied by 2. The ERG corrected this in the model and the impact of including leukaemia recurrence on the final ICER decreased. More details are given in Section 2.14 of the ERG report.

The company did not conduct the scenario analysis requested by the ERG where GvHD independent of CMV status was included in the model. Instead, the company included a scenario where patients with CMV experienced higher rates of GvHD (but did not experience higher mortality) therefore, increasing the benefit associated with maribavir. Nonetheless, and as discussed by the ERG in Section 1.4 of the ERG's original report, chronic GvHD is linked to higher mortality. If treatment-agnostic GvHD events had been included in the model and if these patients were assumed to be dead at 2 years after entering the model (as suggested by the ERG), it is likely that the ICER associated with maribavir would have increased.

Therefore, the ERG recommends including a scenario analysis assuming that the pooled percentage (i.e. not differentiating by CMV or nCMV) of patients with chronic GvHD in OTUS is used in the model and that the company assumes that patients with chronic GvHD do not survive beyond 2 years after transplant.

If the company does not change its current modelling approach, then the ERG reiterates its preference for having an analysis assuming that the pooled percentage (i.e. not differentiating by CMV or nCMV) of patients with chronic GvHD at baseline in SOLTICE were the only patients who had chronic disease over 20 weeks; and another scenario where all acute and new cases in SOLSTICE (in addition to the chronic cases at baseline) are assumed to become chronic during the trial. These scenarios should assume that patients with chronic GvHD do not survive beyond 2 years after transplant.

2.10 Issue 10: Estimation of utilities

The ERG was originally concerned with the company's approach of using simple averages of cross-walked EQ-5D-3L data to estimate health state utility values without consideration for the bias introduced by incomplete follow up. Given there was missing data, a simply average of measurements at weeks 0, 4, 8, 12, 16, and 20 was deemed inappropriate, as was the inclusion of utility scores which occurred before responder identification at week 8.

Therefore, during clarification, the ERG requested that the company used a linear mixed effects model to estimate the health state utility values. Nonetheless, during clarification, the company also provided EQ-5D-5L data which showed a higher loss to follow up in the IAT arm. The ERG was concerned that the substantial difference in missing data observed between the maribavir and IAT arms was likely due to confounding factors and the data was likely missing not at random. Therefore, before TE, the ERG recommended that the company investigated whether multiple imputation and pattern-mixture modelling methodologies could limit or overcome the bias (of unknown magnitude and direction) introduced to the utility estimates by the missing not at random EQ-5D data.

The ERG also disagreed with the implausible transition from the utilities used in the stage 1 and the stage 2 parts of the model. Patients in the SOT CMV state prior to week 52 suffered a drop in utility when the model switched to an alive/dead model. This was inconsistent with the company's assumption that all patients were free from CMV from the end of the stage 1 Markov.

The ERG was also concerned that the utility values applied in the stage 2 Markov underestimated the quality of life experienced by nCMV patients. These patients suffer a considerable drop in their quality of life after week 52 without a plausible explanation, given that their CMV status was considered to not change after that point in time.

Finally, the ERG noted that the company applied age-adjustments to the utility values in the stage 2 Markov, however, used Szende *et al*. 2014 as the source of general population utilities rather than Ara *et al*. 2010. The ERG noted that Ara *et al*. 2010 has been used extensively in previous NICE technology appraisals and provides more granular utility estimates (by age rather than age ranges).

2.10.1 Company's response to technical engagement

The company provided a re-analysis of the EQ-5D-5L data from SOLSTICE with an assessment of missing data, concluding that the difference in dropouts observed between the maribavir and IAT arms was largely attributable to greater discontinuation and initiation of rescue treatment in the IAT arm. The company also observed that, during the treatment period, patients in the IAT arm experienced a larger decline in EQ-5D-5L scores prior to dropout, however, patients dropout during the 8-week treatment period constituted only a small number of patients in each arm (18 for maribavir, 23 for IAT). The majority of patients remained in the study until week 20 for both groups and exhibited similarly stable EQ-5D-5L scores.

The company stated that as a conservative approach, multiple imputation (MI) analysis with the missing at random (MAR) assumption were used in the updated economic analysis. Utility values were imputed using MI techniques including all randomised subjects. The imputation was performed several times and with a fixed seed value using a Markov-chain Monte Carlo method. Utility scores were then recalculated using the imputed values. The mixed models were performed by each imputation and the estimates were combined to produce adjusted results.

The company also updated the utility values to ensure that the 8-week utility values were captured to the corresponding disease response status, which aligned with the primary endpoint date. The company preferred week 8 values over week 0 to 20 values because the fluctuations in health states that occur between week 0 to 20 may compromise the true impact of health state on quality of life. For this reason, the model was updated with the 8-week utility values with the multiple imputation method included (Table 9).

Table 9. Summary of utility values used in company base case

Health state	Utility values used before TE		Utility values used after TE	
	SOT	HSCT	SOT	HSCT
Stage 1 Markov model				
CMV	[redacted]	[redacted]	[redacted]	[redacted]
nCMV	[redacted]	[redacted]	[redacted]	[redacted]
Difference	0.082	0.112	0.111	0.023
Stage 2 Markov alive	0.76	0.66	0.81	0.71

Abbreviations: SOT, solid organ transplant; HSCT, haematological stem cell transplant; csCMV, clinically significant cytomegalovirus; n-csCMV, non-clinically-significant cytomegalovirus.

The company reported to have applied the methodology outlined by Ara *et al.* 2010 to estimate the utility decline of patients' with age, however, the ERG notes that the changes made by the company in the model do not seem to reflect the application of the methods outlined by Ara *et al.* The company's updated base case included updated raw numerical general population utility values based on which age adjustment was applied, however these values did not correspond with the those produced by the Ara *et al.* 2010 regression equation, and the true source could not be ascertained by the ERG.

2.10.1 ERG's critique of company's approach after technical engagement

The ERG considers the EQ-5D-5L analysis indicative of a relationship between early IAT dropout (during the treatment period) and EQ-5D-5L score prior to dropout. As such the EQ-5D-5L data from SOLSTICE is considered by the ERG to be missing not at random (MNAR). The company also acknowledged that the missing at random (MAR) assumption underpinning the original mixed modelling approach of utility data may not hold. The ERG also notes that the MI analysis provided by the company at TE relies on the MAR assumption and hence this analysis has the same limitation.

The ERG notes, however, that the company's original mixed effects model and updated MI utility analyses are likely biased in favour of the IAT arm as prior to dropout, patients on treatment in the IAT arm saw reduced EQ-5D-5L scores and so repeated measures of these patients with reduced utility were missing. Therefore, the ERG agrees with the company's rationale that using the MI model to estimate utilities is a conservative approach when it comes to dealing with missing data.

Finally, although the EQ-5D-5L data from SOLSTICE was mapped to EQ-5D-3L using the van Hout *et al.* 2012 algorithm in the company's original submission it was not clear if this was also done for the company's TE response.

The ERG notes that the company's approach of using week 8 utility values is an improvement in relation of the company's original approach of including utility values from week 0 to week 8 in the analysis (i.e., before patients achieved a response). However, the ERG is unclear why the company excluded the utility data from weeks 12, 16 and 20 from the analysis, and recommends these data points are included in the MI model.

As seen in Table 9, the transitioning from stage 1 to stage 2 Markov for SOT CMV patients is more plausible as patients do not suffer an extreme drop in utility when the model switches. However, the ERG notes that the utility values applied for the stage 2 Markov might still underestimate the quality of life experienced by nCMV patients as these patients suffer a considerable drop in their quality of life after week 78 without a plausible explanation, given that their CMV status was considered to not change after that point in time.

Finally, the ERG does not consider age-related utility decrements to have been appropriately captured by the company's updated base case. As such the ERG has produced a scenario analysis applying the multiplicative age adjustment method outlined by Ara *et al.* and reports the results in Section 2.13.

2.11 Issue 11: Estimation of costs

The ERG had concerns that the administration costs applied for IV drugs in the IAT arm were overestimated as the company assumed that the daily cost of IV administration was equal to an NHS reference cost for complex chemotherapy at first attendance (SB14Z). The ERG considered the company's use of the SB14Z first attendance cost inappropriate for the following reasons:

1. The 2020/21 National cost collection guidance document notes that this cost applies to only the first administration of a chemotherapy cycle and that another lower reference cost for subsequent elements of a chemotherapy cycle (SB15Z) should be used for "Delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance".
2. Feedback from the ERG's clinical experts suggested that administration of the IV treatments for CMV (ganciclovir, foscarnet, cidofovir) would utilise an existing

central line and that approximately 4 hours of ICU nurse time would be required per administration of these IV drugs. As such, the application of a complex chemotherapy at first attendance cost means that costs associated with inserting catheters to facilitate IV treatment would be applied every day for the duration on treatment – this is inconsistent with the ERG's clinical expert feedback.

Therefore, the ERG recommended that the company estimated the administration cost for IV treatments based on the PSSRU hourly staff cost for a critical care staff nurse (band 5) and a hospital pharmacist, with 4 hours nurse time costed per administration of treatment to 2 patients; and 15 minutes hospital pharmacist time per administration.

The ERG also noted that company had applied substantially higher unit hospitalisation costs to patients in the CMV health state compared to the nCMV state. This was based on weighted average NHS reference costs for non-elective long stay for infectious diseases with or without interventions (£7,019.85 versus £1,969.53). The ERG noted that application of the higher cost (with interventions) had resulted in double counting the CMV intervention costs given that acquisition and administration costs for CMV treatment were independently included in the model. As such, the ERG considered the company's approach inappropriate and recommended that the company captured the cost of a CMV-related hospitalisation by weighting average NHS reference costs for non-elective long stay for infectious diseases without interventions (WJ02C to WJ02E) and applied the cost to hospitalisations occurring for both the CMV and nCMV health states.

The ERG considered that the costs associated with IAT retreatment were also overestimated in the model. The ERG noted that even although the company captured treatment discontinuation by applying a time on treatment (ToT) multiplier to the 4-week IAT acquisition and administration costs, no stopping rule was applied to retreatment with IATs, therefore, patients in the CMV state (with a recurrence event) were assumed to be on treatment until they exited the state or reached the end of the stage 1 Markov model. Even though it could be argued that patients with a CMV infection after an 8-week round of treatment with one specific IAT would simply switch to another IAT, recurrences are unlikely to happen with the frequency (and the duration) assumed in the company's model.

Finally, given the ERG's clinical experts' opinion that foscarnet is the most relevant comparator to maribavir, the ERG recommended that a scenario analysis was used where the first line IAT

treatment consists of the cost of foscarnet only, with the other IATs being a retreatment option for further lines.

2.11.1 Company's response to technical engagement

The company reiterated its consideration that the "Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance" NHS reference cost, is the most suitable cost for the administration of intravenously administered drugs in the IAT arm, based on what the company considered to be a precedent set by TA591.

The company updated the unit hospitalisation costs applied to patients in the CMV state, applying £3,100.47 per hospitalisation, which is the weighted average of the WJ02C-WJ02E non-elective long stay NHS reference costs. Unit hospitalisation costs applied to patients in the nCMV state remained unchanged at £1,969.53 (weighted average of all WJ02C-WJ02E service costs as opposed to solely non-elective long stays). The company considered that a higher unit hospitalisation cost should be applied to patients in the CMV state, "*to reflect the differences in severity and intensity of care between CMV and nCMV patients*" but did not provide any supporting rationale or evidence for this assumption.

The company did not undertake the ERG's suggested scenario where the first line IAT treatment consists of the cost of foscarnet only, with the other IATs being a retreatment option for further lines.

2.11.2 ERG's critique of company's approach after technical engagement

IV administration costs

The company did not address the concerns detailed in the ERG report regarding the contextual differences between the company's use of the SB14Z NHS reference cost and that in which it was used in TA591. The ERG reproduces, below, the limitations of the company's use of the SB14Z NHS reference cost as a daily IV administration cost as outlined in the ERG report:

- *"The company originally noted that this approach was in line with TA591. However, the ERG notes that although the SB14Z reference cost was used in TA591, it was used in a much more restricted and temporary manner – for 5% of patients who received an **initial** IV infusion for the mean duration of IV letermovir within the PN001 trial. This was based on the assumption that a proportion of patients would not be able to tolerate the initial oral letermovir*

administration; and that all patients would switch to oral letermovir once the drug was tolerated.

In contrast, for this STA, the SB14Z reference cost is applied daily for all patients receiving IV treatment for the entire duration of treatment. The ERG therefore considers the company's use of the SB14Z first attendance cost as a daily administration cost inappropriate for the following reasons:

- *The 2020/21 National cost collection guidance document notes that this cost applies to only the first administration of a chemotherapy cycle and that another lower reference cost for subsequent elements of a chemotherapy cycle (SB15Z) should be used for, "Delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance".*
- *Feedback from the ERG's clinical experts suggested that administration of the IV treatments for CMV (ganciclovir, foscarnet, cidofovir) would utilise an existing central line and that approximately 4 hours of ICU nurse time would be required per administration of these IV drugs. As such, the application of a complex chemotherapy at first attendance cost means that costs associated with inserting catheters to facilitate IV treatment would be applied every day for the duration on treatment – this is inconsistent with the ERG's clinical expert feedback."*

Therefore, the ERG does not consider this issue to have been properly addressed in the company's response to TE and has conducted two alternative scenario analyses to address the issue:

1. The SB14Z and SB15Z NHS reference cost codes were used as intended by the 2020/21 National cost collection guidance document – SB14Z was used for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle. Due to model structure constraints this was implemented as a weighted average of the two costs (by the number of administrations in each IAT treatment cycle). This scenario resulted in a daily administration IV cost of £343.
2. The daily administration costs for IV treatments were estimated based on the PSSRU hourly cost of a critical care nurse based on the ERG's clinical expert estimates that administration for 2 patients concurrently occupied 4 hours of a nurse's time (Guidelines for Provision of Intensive Care Services [FICM/ICS] outline a 2:1 patient to nurse ratio for level 2 patients).

The cost of 15 minutes of hospital pharmacist time was also added. This scenario resulted in a daily administration IV cost of £180.

Results of these analyses are provided and discussed in Section 2.14.

Hospitalisation costs

The ERG remains unclear why the hospitalisation costs of patients with or without clinically significant CMV would differ beyond CMV-related treatment acquisition and administration costs, which are already separately costed in the company's model. As such, the ERG preference is to apply an equal unit hospitalisation cost to both CMV and nCMV patients. Namely, the weighted average of all WJ02C-WJ02E service costs (£1,969.53) as this reflects hospitalisations due to a variety of infectious diseases of varying duration. The ERG has produced a scenario analysis investigating the impact of this change and presents the results in Section 2.14.

Cost of IAT retreatment

Given the ERG's consideration that recurrences are still likely to be overestimated in the model (see Section 5), the costs associated with IAT retreatment are also likely to continue to be overestimated in the model.

Due to the structural restrictions of the company's model, and the limited review time, the ERG could not undertake the scenario analysis suggested before TE where the first line IAT treatment consisted of the cost of foscarnet only, with the other IATs being a retreatment option for further lines. This would have reflected the ERG's clinical experts' opinion that foscarnet is the most relevant comparator to maribavir, but would also likely decrease the overall costs of retreatment (even though it would have increased the cost associated with the initial round of IAT treatment) given that foscarnet was the most expensive treatment in the IAT basket.

2.12 Company's updated cost-effectiveness results

The deterministic results of the company's updated cost-effectiveness analysis are reported in Table 10. The equivalent probabilistic results are provided in Table 11.

According to the company's analysis maribavir is expected to increase patients' life expectancy by [redacted] years compared with IATs, at a lower cost and incremental QALYs, resulting in the dominance of maribavir. The company's probabilistic results also show dominance and are closely aligned with

the deterministic values. The company did not provide life years gained results in its probabilistic results.

The ERG notes that the company's separate ICERs for SOT and HSCT patients (provided in the company's response to TE document) also show dominance of maribavir. Nonetheless, the HSCT population remains the one where the benefit of maribavir is smaller. Furthermore, the ERG notes that the company's approach to weighting OTUS SOT and HSCT recurrence rates and applying the same weighted rate in both the SOT and HSCT models is incorrect. Given that the population outcomes are weighted for the final ICER, the company effectively "double-weighted" rates from OTUS.

Furthermore, the ERG originally noted its concern that the company was using +/-10% of the mean value to estimate the standard error (SE) in the probabilistic sensitivity analysis when measures of uncertainty were not reported. The ERG noted that a variation of 10% was low and that typically, a SE of 20% is used when measures of uncertainty are unavailable. The ERG added that this might have explained the relatively narrow eclipse of cost-effectiveness iterations. Therefore, the ERG recommended that the company used a 20% variation around means to conduct PSA during TE.

The company did not report changing this in its response to TE, however, the ERG's investigation of the model showed that +/-10% variation is still being used to estimate the uncertainty around key inputs, such as utility values used. The ERG therefore recommends that the company changes this in the model to be 20%.

Table 10. Company's base case deterministic results

Interventions	Total Costs (£)	Total LYG (undiscounted)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Maribavir	[redacted]	[redacted]	[redacted]	-	-	-	-
IAT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 11. Company's base case probabilistic results

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Maribavir	73,296	6.58	-	-	-
IAT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

2.13 ERG scenario analysis

The scenario analyses undertaken by the ERG are explained throughout the report. Results of the exploratory analyses conducted using the trial population are reported in Table 12. The following analyses were condcuted:

1. Using mean TST from SOLSTICE instead of median TST at baseline for SOT and HSCT patients.
2. Limiting the stage 1 Markov to 39.2 weeks.
3. Assuming that the probability of maintaining clearance is independent of the treatment received by patients, and only dependent on time spent in clearance (i.e., the probability of maintaining clearance in the model is the same in both treatment arms, and sourced from the IAT arm).
4. Including leukaemia recurrence in the model and correcting the costs of disease to reflect 6 months of survival.
5. Including GvHD as a disease complication in the model.
6. Applying the multiplicative age adjustment method outlined by Ara *et al.*
7. Using the SB14Z and SB15Z NHS reference cost codes for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle. Due to model structure constraints this was implemented as a weighted average of the two costs (by the number of administrations in each IAT treatment cycle). This scenario resulted in a daily administration IV cost of £343.
8. Estimating the daily administration costs for IV treatments based on the PSSRU hourly cost of a critical care nurse, based on the ERG's clinical expert estimates that administration for 2 patients concurrently occupied 4 hours of a nurse's time (Guidelines for Provision of Intensive Care Services [FICM/ICS] outline a 2:1 patient to nurse ratio for level 2 patients). The cost of 15 minutes of hospital pharmacist time was also added. This scenario resulted in a daily administration IV cost of £180.

9. Applying an equal unit hospitalisation cost to both CMV and nCMV patients. Namely, the weighted average of all WJ02C-WJ02E service costs (£1,969.53) as this reflects hospitalisations due to a variety of infectious diseases of varying duration.

The results in Table 12 show that the company's scenario in the model which allows the consideration of GvHD events in the analysis leads to a decrease in incremental QALYs and in cost savings associated with maribavir (therefore, worsening the cost-effectiveness of the drug). The ERG is surprised with the direction of the impact of including GvHD on the results, however, did not have sufficient time to investigate the issue further. Nonetheless, the ERG notes that the company's approach of including a higher probability of GvHD linked to CMV events should have increased the benefit associated with maribavir and therefore recommends that the company investigates the implementation of this scenario in the model. Notwithstanding, and as discussed in Section 2.9.2, the ERG considers that a more robust approach to including GvHD events in the model would have been to have treatment-agnostic GvHD events with an assumption that patients with chronic GvHD would die 2 years after entering the model. The impact of this would be expected to increase the final ICER for maribavir vs IAT.

The results in Table 12 also show that the model key drivers are the length of the stage 1 Markov, followed by the IV administration costs associated with IATs, and finally the assumption that maribavir patients have a lower probability of recurrence regardless of being off treatment (for the first 12 weeks after stopping treatment).

Decreasing the length of time over which patients can experience CMV recurrences from 78 weeks to 39 weeks after baseline increases the ICER from dominant to [redacted]. The ERG notes that SOLSTICE provided data for CMV clearance and recurrence 20 weeks after patients' index events, and after a mean TST of [redacted] days for SOT patients and [redacted] days for HSCT patients. Therefore, a stage 1 Markov of 39 weeks inform patients' recurrences [redacted] after SOT and [redacted] after HSCT. The ERG caveats the fact that shortening the time horizon of the stage 1 Markov model still relies on the use of the OTUS data and on the company's flawed assumptions that: 1) the populations in SOLSTICE and OTUS are directly comparable and 2) that third and further recurrences in the model happen at the same rate as second recurrences in OTUS, which has not been demonstrated by the OTUS data. When the ERG shortened the time frame of the stage 1 Markov model to be 20 weeks, and therefore reflect the SOLSTICE time horizon, the ICER increased to [redacted] per QALY gained.

The assumptions made to estimate the IV administration costs of IATs in the model also have a considerable impact on the final ICER, where using the SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle increases the ICER from dominant to [redacted]. Alternatively, when the ERG estimated the cost of IV administration using clinical expert input that administration for 2 patients concurrently occupied 4 hours of a nurse's time, with an addition of the cost of 15 minutes of a hospital pharmacist time increased the ICER to [redacted]. The ERG's first IV cost scenario yields a higher IV administration cost, which is why the ICER in the first scenario is lower than the ICER in the second cost scenario.

Finally, assuming that maribavir patients have a higher probability of clearance at week 8 (and therefore a lower probability of graft loss and other CMV-related complications) but have the same probability of recurrence as IAT patients (who have achieved clearance on IATs) increases the ICER from dominant to [redacted].

When the ERG's scenarios are combined, the final ICERs range between [redacted] and [redacted] per QALY gained, depending on the assumption used to estimate the IV administration treatment costs and, on the assumption made for the maribavir treatment effectiveness (Table 13). The ERG notes that when these scenarios are run assuming a 20-week stage 1 Markov model the equivalent ICERs range from [redacted] to [redacted] per QALY gained.

When the ERG disaggregated the results by type of transplant, the range provided above varied from [redacted] and [redacted] for SOT and HSCT patients, respectively, at the "best-case scenario" end of the ERG's range (i.e., the equivalent to the [redacted] "combined" ICER). At the more conservative end of the ERG's range, ([redacted]), the disaggregated ICERs are [redacted] and [redacted] for SOT and HSCT patients, respectively.

The ERG notes that all the scenarios reported are using the SOLSTICE data as the main source of clinical outcomes in the model. However, the ERG's preferred approach would be to use OTUS data to model the IAT arm of the model, and to then apply the relative treatment effect from SOLSTICE in order to estimate outcomes for the maribavir arm.

Table 12. Deterministic results

		Incremental costs	Incremental QALYs	ICER
0	Company's base case	[redacted]	[redacted]	[redacted]

1	Using mean TST	[redacted]	[redacted]	[redacted]
2	Limiting the stage 1 Markov to 39.2 weeks	[redacted]	[redacted]	[redacted]
3	Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)	[redacted]	[redacted]	[redacted]
4	Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival	[redacted]	[redacted]	[redacted]
5	Including GvHD in the model	[redacted]	[redacted]	[redacted]
6	Including the Ara *et al.* adjustment	[redacted]	[redacted]	[redacted]
7	Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle	[redacted]	[redacted]	[redacted]
8	Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time	[redacted]	[redacted]	[redacted]
9	Applying an equal unit hospitalisation cost to both CMV and nCMV patients	-£140	0.209	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 13. Deterministic results for overall population incremental

		Incremental costs	Incremental QALYs	ICER
0	Company's base case	[redacted]	[redacted]	[redacted]
1	Using mean TST	[redacted]	[redacted]	[redacted]
1+2	Using mean TST Limiting the stage 1 Markov to 39.2 weeks	[redacted]	[redacted]	[redacted]
1+2+4	Using mean TST Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival	[redacted]	[redacted]	[redacted]
1+2+4+5	Using mean TST Limiting the stage 1 Markov to 39.2 weeks	[redacted]	[redacted]	[redacted]

	Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model			
1+2+4+5+6	Using mean TST Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Including the Ara *et al.* adjustment	[redacted]	[redacted]	[redacted]
1+2+4+5+6+9	Using mean TST Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Including the Ara *et al.* adjustment Applying an equal unit hospitalisation cost to both CMV and nCMV patients	[redacted]	[redacted]	[redacted]
1+2+4+5+6+9+7	Using mean TST Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Including the Ara *et al.* adjustment Applying an equal unit hospitalisation cost to both CMV and nCMV patients Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle	[redacted]	[redacted]	[redacted]
1+2+4+5+6+9+8	Using mean TST Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Including the Ara *et al.* adjustment Applying an equal unit hospitalisation cost to both CMV and nCMV patients	[redacted]	[redacted]	[redacted]

	Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time			
1+2+4+5+6+9+7+3	Using mean TST Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Including the Ara *et al.* adjustment Applying an equal unit hospitalisation cost to both CMV and nCMV patients Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)	[redacted]	[redacted]	[redacted]
1+2+4+5+6+9+8+3	Using mean TST Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Including the Ara *et al.* adjustment Applying an equal unit hospitalisation cost to both CMV and nCMV patients Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

2.14 Conclusions and list of ERG's recommendations

The ERG considers that the OTUS study is a valuable source of evidence to inform further recurrence in the model. However, the company's methodology for using data from OTUS is inappropriate for decision making given the company's assumption that not only the populations, but also clearance and recurrence in both studies are directly comparable and interchangeable.

The ERG considers that a more robust approach would have been to use the OTUS data to model the probability of clearance and recurrence for IAT in the stage 1 Markov model, and then apply the relative risk of recurrence and clearance observed for maribavir compared to IAT from SOLSTICE to the IAT OTUS data. In order to maintain consistency in the clinical outcomes used in the model, the company should also use OTUS to model clinical outcomes such as mortality and mean time since transplant (TST) and, if available, data on graft failures and GvHD events. This would ensure that the IAT treatment arm (and by extension the maribavir treatment arm) are informed by internally consistent parameter estimates in the model. This would alleviate any concerns for using different and potentially incompatible sources of data.

The company's updated model alleviated some of the ERG's original concerns, however, it did not fully mitigate these. Specifically, the ERG was originally concerned that having the stage 1 Markov model extended to 52 weeks did not add any methodological or conceptual benefit to the economic analysis, and only introduced bias in favour of maribavir. The company's updated approach extended the stage 1 Markov to 78 weeks without a clear and consistent justification for this choice. The ERG, therefore, disagrees with the company's chosen duration of a "full cycle" of events and considers that this should match the time to second events in OTUS, which is 39.3 weeks.

Given the number of patients with third (or further) recurrences in OTUS was very low and the fact that OTUS patients were likely to be at a higher risk of recurrence events (due to the discrepancy between TST in SOLSTICE and OTUS – around [redacted] months for SOT patients and [redacted] months for HSCT patients in SOLSTICE, compared to 7 months for SOT patients and 1.7 months for HSCT patients in OTUS) – the ERG concludes that the OTUS data does not provide sufficiently robust evidence to model recurrence events beyond second recurrences after transplant.

Furthermore, the company's updated model uses different rates of recurrences for patients depending on how long they have been in the nCMV (i.e., clearance) state and based on the event being a first versus a second recurrence. This improves on the company's previous assumption of a constant rate of recurrence. Nonetheless, the company's updated model still includes multiple recurrences beyond a second event and assumes that the rate of third and further recurrences is the same as that observed for second recurrences in OTUS. Data from OTUS shows that the rates of subsequent recurrences were much lower after second recurrence, thus, the company's approach is still overestimating the recurrences in the model and, therefore, the benefit associated with

maribavir. The ERG's approach to limiting the stage 1 Markov model to 39 weeks (time to second recurrence in OTUS) helps to mitigate this issue.

Furthermore, given the newly presented OTUS study, the ERG considers that the available KM OTUS data should be used to estimate time to first clearance; time to first recurrence and second clearance; and time to and second recurrence and third clearance in the IAT arm of the stage 1 Markov model, with the duration of 39 weeks. The relative effect of maribavir vs IAT could then be taken from the SOLTICE trial.

Additionally, the ERG recommends that the company clarifies/investigates the following issues:

1. The potential impact on recurrence of adjusting for the imbalances of mean time since transplant at baseline across treatment arms in SOLSTICE.
2. The OTUS KM mortality data are used to estimate mortality in the IAT arm of the model, separated by HSCT and SOT. The ERG recommends that the company investigates if mortality by CMV status (within each population) is statistically significantly different for CMV and nCMV IAT patients. If this is the case, then the company would not have to use external literature to estimate CMV-related mortality, and the maribavir treatment effect derived from SOLSTICE leading to the difference in CMV events in the maribavir and IAT arms would generate the survival benefit associated with maribavir. If mortality by CMV status (within each population) is not statistically significantly different for CMV and nCMV IAT patients in OTUS, then CMV-related mortality from literature sources from Hakimi et al. 2017 and Camargo et al. 2018 should be applied to the OTUS KM data.
3. Including a scenario analysis assuming that the pooled percentage (i.e. not differentiating by CMV or nCMV) of patients with chronic GvHD in OTUS is used in the model and that the company assumes that patients with chronic GvHD do not survive beyond 2 years after transplant.
4. Including the utility data from weeks 12, 16 and 20 from SOLSTICE in the MI model.
5. Running a scenario analysis whereby first line IAT treatment costs consist of foscarnet only, with the other IATs being a retreatment option for further lines.
6. Removing the "double-weighting" effect of recurrence and clearance rates used from OTUS in the model.
7. Using +/-20% of the mean values to estimate the standard error in the probabilistic sensitivity analysis, when these are not available.

3 References

Hakimi Z, Aballéa S, Ferchichi S, et al. Burden of cytomegalovirus disease in solid organ transplant recipients: a national matched cohort study in an inpatient setting. *Transplant Infectious Disease* 2017;19(5):e12732.

NHS Blood and Transplant. Organ and Tissue Donation and Transplantation Annual Activity Report 2020/2021 2021 [Available from: https://www.odt.nhs.uk/statistics-and-reports/annual-activity-report/].

Camargo, J.F., 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, 2018. 24(4): p. 806-814.

Martin, P.J., et al., Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. J Clin Oncol, 2010. 28(6): p. 1011-6.

Ara, R. and J.E. Brazier, Populating an economic model with health state utility values: moving toward better practice. Value Health, 2010. 13(5): p. 509-18.

Hahn, T., 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. 26(35): p. 5728-34.

4 Appendix

Table A. Subgroup Analysis of Confirmed CMV Viremia Clearance Response at Study Week 8 by Duration From Current Transplant and Treatment Group (Modified Randomized Set)

1. McElreath R. *Statistical Rethinking*2015.

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]
Takeda reply to ERG review of company's response to the TE
11 July 2022

1. Introduction

Takeda received the ERG's response to the additional data and comments provided at technical engagement on 28 June 2022. This document contains Takeda's comments and response for each issue. We hope the additional information below can help resolve the outstanding issues for the Committee.

2. Review of issues

2.1 Issue 1: numerical imbalance in time since transplant in SOLSTICE

The ERG noted that two sets of data were presented for the mean TST for the SOT subgroup. The data in Table 1 below are the correct version, we had duplicated the overall mean results for the SOT subgroup in our previous response. We confirm all statistics were performed on the correct dataset, and that there is no meaningful statistical difference between treatment arms in the mean or median time since transplant.

Table 1. Mean and median time since transplant by treatment arm

Category	IAT (N=116)	Maribavir (N=234)
Time since solid organ transplant (days)		
N (%)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value		[redacted]
Mean	[redacted]	[redacted]
SEM	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value		[redacted]
Min, Max	[redacted]	[redacted]
Time since haematopoietic stem cell transplant (days)		
N (%)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value		[redacted]
Mean	[redacted]	[redacted]
SEM	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value		[redacted]

Min, Max	[redacted]	[redacted]
Overall time since transplant (days)		
N (%)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SEM	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value		[redacted]
Min, Max	[redacted]	[redacted]
		[redacted]

To address the ERG's concern that the logistic regression results may not show an effect due to the small time unit of days since transplant, Takeda performed an updated set of analyses with time since transplant defined in months. The updated results are provided in Table 2 and Table 3 for clearance and recurrence requiring treatment, respectively.

Table 2. Logistic regression of confirmed CMV viraemia clearance response at week 8, with time since transplant defined in months

Covariate	Adjusted OR (95% CI)	P-value
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Time since transplant (months)	[redacted]	[redacted]
Transplant type (HSCT vs SOT)	[redacted]	[redacted]
Prior use of CMV prophylaxis (Yes/No)	[redacted]	[redacted]

Table 3. Logistic regression of confirmed CMV viraemia recurrence requiring treatment after clearance at week 8, with time since transplant defined in months

Covariate	Adjusted OR (95% CI)	P-value
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Time since transplant (months)	[redacted]	[redacted]
Transplant type (HSCT vs SOT)	[redacted]	[redacted]
Time since clearance (months)	[redacted]	[redacted]

The results of these updated analyses, with time since transplant defined in months rather than days, show that time since transplant does not have a statistically significant impact on the odds of clearance and actually demonstrate a greater treatment effect for recurrence requiring treatment after adjustment for key clinical covariates. In summary, TST, whether measured in days or months, has a negligible impact on clearance or recurrence requiring treatment.

Given the ERG's concerns around the potential influence of non-significant effects included within the full model, Takeda have also explored the impact on results by adjusting for individual covariates alone. The results of these analyses are provided in

Table 4 and Table 5 for clearance and recurrence requiring treatment, respectively.

Table 4. Single covariate logistic regressions of confirmed CMV viraemia clearance response at week 8

Covariate	Adjusted OR (95% CI)	P-value
Model 1		
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Time since transplant (months)	[redacted]	[redacted]
Model 2		
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Transplant type (HSCT vs SOT)	[redacted]	[redacted]
Model 3		
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Prior use of CMV prophylaxis (Yes/No)	[redacted]	[redacted]

Table 5. Single covariate logistic regressions of confirmed CMV viraemia recurrence requiring treatment after clearance at week 8

Covariate	Adjusted OR (95% CI)	P-value
Model 1		
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Time since transplant (months)	[redacted]	[redacted]
Model 2		
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Transplant type (HSCT vs SOT)	[redacted]	[redacted]
Model 3		
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Time since clearance (months)	[redacted]	[redacted]

Given the unadjusted odds ratio for clearance from SOLSTICE of [redacted] (55.7% maribavir vs 23.9% IAT), the adjusted results show very little difference in the treatment effect. This demonstrates that the trial results are reliable and therefore the results of the economic model are robust to uncertainty in this estimate.

For recurrence requiring treatment, the unadjusted odds ratio for maribavir compared to IAT is [redacted] (27.0% maribavir vs 37.0% IAT). When adjusting for all key clinically relevant covariates, the treatment effect is much improved with an odds ratio of [redacted], showing that treatment with maribavir reduces the odds of a recurrence requiring treatment by [redacted] compared to IAT. Takeda note that there is some uncertainty in this estimate; however, when adjusting for only time since transplant, the key covariate raised by the ERG, the results still show a greater treatment effect compared to the unadjusted results. This provides further evidence that the treatment-specific recurrence probabilities used in the economic model are appropriate and not influenced by any differences in time since transplant.

Due to time constraints Takeda have not been able to generate the correlation estimates between covariates or conduct a variable selection procedure on the regression models. These can be provided at a later date if required.

2.2 Issue 2: Trial conduct and design leading to uncertainty

The ERG have noted that clinical opinion is needed to determine if the level of renal impairment at baseline is representative of the UK patient population and whether investigators would choose ganciclovir/valganciclovir as treatment options due to lower renal toxicity seen with these therapies. Takeda have reached out to a UK renal transplant surgeon (who was also a SOLSTICE UK trialist) who confirmed that repeat use of ganciclovir/valganciclovir was appropriate given the baseline measurements. Furthermore our HCP stated:

> *Renal impairment is very common in kidney transplant recipients (and probably relatively common in other solid organ transplants) this engenders a very significant anxiety about using foscarnet and any alternative is often considered such as a further reduction in immunosuppression coincident with reintroduction of vangancyclovir or IVIg. In short, caught between a rock and a hard place one is often tempted to try a further reduction in IS* [immunosuppression] *plus antiviral if not winning in the hope of avoiding* AKI [acute kidney injury] *in the context of foscarnet.*

With regards to the uncertainty around the subjective definition of clinically relevant recurrence, Takeda would like to re-iterate our previous responses on this point, and we maintain that a *clinically relevant* recurrence is one requiring treatment with anti-CMV therapy.

Furthermore, from a clinical perspective, CMV requiring treatment is associated with an impact on morbidity, quality of life and mortality therefore this outcome is more reflective of the key differences between patients who benefit from anti-CMV therapy.

2.3 Issue 3: Assumption of time elapsed since transplant at baseline in the model

Given the data provided at TE on duration from transplant date to start of antiviral treatment are not normally distributed, Takeda maintain that median values are most reliable, however we also note the minimal difference in cost effectiveness if the mean values are used. For the company's base case analysis, the incremental net monetary benefit increases by just [redacted] when the mean TST values are applied.

The ERG raised concerns about potential differences between the populations of the SOLSTICE trial and the OTUS study that may limit the reliability of using both data sources to inform different time points of the model. A key point the ERG raised was a difference between the clearance rates for the IAT or standard of care received, stating that the OTUS study showed a clearance at 8 weeks of [redacted], whereas the SOLSTICE trial had a clearance probability of just [redacted] at week 8. However, this comparison is comparing two different measures, as the OTUS value is based on Kaplan-Meier (KM) estimates and the SOLTICE value on response rates. As KM estimates for clearance are likely to be influenced by informative censoring (i.e., individuals who do not respond are discontinued but by censoring are assumed to have the same chance of a later clearance as those who are not censored) this comparison is unreliable. The OTUS study for solid organ transplant (SOT) showed that there were [redacted] clearance events from the population of [redacted] patients with R/R CMV, giving a probability of [redacted] for clearance in standard care. While this is greater than the estimate from SOLSTICE, the difference is not as stark as the ERG suggest. Unfortunately, data for the HSCT population are not currently available. Takeda will happily provide these values when available.

Takeda accept that there are some other differences as outlined by the ERG, and as such, Takeda have taken their suggestion to explore the impact of using OTUS to inform standard care for the first

clearance and recurrence as well to ensure alignment. The following changes were applied to the economic model to implement this approach:

1. Clearance probability for IAT changed to [redacted]
2. The unadjusted odds ratio ([redacted]) for clearance from SOLSTICE applied to estimate the probability of clearance for maribavir relative to the OTUS standard of care ([redacted]);
3. The probabilities given in Table 6 for first recurrence requiring treatment from OTUS applied for IAT, with the unadjusted odds ratio of [redacted] applied to estimate maribavir probabilities.
4. Apply all-cause mortality from both SOT and HSCT populations to inform mortality risks for those with n-csCMV, and apply relative risks from published literature[1, 2] to estimate the mortality risks for csCMV. See Table 7 for the complete set of mortality risks applied in the model. The KM data used to estimate these values is provided in Table 8 and Table 9 towards the end of this document.
5. Time since transplant based on OTUS data, using a median of [redacted] days for SOT and [redacted] days for HSCT.

The results of this analysis are given in Table 10 at the end of this document. The following additional scenarios were also performed around this analysis:

1. Using the standard care recurrence probabilities from OTUS for both maribavir and IAT arms;
2. Applying mean TST from OTUS.

Table 6. Probabilities for first recurrence requiring treatment for the OTUS baseline scenario analysis

Time since clearance	IAT/SC	Maribavir
4 weeks	[redacted]	[redacted]
8 weeks	[redacted]	[redacted]
12 weeks	[redacted]	[redacted]
16 weeks	[redacted]	[redacted]
20 weeks	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]

Table 7. Probabilities for mortality for the OTUS baseline scenario analysis

Input	SOT	HSCT
Up to week 8	[redacted]	[redacted]
n-csCMV (weeks 8 to 20)	[redacted]	[redacted]
csCMV (weeks 8 to 20)	[redacted]	[redacted]
n-csCMV (week 20 onwards)	[redacted]	[redacted]
csCMV (week 20 onwards)	[redacted]	[redacted]

The results of this scenario demonstrate that maribavir remains very cost-effective with an ICER of [redacted] per QALY gained. The full results are presented in Table 10, along with a range of additional scenario analyses relating to the OTUS baseline for standard care.

While Takeda consider the scenario using the OTUS study to inform the baseline treatment effects to be a useful exploratory analysis, we consider the current company base case to be the most appropriate. As SOLSTICE provides the most reliable source of evidence to inform treatment

effectiveness, we consider it most appropriate to align those treatment effects with the population from which they were measured. Hence, we consider focusing the economic analysis around the SOLSTICE trial for the first clearance and recurrence to be most appropriate.

Takeda acknowledge some uncertainties in modelling the post-trial effects, however, the OTUS study provides the most reliable evidence available to inform the likelihood of further recurrences beyond the SOLSTICE trial period. Given the company's base case analysis lies well below the lower NICE preferred willingness-to-pay threshold of £20k per QALY, Takeda believe any remaining uncertainties or decision risks are mitigated by these results.

2.4 Issue 4: Structural assumptions in the company's model

The ERG note that the evidence for multiple recurrences within the OTUS data is very low, however Takeda note that there is evidence within both OTUS and GENOME presented at ESOT 2021[3] that demonstrates up to six recurrences in SOT for OTUS, four recurrences for HSCT in OTUS and four recurrences in GENOME. The limited number of multiple recurrences observed reflect the small population of post-transplant patients who are refractory or resistant to prior anti-CMV therapies, and we acknowledge there may be some uncertainty here however the approach the ERG suggest of limiting the number of recurrences will not help resolve the uncertainty.

The literature also provides further evidence of multiple CMV recurrences with a paper by Chakrabarti (2002)[4] in 51 HSCT transplant patients where 11 patients had 3 or more episodes of CMV infection, and a paper by Melero-Ferrer (2012)[5] demonstrating six reinfections in a patient following a heart transplant.

We maintain that the 18-month length of stage 1 of the Markov model allows a more clinically plausible flow of patients in the model and allows the full capture of all recurrence events in this population, which has been ratified by data from OTUS, GENOME and discussions with clinicians. Furthermore, the length of stage 1 results in no CMV events occurring in stage 2 of the model, and we note the ERG are satisfied this is the case.

It should also be noted that the company's base case analysis results in an average of [redacted] recurrences in the IAT arm. The OTUS study reports a total of [redacted] recurrences ([redacted]) for SOT and [redacted] ([redacted]) for HSCT. When weighted by the proportion of SOT and HSCT patients in SOLSTICE, this results in an estimated overall recurrence rate of [redacted], demonstrating that the company's base case analysis is a reasonable reflection of the number of recurrences that would be expected to occur in the real world, and therefore, that the 78-week period for stage 1 of the Markov model is reasonable.

2.5 Issue 5: Overestimation of recurrence in the model

Takeda disagrees with the ERG's suggestion that the model should be restricted to allow only two CMV episodes i.e., only one recurrence. The OTUS study and the GENOME study both give clear evidence that many patients have more than two recurrences. patients can have far more than one recurrence, even as many as 5 recurrences after their index R/R CMV episode. Furthermore, as discussed in issue 4, the model prediction for the number of recurrences is a reasonable reflection of that observed in the OTUS study.

As SOLSTICE provides the most reliable source of evidence to inform treatment effectiveness, we consider it most appropriate to align those treatment effects with the population from which they were measured. Hence, we consider focusing the economic analysis around the SOLSTICE trial for

the first clearance and recurrence to be most appropriate rather than using OTUS to inform IAT clearance and recurrences rates.

We note the ERG stated that Takeda has not provided any justification for why the benefit associated with maribavir would only be observed for the first 12 weeks after clearance. We would like to clarify that this 12-week duration is the timepoint from the output of the primary endpoint at 8 weeks to the end of the duration of the SOLSTICE study at Week 20. Furthermore, the ERG mention that the justification for assuming a benefit associated with maribavir was also not clearly stated, however the benefit for maribavir has been demonstrated in the outcomes of the primary study endpoint of the SOLSTICE trial that demonstrated maribavir was statistically superior to conventional therapies for the clearance of R/R CMV at Week 8, and for the key secondary endpoint, maribavir was statistically significant to conventional therapies in a composite achievement of CMV DNA level < the lower limit of quantification (LLOQ) and symptom control at Week 8 with maintenance through Week 16.

2.6 Issue 6: Modelling of mortality in stage 1 Markov

The ERG raised concerns around the cross-over adjusted mortality analyses based on the SOLSTICE study and the justification for using the Inverse Probability of Censoring Weights (IPCW) method of adjustment rather than more advanced methods such as the Rank-Preserving Structural Failure Time model (RPSFTM). Takeda provided as part of the statistical analysis report the IPCW analysis as the primary adjusted analysis but also the RPSFTM method as a scenario analysis. The results of the RPSFTM were similar to those generated by the IPCW. For the IPCW, as can be seen in Section 3.3.2 of the IPD statistical analysis report for SOLSTICE, the estimated adjusted hazard ratio (HR) was [redacted]. For the RPSFTM method, Appendix B of the IPD statistical analysis report shows that the estimated adjusted HR was [redacted], demonstrating that the IPCW analysis is robust and reliable. Although the analyses demonstrate a non-significant difference, it does support the plausibility that CMV is causing an impact on mortality even in the short-term SOLSTICE trial, thus, supporting the CMV-related mortality risks derived from SOLSTICE in the model.

Takeda have also provided an economic analysis based on the OTUS study as a baseline and using published literature to inform the relative mortality risks for the n-csCMV and csCMV heath states. We believe that this analysis demonstrates that the company's base case is clinically plausible and may well underestimate the mortality impact that CMV has in the long term, given the mortality risks for the base case are based on only 20 weeks of data from SOLSTICE.

The ERG requested KM data from SOLSTICE split by transplant type as well as CMV status. However, given the cyclical nature of CMV with patients switching in and out of clearance and recurrence status, it is not feasible to provide KM curves by CMV status. KM plots can in theory be produced by defining the CMV status at a particular time point, but that status will not necessarily be maintained beyond that time point. Therefore, the KM plots would not fully represent CMV status as requested.

2.7 Issue 7: Modelling of mortality in stage 2 Markov

To inform the time frame for which stage 2 mortality estimates should be derived, Takeda considers the company's base case to be reasonable in the use of median TST given the influence of extreme outliers increasing the mean estimate. However, as noted by the ERG, the impact on the model of using the mean TST rather than the median is negligible ([redacted] difference in net monetary benefit) and, therefore, the uncertainty around this aspect of the model is not important to the decision problem.

Similarly, Takeda consider the use of the relative risk from Martin *et al.* to be methodologically flawed. However, as the ERG noted, the impact on the results is negligible and, therefore, the company's base case modelling for the stage 2 Markov can be considered appropriate.

2.8 Issue 8: Modelling of graft failure

The ERG have requested that we investigate graft failure events in OTUS. Overall, in OTUS-SOT graft loss occurred in [redacted] ([redacted]) patients including [redacted] patients following allograft rejection and [redacted] patients following graft infection. The estimated number of graft loss events in the company's base case analysis for the IAT arm is [redacted]%. Although this may be a slight underestimate in comparison to the real-world data from OTUS, the impact in terms of costs and quality of life in the model is relatively small. Therefore, the impact of this difference in the model results would be negligible and Takeda note the ERG are satisfied with the updated approach used to model graft failure.

2.9 Issue 9: Modelling of disease complications

The ERG suggested the inclusion of a scenario in which leukaemia disease recurrence is captured within the model, factoring in the costs, quality of life impact as well as the expected mortality associated with progressed disease. This scenario was based on an analysis suggested during the NICE appraisal of letermovir (TA591), which applied scenarios assuming survival up to 2 years. Our approach therefore used the assumption of 2 years of survival following a relapse; however, the ERG have suggested the 6 month survival scenario is more appropriate. The impact of this change does not have a meaningful impact on the results of the analysis.

Takeda consider the inclusion of leukaemia relapse mortality to potentially introduce double counting, given that the HSCT-specific mortality estimates applied in the economic model will already include the impact of disease recurrence. This scenario should, therefore, not be considered reliable.

The ERG have suggested a scenario analysis assuming a pooled percentage of patients with chronic GvHD in OTUS is used in the model. Unfortunately, the full OTUS HSCT report is not yet available. Takeda expect this will be delivered within two months of this document.

2.10 Issue 10: Estimation of utilities

The ERG requested clarity in the mapping algorithm used to estimate EQ-5D-3L values from the reported EQ-5D-5L data collected in the SOLSTICE trial for the analyses post-technical engagement. As per the original analyses, Takeda can confirm that the Van Hout 2012 algorithm was used for mapping of all EQ-5D IPD analyses we have provided based on the SOLSTICE trial.

With regards to the imputation of missing EQ-5D data, the ERG agreed that the multiple imputation method was likely to bias in favour of IAT and, therefore, the results were likely to be conservative estimates. As a result of this bias, Takeda focused the analysis on the Week 8 data to limit any further impact of missing data at later time points, and align with the primary endpoint of the trial. In addition to this, given the cyclical nature of CMV, the Week 8 time point is the point at which we are most likely to have the greatest differentiation of patients between the health states as they have completed up to a full course of treatment. Beyond this time point, some patients start to have recurrences and the number of patients who are cleared and experience the full quality of life benefit of treatment will reduce, limiting the ability to reliably estimate the health state impact on quality of life.

To provide clarity on the company's age adjustment to utilities, in the original ERG report, the ERG stated that "In line with TA591, it is recommended that the company utilises Ara *et al.* 2010 to

estimate the age-related utility decrements applied in the model." The Ara *et al* 2010 reference was "Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13(5):509-18. doi: 10.1111/j.1524-4733.2010.00700.x [published Online First: 2010/03/17]".

However, in TA591, the company applied the general population utility values from Ara and Brazier (2011), which was referenced as "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;14:539-45. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21669378". The utility values from Ara and Brazier (2011) were used by Takeda in the updated economic model; however, this was incorrectly referenced as the 2010 publication.

The impact on the economic model between the two approaches is not meaningful so the company has maintained its base case approach.

2.11 Issue 11: Estimation of costs

Takeda would like to clarify some confusion around what was performed in TA591, as the current ERG report risks the wrong precedence being advised to the committee. Rather than simply citing TA591 as precedence Takeda would like to provide additional clarity to the specific points raised in TA591.

The ERG note the following in their latest report (Section 2.11.2; pg 45-46)

> *""The company originally noted that this approach was in line with TA591. However, the ERG notes that although the SB14Z reference cost was used in TA591, it was used in a much more restricted and temporary manner – for 5% of patients who received an initial IV infusion for the mean duration of IV letermovir within the PN001 trial. This was based on the assumption that a proportion of patients would not be able to tolerate the initial oral letermovir administration; and that all patients would switch to oral letermovir once the drug was tolerated."*

Here, the ERG is assuming that precedence being cited are around the assumptions for the IV costs for letermovir, which the manufacturer of that submission would be inclined to being very precise on as well as sitting on the lower end of a plausible range.

However, the precedence which Takeda is referring to are the assumptions around the IV costs for pre-emptive therapy infusion (p 442 of letermovir TA591 committee paper PDF or p 117 of ERG report):

> *"The company's approach to estimating the costs associated with administering the multiple infusions required per day by patients receiving PET was to multiply the administration cost by the number of infusions required. The ERG considers this to be potentially overly simplistic and likely to overestimate the costs of providing PET. The ERG, therefore presents and alternative scenario in which the cost of single complex infusion is applied instead; £383.13 SB14Z - "Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance". This cost is only applied once per day of treatment, regardless of the setting and number of IV doses required."*

This is the approach taken within the maribavir model. We therefore do not consider the scenarios of using SB14Z for first administration, and SB15Z for all subsequent – (daily IV cost of £343) or a

PSSRU hourly cost of critical care nurse plus pharmacist time – (daily IV cost of £180) to be appropriate. We have not modelled for the use of a central line, given the morbidity and mortality associated with this procedure and we have no insight into how many patients across each transplant / organ type would have a central line, and our approach to use tariff costs is better reflective of the potential patient population for maribavir.

With regards to hospitalisation costs, Takeda re-iterate the point that the ERG preference of applying the weighted average of WJ02C-WJ02E (non-elective long stay for infectious diseases) to csCMV and n-csCMV is inappropriate because csCMV patients would require additional care and incur greater costs compared with patients in the n-csCMV state. Our approach remains a conservative one; If a more generic cost code was used for the n-csCMV health state, the differences in hospitalisation costs between the health states would be wider and thus the assumption would favour maribavir.

The ERG have also noted that due to limited review time they were unable to undertake the scenario where first line treatment would be foscarnet only with other IAT's being a retreatment option for further lines. Takeda note that foscarnet would only be used in extreme circumstances where patients would have a problem with first line valganciclovir or ganciclovir, and modelling in this way would not be appropriate for the population as a whole. Foscarnet is not an appropriate therapy option for patients with renal impairment (see quote from our clinical expert above in Section 2.2). Despite this, we have performed the scenario and it demonstrates maribavir [redacted] compared to foscarnet.

3. Comments on the ERG scenario analyses

Takeda do not believe the scenarios presented by the ERG are appropriate given the evidence for multiple recurrences / length of stage 1 of the model and the IV administration costs. We have presented additional scenarios in Table 8 for the Committee to consider, however we consider our basecase to be the most appropriate representation of the cost effectiveness of maribavir.

4. Additional clarifications and investigations

4.1 OTUS KM mortality data

The KM data from OTUS used to estimate the model parameters for the OTUS baseline scenarios are provided in Table 8 and Table 9 for SOT and HSCT, respectively.

Table 8. KM Estimates for Time from Index CMV date to all-cause mortality (SOT)

Time	Percentage (95% CI)
Day 56 (week 8)	[redacted]
Day 140 (week 20)	
Day 365 (week 52)	
Day 730 (week 104)	

Table 9. KM Estimates for Time from Index CMV date to all-cause mortality (HSCT)

Time	Percentage (95% CI)
Day 56 (week 8)	[redacted]

Day 140 (week 20)		[redacted]	
Day 365 (week 52)			
Day 730 (week 104)			

4.2 Scenario analysis assuming that the pooled percentage (i.e. not differentiating by CMV or nCMV) of patients with chronic GvHD in OTUS is used in the model and that the company assumes that patients with chronic GvHD do not survive beyond 2 years after transplant

Unfortunately GvHD data from OTUS are not currently available to us. We can look to provide this analysis at a later date if required.

4.3 Scenario analysis where first line IAT treatment is foscarnet only

Takeda have provided a scenario analysis that assumes only foscarnet is given to all patients as the first IAT treatment, and foscarnet is then not given as an option for retreatment. The other options are reweighted to ensure the total of the proportions sum to 100%. This scenario remains [redacted]. The full results are provided in Table 10 at the end of this document.

4.4 Removing "double-weighting" effect of clearance and recurrence used from OTUS in the model

There is no error introduced by weighting the input values before applying them to both SOT and HSCT inputs, followed by weighting the cost effectiveness results. Applying the same weights again to two equivalent weighted values results in the same previously weighted value.

For example, if the original unweighted values are *p* and *q*, with a weighted value of *wp + (1-w)q*, applying the weight, *w*, again would give *w(wp+(1-w)q) + (1-w) (wp+(1-w)q).* This is equivalent to *wp + (1-w)q*, the original weighted value.

4.5 +/- 20% of mean values in the PSA when SE is not available

The ERG appear to have implemented their scenario analyses in an older version of the submitted model. While the results produced appear to be correct, the values for the PSA are not the most up to date. The latest results provided by the latest version of the model were based on +/- 20% of mean values where standard errors were not available.

Takeda have re-implemented the ERG's analyses in the updated model, also ensuring that the model can be reset without breaking formulae that the ERG applied to cells that are user input cells. These cells should only contain numerical values as they are reset by macros for the base case settings.

5. Final comments

Takeda are pleased that the updated model alleviates many of the ERG's original concerns and that many of the approaches taken are acceptable, particularly around using the primary outcome to inform clearance, and the way that time has now been incorporated in the model. We maintain that the length of stage 1 of the Markov model allows a more clinically plausible flow of patients in the model and allows the full capture of all recurrence events in this population, which has been ratified by data from OTUS and discussions with clinicians.

We have presented the results of further regression analyses, which show that time since transplant has a negligible impact on the odds of clearance and actually demonstrate a greater treatment effect for recurrence requiring treatment after adjustment for key clinical covariates.

The SOLSTICE trial provides the most robust evidence source for both the maribavir and IAT arms and although we are pleased to see the ERG agree that OTUS is a valuable source of evidence to inform further recurrence in the model, we do not think it appropriate to use OTUS to inform the comparator arm when the SOLSTICE trial is the most superior source of evidence in this population.

Takeda recognise the SOLSTICE trial was not long enough to capture the full number of recurrences seen in this R/R population however we have compelling evidence in the OTUS data, GENOME data and the literature which shows that limiting the number of recurrences to two would not reflect the population under investigation in this appraisal.

We hope the explanation above of how IV administration costs have been captured in the model can satisfy the Committee that we have used the precedent set by TA591.

Takeda recognise there may still be uncertainty around some of the assumptions within this appraise. We recommend the Committee get input from all relevant transplant surgeons (both HSCT and SOT) to resolve any clinical queries, as we have during our advisory boards throughout development of this submission.

Table 10. Additional scenario analyses relative to the company's base case

Scenario, Description	Incremental costs (£)	Incremental LYs	Incremental QALYs	Incremental Net Monetary Benefit (£)	ICER (£/QALY) gained
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 SOLSTICE clearance and recurrence estimates adjusted using "full" model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 SOLSTICE clearance and recurrence estimates adjusted for time since transplant (TST) only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 OTUS clearance and recurrence estimates used as baseline standard of care (instead of IAT), with maribavir treatment effects for clearance and recurrence taken from SOLSTICE OTUS all-cause mortality used for n-csCMV health state, with literature-based relative risks used to estimate csCMV risk OTUS median TST applied	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 Scenario 3 using mean TST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 Scenario 3 limiting stage 1 Markov to 40 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 Scenario 3 with standard care OTUS recurrence rates applied in both treatment groups i.e. removing the SOLSTICE treatment effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7 Scenario 3 including leukaemia recurrence with costs for treatment to reflect 6 months of survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8	Scenario 3 including GvHD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	Scenario 3 including alternative Ara *et al.* adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	Scenario 3 including IV administration cost of £342.73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	Scenario 3 including equal unit hospitalisation cost to both CMV and nCMV patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	Base case but with foscarnet only as IAT first line, and foscarnet removed from retreatment (other options reweighted to sum to 100%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6. References

1. Hakimi, Z., et al., *Burden of cytomegalovirus disease in solid organ transplant recipients: a national matched cohort study in an inpatient setting.* Transpl Infect Dis, 2017. **19**(5).
2. Camargo, J.F., 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, 2018. **24**(4): p. 806-814.
3. Dobrer S, e.a. *Impact of Magnitude and Duration of Cytomegalovirus Viremia on Graft and Mortality Outcomes in Transplant Recipients: Genome Canada Precision Medicine Analysis*. in *8th International Congenital CMV Conference & 18th International CMV Workshop. March 28 – April 1, 2022. Virtual*. 2022.
4. Chakrabarti, S., et al., *High incidence of cytomegalovirus infection after nonmyeloablative stem cell transplantation: potential role of Campath-1H in delaying immune reconstitution.* Blood, 2002. **99**(12): p. 4357-63.
5. Melero-Ferrer, J., et al., *Repeated CMV Infection in a Heart Transplantation Patient.* Case Reports in Transplantation, 2012. **2012**: p. 305920.

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

ERG review of company's response to the ERG TE critique

August 2022

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1 Introduction

This document provides the Evidence Review Group's (ERG's) response in relation to the company's comments and additional data presented as a response to the ERG critique of the company's technical engagement document (TE).

2 ERG review of comments

2.1 Issue 1: Numerical imbalance in time since transplant in SOLSTICE

In their original TE response, the company provided regression analyses exploring the impact of a set of variables on the outcomes of clearance and clinically significant recurrence in the SOLSTICE trial. The ERG had concerns about the company's analyses as the company did not conduct a variable selection procedure on the regression models or assess correlation between variables. The company states that due to time constraints they have not been able to generate either of these for their second TE response. However, the company has provided results of the regression analyses adjusted by individual covariates (Table 1).

For recurrence requiring treatment (after clearance at week 8), there were fewer events among patients treated with maribavir than in the IAT arm of SOLSTICE (27.0% maribavir vs 37.0% IAT), [redacted]). This corresponds to an unadjusted odds ratio for maribavir compared to IAT of [redacted]. Based on the company's regression analysis, the odds ratio for maribavir compared to IAT adjusted for either time since transplant (TST) or transplant type both show similar treatment effects compared with the unadjusted result (Table 1). The clinical experts, advising the ERG, consider TST to be an important prognostic factor with a strong clinical rationale for its likely effect on recurrence and later outcomes. The risk of CMV infection (initial event or recurrence) is greatest during the first 3 months after transplant. The risk of CMV disease reduces with increasing TST, and after the first year post-transplant, a patient's own immune system is more able to combat viral replication and so the risk of clinically significant CMV is reduced even further.

In SOLSTICE, the mean TST was around [redacted] and [redacted] months in the IAT and maribavir arm of the SOT subgroup, respectively. That is, although there was some imbalance between the treatment arms in TST, SOT patients were at the end or outside of the high-risk period for both treatment arms. In the HSCT population, the mean TST was shorter at [redacted] and [redacted] months for IAT and maribavir,

respectively, and thus, there may still be a bias in favour of maribavir in this population. However, as indicated by the results of the company's regression analysis, the imbalance in TST between the maribavir and IAT arms at baseline in the overall trial population is unlikely to have a substantial impact on recurrence requiring treatment in SOLSTICE.

Table 1. Single covariate logistic regressions of confirmed CMV viraemia recurrence requiring treatment after clearance at week 8 (reproduced from company response to ERG TE critique, Table 5)

Covariate	Adjusted odds ratio (95% CI)	P-value
Model 1		
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Time since transplant (months)	[redacted]	[redacted]
Model 2		
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Transplant type (HSCT vs SOT)	[redacted]	[redacted]
Model 3		
Treatment (maribavir vs IAT)	[redacted]	[redacted]
Time since clearance (months)	[redacted]	[redacted]
Abbreviations: HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant; IAT, investigator-assigned anti-CMV treatment		

Based on the single covariate regression analyses, the company has provided, it could be inferred that longer time since clearance is correlated with a lower probability of recurrence ([redacted]), but, the odds ratio for maribavir compared to IAT did not reach statistical significance irrespective of adjusting for this covariate (Table 1).

The company concludes that the results of the regression analyses provide evidence that the treatment-specific recurrence probabilities used in the economic model are appropriate and not influenced by any differences in TST. The company, therefore, maintains their position not to adjust the effectiveness data used in the model, but based on the statistically significant effect of time since clearance on recurrence, the model allows for a dependence between the time spent in the non-clinically significant CMV state and the probability of a recurrence.

The ERG agrees with the company that the recurrence results for the full trial population seem unlikely to be influenced by baseline differences in TST, but highlights that if there is an impact, it is more likely to be for the HSCT population, for which the baseline difference in TST was less pronounced but which were still within the higher risk time period for CMV infection.

The ERG also agrees with the company's approach to allow for a dependence between time since clearance and recurrence in the model. However, the company's use of treatment-specific recurrence probabilities implies that the difference in recurrences requiring treatment is due to maribavir keeping patients clear of CMV infection for longer, which indirectly keeps patients at a lower probability of recurrence. The ERG acknowledges that the SOLSTICE trial results show a numerical difference in the rates of clinically relevant recurrence between maribavir and IAT. However, the ERG reiterates the view of its clinical experts that there is no clinical rationale for treatment received affecting the risk of, or time to, recurrence. Anti-CMV treatments, including maribavir, supress the virus and there is no clear rationale for why the suppression would be sustained or have a lingering effect once treatment is stopped. In addition, due to the uncertainties in the assessment of clinically relevant recurrence (see Issue 2, Section 2.2), the ERG cannot be sure that SOLSTICE data provide a robust estimate of the difference in recurrence between maribavir and IATs.

The ERG does not consider the regression analysis or the unadjusted trial results for recurrence to constitute robust evidence for a treatment effect of maribavir on recurrence. In order for the company to demonstrate that maribavir treatment results in fewer recurrences or a longer time to recurrence than IATs, a suitable powered clinical trial would be required. In addition, the ERG suggests the company assess the correlation between treatment, TST, transplant type and times since clearance using the variance inflation factors (VIF). If any of the variables are highly correlated (VIF>5) then the company needs to resolve the data multicollinearity in the regression analysis (e.g. by combining variables) or by performing an analysis designed for highly correlated variables. In SOLSTICE, because recurrence was assessed at week 20 for patients who achieved clearance at week 8, patients in both the maribavir and IAT arm were in clearance for the same duration of time (12 weeks). The ERG, therefore, also recommends the company presents data on the mean time since clearance (at week 8) to clinically relevant recurrence (from week 8 to week 20).

Due to the uncertainty around the results of clinically relevant recurrence (non-statistically significant result, whether unadjusted or adjusted for key variables), and the lack of clinical rational

for a treatment effect of maribavir on recurrence, the ERG considers its scenario analysis exploring the impact of assuming no treatment specific effect on recurrence by removing the non-statistically significant difference in recurrence between the treatment arms, to be important for the committee (results provided in Section 2.12).

2.2 Issue 2: Trial conduct and design leading to uncertainty

The ERG maintains its concerns around the conduct and design of the SOLSTICE trial, which leads to uncertainty around the trial results.

A large proportion of patients in the IAT arm were assigned to an anti-CMV treatment for which they had confirmed resistance. The ERG considers that this is likely to lead to an underestimate of clearance in the IAT arm and therefore an overestimate of the relative efficacy of maribavir compared to what would be expected in clinical practice. The size of the overestimate due to the imbalance between the treatment arms is difficult to determine but clinical opinion could provide some reassurance around the level of renal impairment among patients resistant to ganciclovir and valganciclovir among patient in UK clinical practice.

In addition, the ERG maintains its concern that the assessment of clinically relevant recurrence, although a clinically relevant outcome, is highly subjective and at a high risk of bias due to the open label trial design and the need for alternative anti-CMV treatment at the discretion of the investigator. As stated previously, no additional data or analysis can resolve this uncertainty, however, the uncertainty around the recurrence outcome data should be borne in mind when considering the clinical and cost effectiveness results.

2.3 Issue 3: Assumption of time elapsed since transplant at baseline in the model and use of OTUS data

Time elapsed since transplant at baseline

The company reiterated its preference for using the SOLSTICE median TST at baseline of [redacted] days for SOT patients and [redacted] days for HSCT patients and noted that the impact of using mean TST instead of median TST at baseline is minimal. The ERG agrees that using mean instead of median values has a small impact on the ICER, however, reiterates its view that a mean-based approach is a better reflection of the whole population under consideration, particularly when dealing with a therapeutic

area where there is a wide range of outcomes as is the case here with CMV infection occurring after transplant.

As originally stated in the ERG report, there is a marked difference between mean and median times since transplant at baseline in SOLSTICE, with overall mean TST for SOT patients of [redacted] days and [redacted] days for HSCT patients.

Use of OTUS data

After TE, the ERG recommended the company's economic analysis to be based on OTUS, with the maribavir relative treatment effect taken from SOLSTICE. The ERG noted that OTUS provides a larger sample size and a much longer follow up period for IAT patients than SOLSTICE, and as a real-world data source, the outcome data captured in OTUS are likely to be more generalisable to UK clinical practice. The ERG also considered the company's methodology regarding the OTUS data to be inappropriate for decision making. By using OTUS recurrence data to model subsequent CMV events after first events modelled with SOLSTICE data (and particularly by assuming that the probability of second clearance could be estimated from SOLTICE while the probability of remaining in the second clearance state was estimated from OTUS), the company assumed that not only the populations, but also clearance and recurrence in both studies were directly comparable and interchangeable. The ERG pointed to the fact that the available data from both studies suggest otherwise.

As a response to the ERG's concerns, the company provided a scenario analysis (as requested by the ERG) where clearance and recurrence for the IAT arm in the entire model was estimated with the OTUS data, together with using all-cause mortality from OTUS and median TST from the study. The company applied the treatment effect from SOLSTICE to estimate the probability of recurrence and clearance associated with maribavir. The results of this scenario increased the ICER from dominant in favour of maribavir to [redacted] per QALY gained.

Nonetheless, the company did not change its base case preference of using SOLSTICE data to model first clearance and first recurrence events in both treatment arms of the model and OTUS data to model subsequent CMV events (and estimating the probability of second clearance from SOLTICE while the probability of remaining in the second clearance state is estimated from OTUS). The company stated that, "*SOLSTICE provides the most reliable source of evidence to inform treatment effectiveness, [thus] it is considered most appropriate to align those treatment effects with the population from which they were measured*."

The ERG reiterates its view that SOLSTICE and OTUS differ from each other both in terms of study design (randomised controlled trial vs retrospective observational study) and patient characteristics, which are likely to lead to differences in outcomes. Notable differences in baseline characteristics included a larger proportion of patients with a liver transplant in the OTUS SOT cohort ([redacted] compared with the SOT subgroup of SOLSTICE ([redacted]). Additionally, mean TST in SOLSTICE was around [redacted] months for SOT patients and [redacted] months for HSCT patients, which compares to 7 months for SOT patients and 1.7 months for HSCT patients in OTUS. Given the ERG's clinical experts' view that the first 6 months post-transplant pose the highest risk for CMV recurrences (followed by the next 6 months up to 1 year after surgery), it could be argued that patients in OTUS were at higher risk of recurrences than patients in SOLSTICE. Furthermore, as discussed in the ERG's original report, SOLSTICE only captured patients' first clearance and first recurrence events, whereas OTUS captured up to five episodes of recurrences.

During TE, the ERG noted the difference in the probability of clearance in both studies at week 8, with KM from OTUS reporting that [redacted] of patients achieved clearance, compared to 24% of IAT patients in SOLSTICE. In their response, the company stated that the comparison of clearance probabilities in SOLSTICE and OTUS undertaken by the ERG was inappropriate as the OTUS value is based on KM estimates and the SOLTICE value is based on response rates, and that KM estimates in this case are influenced by informative censoring. This means that individuals with CMV who do not respond to treatment are discontinued (and thus censored) when in reality these patients reflect treatment failures and should be counted as events in a KM curve. Upon reflection, the ERG acknowledges that KM data for clearance is meaningless in this case, as patients being censored from the KM curves (due to treatment failure and treatment switching) should have counted towards failure events (i.e., patients not achieving clearance), instead of being censored.

The company added that in OTUS there were [redacted] clearance events for the SOT population (out of [redacted] patients with R/R CMV), giving a probability of [redacted]% for clearance in the IAT arm. The company added that the [redacted]% is more closely aligned with the 24% of clearance in the IAT arm of SOLSTICE. The ERG notes that there is come uncertainty around this comparison given that:

1. The [redacted]% estimate does not include HSCT clearances (as the company reported that these are not available), and the company is comparing this with the aggregated clearances for SOT and HSCT patients in SOLSTUCE. The KM data on clearance for OTUS provided by the company suggest that clearances for HSCT patients at 8 weeks might have been higher ([redacted])

than those observed for SOT patients [redacted]. If that is the case, including HSCT clearances in the final estimate (to be compared with the 24% estimate for SOLSTICE) would increase the OTUS value at 8 weeks.

2. The only incidence data previously provided to the ERG in the document sent on 24 May 2022 entitled, "*Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]: Further response to ERG technical engagement questions"* reported a total of [redacted] cumulative number of clearances for SOT patients ([redacted]) and a total of [redacted] cumulative number of clearances for HSCT patients ([redacted]) in the same document. Therefore, the ERG has not seen any source of data containing the [redacted] clearance events for the SOT population referred by the company after TE.

In conclusion, the ERG remains concerned that the populations in OTUS and SOLSTICE are not comparable, which renders the company's base case methodology for using OTUS data not appropriate. The ERG also recommends that the company provides the additional clearance data used to estimate the [redacted] probability of clearance for SOT 8 weeks, available from OTUS (for all time points and for HSCT patients if possible) before the committee meeting.

Company's scenario analysis using OTUS

The company used the [redacted] probability of clearance from OTUS at 8 weeks reported above. To this estimate of clearance, the company applied the unadjusted odds ratio ([redacted]), for clearance from SOLSTICE and obtained the probability of clearance for maribavir relative to the OTUS standard of care ([redacted]).

For IAT recurrence, the company used recurrence data from OTUS and then applied the unadjusted odds ratio of [redacted] (Section 2.1), to estimate maribavir probabilities (Table 2).

Table 2. Probabilities for first recurrence requiring treatment for the OTUS baseline scenario analysis

Time since clearance	IAT	Maribavir
4 weeks	[redacted]	[redacted]
8 weeks	[redacted]	[redacted]
12 weeks	[redacted]	[redacted]
16 weeks	[redacted]	[redacted]
20 weeks	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]

The company also included all-cause mortality for both SOT and HSCT populations from OTUS to inform mortality risks for patients without CMV in the model and applied relative risks from

published literature to estimate the mortality risks for CMV. This issue is discussed in detail in Section 2.5, issue 6.

Furthermore, the company included the median TST from OTUS ([redacted] days for SOT and [redacted] days for HSCT), and a scenario analysis where mean TST from OTUS was used ([redacted] months for SOT patients and [redacted] months for HSCT patients).

Finally, the company also included a scenario analysis where recurrence was assumed to be the same in both treatment arms, i.e., where maribavir only impacts patients' probability of first clearance. This scenario increases the ICER to [redacted] per QALY gained. This scenario is further discussed in the next section.

2.4 Issue 4 and Issue 5: Structural assumptions in the company's model and overestimation of recurrences

In its review of the company's first response to TE, the ERG noted the two following concerns:

1. The company's updated model included multiple recurrences beyond a second event and assumed that the rate of third and further recurrences in the model was the same as that observed for second recurrences in OTUS. The ERG noted that the rates of subsequent recurrences in OTUS were much lower after second recurrence, thus, the company's approach overestimated the recurrences in the model and, therefore, the benefit associated with maribavir.
2. The ERG was unclear on the company's justification for choosing 78 weeks for the duration of the stage 1 Markov. The ERG noted that the company's rationale for justifying the 78 weeks' timeframe, which included looking into the occurrence of CMV events in OTUS up to the start of the 4th recurrence and the start of the 6th recurrence, for SOT and HSCT patients, respectively, was highly inconsistent with the company's use of the OTUS data in the model, given that the probability of second recurrences was used to model subsequent events.

   The ERG concluded that given that the number of patients with third (or further) recurrences in OTUS was low (see **Error! Reference source not found.** in the ERG's review of the company's first response to TE) and the fact that the company only included OTUS recurrence data up to second recurrence in the model, a more robust approach would have been to not model recurrence events beyond second recurrences after transplant. Crucially, the ERG considered that if the OTUS data were to be used to estimate the probability of events in the IAT arm of the model

(from baseline), then the duration of the stage 1 Markov model should reflect the time frame over which first and second recurrences happened in OTUS, which was 39.3 weeks (34.1 weeks of cumulative duration since index episode to second episode plus the duration of 5.14 weeks of treatment for the second episode).

Alternatively, the ERG noted that if the company did not change its modelling approach (where SOLSTICE data were used to estimate first events in both arms of the model), then the duration of the stage 1 Markov should be limited to 20 weeks, and the "full cycle" of events should consist of a maximum of 2 episodes of clearances and one episode of recurrence per patient in the stage 1 Markov model to reflect the duration of events captured in SOLSTICE.

As a response to the ERG's concerns, the company noted that there is evidence within both OTUS and GENOME presented at ESOT 2021[3] that demonstrates up to six recurrences for SOT in OTUS; four recurrences for HSCT in OTUS; and four recurrences in GENOME. The ERG notes that the ESOT reference (Dobrer *et al*. 2022[3]) provided by the company only gives evidence from GENOME and not from OTUS. Furthermore, Dobrer *et al*. 2022 does not differentiate between SOT or HSCT and reports a mean number of viremia episodes of 1.2 (standard deviation of 0.5); and crucially, does not differentiate between recurrences requiring treatment and viraemia recurrences not requiring treatment, or patients being relapsed/refractory.

The company also reported a paper by Melero-Ferrer 2012[5] demonstrating six reinfections in a patient following a heart transplant. The ERG notes that this is a case study of a single patient who notably had 6 CMV reinfections over 9 years after receiving a heart transplant. The ERG notes that a single case study does not constitute a robust source of evidence generalisable to a population.

The company also reported the Chakrabarti 2002[4] study as a source to justify multiple CMV recurrences, stating that out of 51 HSCT transplant patients with initial CMV infection in the study, 11 patients had 3 or more episodes of CMV infection. Overall, the ERG acknowledges that it is possible that patients experience more than two recurrences of CMV infection (after initial CMV infection post-transplant). Nonetheless, the ERG does not consider that the company has provided a source containing evidence sufficiently robust to model third or subsequent CMV recurrences. Crucially, the company has not provided any evidence to justify the assumption that third and subsequent recurrences occur at the same rate as second recurrences. As observed in OTUS, the rates of subsequent recurrences were much lower after second recurrence, thus, the company's

approach overestimates the recurrences in the model and, therefore, the benefit associated with maribavir.

The company also noted that their base case analysis results in an average of [redacted] recurrences in the IAT arm and that the OTUS study reports a total of [redacted] recurrences ([redacted]) for SOT and [redacted] ([redacted]) for HSCT. When weighted by the proportion of SOT and HSCT patients in SOLSTICE, this results in an estimated overall recurrence rate of [redacted], which the company considered to be a validation of the number of recurrences estimated in the model and the 78-week period for the stage 1 Markov. The ERG notes that the recurrence rate from OTUS of [redacted] occurred over more than 3 years, in comparison with the 1.5 years of the model, reinforcing the ERG's view that the model overestimates recurrences (due to the company using the probability of second recurrences from OTUS to model third and subsequent recurrences in the model).

The lower probability of recurrence associated with maribavir (regardless of how long patients have been off treatment)

The clinical benefit associated with maribavir works through two ways in the model: 1) the higher probability of clearance for maribavir patients at week 8 (56% vs 24% for IAT, when data from SOLSTICE is used); and 2) the lower probability of recurrence for maribavir patients in the 12 weeks following clearance, which means that a higher proportion of maribavir patients are in the clearance state at week 24 in the model, when the rates of recurrence become independent of treatment.

The company clarified that the 12-week assumption of treatment duration with maribavir is based on the timepoint from the output of the primary endpoint in SOLSTICE at 8 weeks to the end of the duration of the trial follow up at 20 weeks.

As discussed in Section 2.1, SOLSTICE data shows a numerical advantage to maribavir in the number of patients with sustained clearance from week 8 to week 20, compared to IAT patients. However, due to the uncertainties in these data (see Section 2.1 and Section 2.2), the ERG cannot be sure that SOLSTICE data are robust enough to confirm that patients are likely to maintain clearance with maribavir for longer than with IATs. Importantly, the company has still not provided a clinical rationale for why maribavir would keep patients in clearance for longer than IATs (even if maribavir is more effective than IATs at helping patients achieve clearance).

During TE, the company implied that the impact of maribavir on the probability of recurrence works through the impact of maribavir on the duration of clearance and its impact on recurrence. Nonetheless, the company failed to explain (or acknowledge) why maribavir patients achieving clearance for the same duration of time as IAT patients in the model (during the first 12 weeks of clearance achieved at week 8) have an added benefit of having a lower probability of recurrence in the model (14% vs 10% as per Table 5 in the ERG's review of the company's response to TE), despite being in the clearance state for the same period of time.

Therefore, the ERG conducted a scenario analysis whereby the probability of maintaining clearance in the model was independent of the treatment received by patients, and only dependent on time spent in clearance (i.e., the probability of maintaining clearance in the model was the same in both treatment arms). Results of this scenario analysis are reported in Section 2.12.

When the rate of recurrence during the initial 12 weeks after clearance in the model is assumed to be the same across treatment arms (but still decreasing with time since clearance), the benefit associated with maribavir in the model would be the 8-week differential observed in clearance rates in the model, propagated until the end of the stage 1 Markov, or until the same proportion of patients had cleared their CMV in both arms.

2.5 Issue 6: Modelling of mortality in stage 1 Markov

The ERG's key concern regarding the company's estimation of mortality in the original stage 1 Markov model was the company's approach of using SOLSTICE data to model a differential in survival related to CMV presence. The trial data (which, by default, incorporated the difference in CMV events across treatment arms) showed no significant difference in overall mortality between maribavir and IAT patients (ITT population), thus suggesting that CMV-related mortality in the trial was also not significantly different across treatment arms.

After TE, the ERG reiterated its view that even when the company provided the survival data from SOLSTICE adjusted for crossover, the 95% confidence intervals reported (reproduced in Figure 1) suggested that there was still no statistically significant difference between survival in both treatment arms. Furthermore, the ERG noted that no details on the method used to adjust the curves was provided, other than reporting that the Inverse Probability of Censoring Weights (IPCW) method had been used. The ERG also noted that the choice of method used to adjust trial outcomes for crossover, "*often drastically alters the estimated incremental cost effectiveness ratio*" (NICE DSU

TSD 16). The ERG added that NICE DSU TSD 16 also reports that the IPCW method will be prone to bias if out of those patients who switched, there is a high proportion (around 90%) of patients who experienced disease progression (and thus became eligible to switch). Therefore, the ERG could not validate the use of the adjusted survival data without understanding how the adjustment was carried out.

Crucially, the ERG noted that the company did not use the survival estimates adjusted for crossover in the model, but instead, used the unadjusted survival by type of transplant in the first 8 weeks of the model (Table 3), and from week 8 to week 78, by CMV status (Table 4).

Figure 1. Kaplan-Meier plot of time to all-cause mortality by treatment arm adjusted for treatment switch by Inverse Probability of Censoring Weights method (TRTPN=1 is IAT; TRTPN=2 is maribavir)

Table 3. Mortality rates in first 8 weeks of the model

Time period	Solid organ transplant (SE)	Haematopoietic stem transplantation (SE)
Week 0 to week 8	[redacted]	[redacted]

Table 4. Mortality rates in week 8 to week 78 in the model

Time period	CMV state (SE)	nCMV state (SE)
Week 8 to week 78	[redacted]	[redacted]

After TE, the company noted that it had provided the IPCW analysis as the primary adjusted analysis but also the rank preserving structural failure time model (RPSFTM) as a scenario analysis. The company added that the results of the RPSFTM were similar to those generated by the IPCW. The company reported an adjusted HR of [redacted] for the IPCW analysis, while for the RPSFTM method the estimated adjusted HR was [redacted], leading the company to conclude that the IPCW analysis was robust. The company added that, although the analyses demonstrate a non-significant difference in mortality, it supports the plausibility that CMV is causing an impact on mortality even in the short-term SOLSTICE trial, thus, supporting the CMV-related mortality risks derived from SOLSTICE in the model.

The ERG also notes the following issues around the company's RPSFTM analysis:

1. Figure 2 shows that the RPSFTM-adjusted curves are very different from the IPCW-adjusted curves (Figure 1);
2. even though the 95% CI for the RPSFTM-adjusted HR were not available, the 95% confidence intervals reported in Figure 2 suggest that there is no statistically significant difference between survival in both treatment arms;
3. the ERG is unclear if the RPSFTM HR provided by the company is the correct one, as the IPD statistical analysis document provided by the company labels the RPSFTM HR in Table B4 as [redacted]. This HR is considerably different from the IPCW HR, which would make sense, given that the two methods "*work in very different ways and make very different assumptions*" hence "*are likely to produce different results*" (NICE DSU TSD 16).

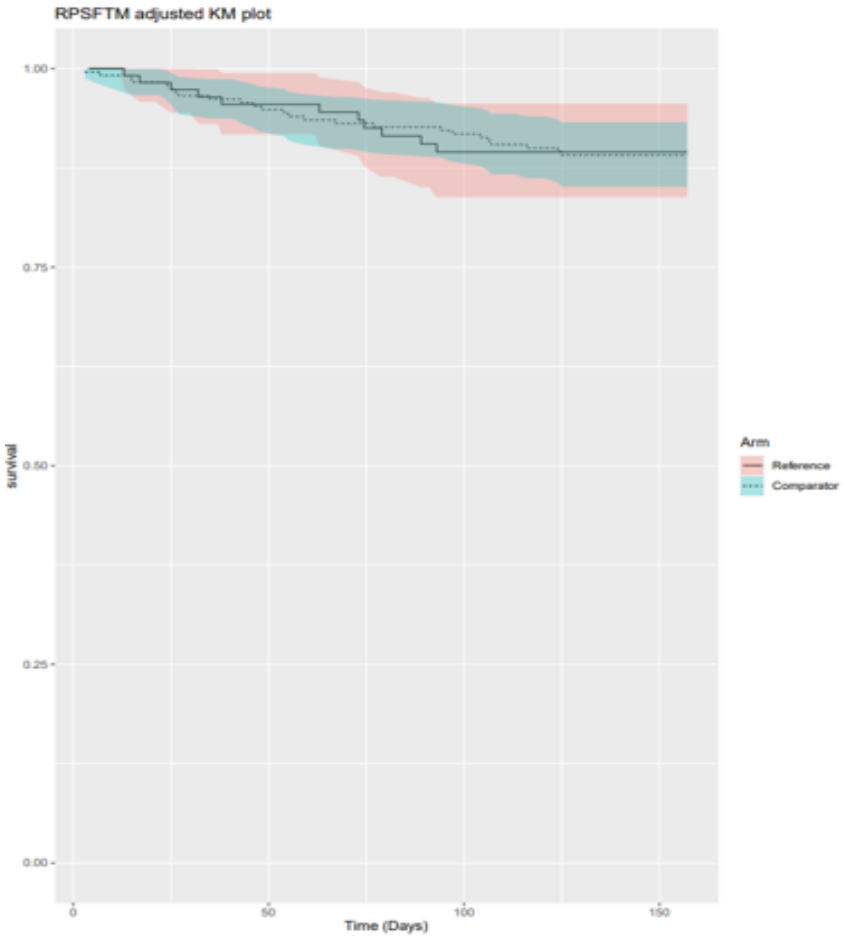
The ERG notes that the adjusted HRs for other methods, such as the two-stage estimation (TSE) and iterative parameter estimation (IPE) were presented; however, due to the same labelling issues the ERG cannot reconcile which method produced which HR. Nonetheless, none of the HRs presented were statistically significant, and results ranged from [redacted]) to the IPCW HR of [redacted].

In summary, and as reported in NICE DSU TSD 16, the choice of the method to adjust for trial cross-over should take into account the characteristics of the trial, the switching mechanism, the

treatment effect, the data availability and include an appropriate justification for the chosen method. The ERG has not seen any discussion around these issues accompanying the outputs of the company's adjustment analysis. Nonetheless, the ERG notes that none of the analyses undertaken by the company provide evidence against the ERG's conclusion that SOLSTICE data do not shows a statistically significant difference in overall mortality for maribavir and IAT patients, thus suggesting that the CMV-related mortality in the trial was also not significantly different across arms.

Importantly, the ERG notes again that the company did not use any of the adjusted HRs in their analysis and kept its preference for the unadjusted mortality data from SOLSTICE, modelling a survival benefit for patients without CMV, from week 8 to week 78 in the model. Overall, the ERG reiterates its view that the SOLSTICE CMV-related mortality data are not robust enough to be included in the economic model.

Figure 2. Kaplan-Meier plot of time to all-cause mortality by treatment arm adjusted for treatment switch by RPSFTM method



The ERG has also continuedly asked the company to provide KM data from SOLSTICE split by transplant type as well as CMV status to try to further understand the differences in mortality between these populations in SOLSTICE. The ERG previously noted that the much higher mortality rates observed in the HSCT population compared with SOT patients were likely to be driving the mortality estimates upwards.

The company has not yet provided these data and has reported that with the, "*cyclical nature of CMV, with patients switching in and out of clearance and recurrence status, it is not feasible to provide KM curves by CMV status*". The ERG acknowledges the company's reasoning, however, notes that IPD from SOLSTICE are available to the company, which would allow the company to retrospectively select patients who had survival KM data at the moment of CMV or no CMV presence. Furthermore, the ERG considers that the cyclical nature of CMV pointed out by the company is an issue in any type of analysis, including the company's base case approach where number of deaths was estimated by CMV status (see Table 4). The ERG is unware how the company attributed deaths to CMV events in the latter analysis, but hypothesises that a clinical decision uderpinned the analysis to determine the relevant factor for survial (i.e., present CMV; past CMV; duration of CMV, etc). The same argument could, therefore, be made in the analysis requested by the ERG. Finally, the company has not provided any justification for why KM survival data by transplant type could not be provided.

After TE, the ERG recommendations were the following:

- Using the OTUS KM mortality data to estimate mortality in the IAT arm of the model, separated by HSCT and SOT. The ERG recommended that the company investigated if mortality by CMV status (within each population) was statistically significantly different for CMV and nCMV IAT patients. If this was the case, then the company would not have to use external literature to estimate CMV-related mortality, and the maribavir treatment effect derived from OTUS leading to the difference in CMV events in the maribavir and IAT arms would generate any potential survival benefit associated with maribavir.

  If mortality by CMV status (within each population) was not statistically significantly different for CMV and nCMV IAT patients in OTUS, then CMV-related mortality from literature sources from Hakimi *et al*. 2017 and Camargo *et al.* 2018 should be applied to the OTUS KM data.

- If the company decided to keep the use SOLSTICE data (and not OTUS data as proposed by the ERG) to estimate clearances and recurrences in the IAT arm, then the ERG reiterated the importance of having SOLSTICE data (particularly KM data) by type of transplant and by CMV status, to try to further understand the differences in mortality between these populations in SOLSTICE. The ERG recommended that the effect of CMV on mortality from Hakimi *et al*. 2017 and Camargo *et al.* 2018 was applied to the SOLSTICE KM data as a scenario analysis.

As a response to the ERG's concerns after TE, the company provided an economic analysis based on the OTUS study as a baseline and used published literature to inform the relative mortality risks for the nCMV and CMV heath states. The company split all-cause KM mortality data from OTUS by SOT and HSCT populations and applied the relative risks from Hakimi *et al*. 2017 (SOT) and Camargo *et al*. 2018 (HSCT) to the OTUS KM data to estimate the mortality risks for patients with CMV (Table 5). The ERG has three concerns regarding the company's analysis:

1) The company's methodology implies that the KM data from OTUS captured deaths for patients without CMV (given that a HR from literature is applied to estimate CMV deaths). However, the ERG has not seen the data or a confirmation that is the case, where the only label available for the KM data is "*KM Estimates for Time from Index CMV date to all-cause mortality* ", suggesting that this included patients with and without CMV.
2) The company did not provide the analysis recommended by the ERG looking at the statistically significance of CMV vs nCMV mortality data from OTUS, which might have eliminated the need for the use of external literature.
3) The ERG is unclear why only 20 weeks of mortality data were used, in combination with the assumption that the mortality from week 20 to week 78 would be the same in the model, when longer follow up mortality data were available from OTUS.

The ERG, therefore, recommends that the company clarifies if the KM mortality data from OTUS only included patients without CMV recurrence, and asks that the company includes the longer-term data from the study for time points beyond 20 weeks in the model. The ERG also notes that as it stands, the company analysis is likely to overestimate CMV-related mortality in the OTUS scenario analysis, which has a considerable impact on the results of these analyses (this is discussed in detail in Section 2.12).

With regards to using SOLSTICE data, the company did not undertake the scenario analysis requested by the ERG of having SOLSTICE data split by (at least) type of transplant, to then apply the effect of CMV on mortality from Hakimi *et al*. 2017 and Camargo *et al.* 2018.

In comparison with the SOLSTICE data, patients in OTUS seem to have a higher probability of death. For example, at week 20, the KM mortality estimate was [redacted] (weighted by SOT and HSCT according to the SOLSTICE distribution), whereas the corresponding KM estimate in SOLSTICE was approximately [redacted]. This is being driven by HSCT patients (as seen in Table 5 and in Table 4, and as discussed in Section 2.12). This is also to be expected, considering the difference in mean TST between the studies – in SOLSTICE mean TST was around [redacted] months for SOT patients and [redacted] months for HSCT patients, compared to 7 months for SOT patients and 1.7 months for HSCT patients in OTUS. Therefore, it could be argued that patients in OTUS were at higher risk of recurrences, and death, than patients in SOLSTICE.

Finally, the company added that its base case approach may underestimate the long-term impact of CMV-related mortality, given the mortality risks for the base case are based on only 20 weeks of data from SOLSTICE. The ERG notes that for their scenario analysis using OTUS, the company could have used data with a longer follow-up period than 20 weeks but did not use the available data. Crucially, the ERG notes that the OTUS; the Hakimi and the Camargo data all show evidence that CMV-related (and non-CMV related) deaths decrease over time, as time since transplant elapses (as discussed in the ERG's original report and in the ERG's review of the company's response to TE). Therefore, the company's approach is likely to overestimate CMV-related mortality and not underestimate it, as suggested by the company.

Table 5. KM estimates for all-cause mortality from CMV index event

Input	SOT	HSCT
CMV up to week 8	[redacted]	[redacted]
nCMV (weeks 8 to 20)	[redacted]	[redacted]
CMV (weeks 8 to 20)	[redacted]	[redacted]
nCMV (week 20 onwards)	[redacted]	[redacted]
CMV (week 20 onwards)	[redacted]	[redacted]

2.6 Issue 7: Modelling of mortality in stage 2 Markov

All the issues regarding the modelling of mortality in the stage 2 Markov have been resolved during TE. The only remaining aspect of the company's analysis, which impacts long-term mortality, is the use of mean TST instead of median TST, as discussed in Section 2.3.

2.7 Issue 8: Modelling of graft failure

After TE, the ERG recommended that the company investigated graft failures in OTUS, and used these data in the model, if the treatment effect for the IAT arm was to be estimated with OTUS data.

The company reported that in OTUS, graft loss occurred in [redacted] ([redacted]%) of SOT patients and added that this estimate compares to [redacted]% (the estimated number of graft loss events in the company's model in the IAT arm taken from literature). The ERG notes that this comparison lacks clarity, as the company did not report over how long the graft losses occurred in OTUS for comparison with the graft losses occurring in the model over 78 weeks.

The company's model uses the estimate from Hakimi, which reports that patients with a CMV episode at 6 months (or after) after transplant have a 5.12% chance of graft failure, compared to 1.69% for patients without CMV, over 1 year. These estimates are [redacted] than those observed in OTUS, which could potentially be explained by the fact that the follow up period for graft failures in OTUS was longer than 1 year.

The company added that the estimates from Hakimi used in the model are an underestimate in comparison to the real-world data from OTUS, however, added that the impact in terms of costs and quality of life in the model is relatively small, which the ERG agrees with.

2.8 Issue 9: Modelling of disease complications

As per the NICE appraisal of letermovir (TA591), the ERG recommended including a scenario analysis where recurrences of underlying disease for HSCT patients were considered in the economic analysis. After TE, the ERG noted that the company's scenario estimated 2 years of leukaemia recurrence costs, when the scenario suggested by the ERG was that patients would incur costs for 6 months (see the original ERG report and the ERG review of the company's response to TE for more details).

After TE, the company did not change this in the model, therefore, the ERG corrected this in the model and the impact of including leukaemia recurrence on the final ICER decreased. The results of this scenario analysis are given in Section 2.12 of this ERG report.

The company added that the inclusion of leukaemia relapse-related mortality potentially introduces double counting in the model, given that the HSCT-specific mortality estimates applied in the economic model will already include the impact of disease recurrence. The ERG disagrees with the

company's view as patients were assumed to have recurrent leukaemia within the stage 1 Markov model, where the mortality estimates from Camargo were used by the company to estimate HSCT-related mortality. The latter were based on deaths without recurrent or progressive disease after HSCT, therefore, there is no double counting of deaths when leukaemia recurrence is included in the model.

Clinical expert opinion provided to the ERG indicated that HSCT patients with chronic graft versus host disease (GvHD) have a higher probability of death. However, as also acknowledged by the company, the causal relationship between GvHD and CMV is not well established in literature. Therefore, the ERG suggested that the company included a scenario analysis where GvHD independent of CMV status was included in the model. If treatment-agnostic GvHD events are included in the model and if these patients were assumed to be dead at 2 years after entering the model (as suggested by the ERG's clinical experts), it is likely that the ICER associated with maribavir would have increased.

The ERG-suggested scenario analysis including GvHD independent from CMV (from SOLSTICE) has been included in the company's updated model, however, it appears to the ERG that the company has not assumed GvHD patients to have a higher mortality in the model. Therefore, the ERG recommends that the company adds this assumption to their scenario analysis.

With regards to GvHD from OTUS, the company replied that the full OTUS HSCT report is not yet available but that it is expected that the latter will be ready within two months of their second response to TE.

2.9 Issue 10: Estimation of utilities

In general, the ERG considers that the issues related to the estimation of quality of life in the model are mainly resolved. Nonetheless, the ERG notes that the company has maintained its approach of using week 8 utility but excluding the utility data from weeks 12, 16 and 20 from the analysis, and recommends these data points are included in the MI model.

Furthermore, the ERG reiterates its original view that the utility values applied for the stage 2 Markov might still underestimate the quality of life experienced by nCMV SOT patients as these suffer a drop in their quality of life after week 78 without a plausible explanation, given that their CMV status was considered to not change after that point in time (in Table 6). Conversly, HSCT nCMV patients experience an increase in quality of life when the model switches to the dead/alive

stage 2 Markov, an assumption that also carries uncertanty given that these patients did not have CMV at the end of the stage 1 Markov.

Table 6. Summary of utility values used in company base case

Health state	Utility values used after TE	
	SOT	HSCT
CMV	[redacted]	[redacted]
nCMV	[redacted]	[redacted]
Difference	0.111	0.023
Stage 2 Markov alive	0.81	0.71

Finally, the company clarified that the study used to adjust utilities by age was the, "*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;14:539-45*. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21669378", and not the, "*Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13(5):509-18. doi: 10.1111/j.1524-4733.2010.00700.* [published Online First: 2010/03/17]" as requested originally by the ERG. The company added that the impact on the economic model between the two approaches is not meaningful, thus the company has maintained its base case approach. The ERG agrees with the company assessment.

2.10 Issue 11: Estimation of costs

IV administration costs

The ERG's concerns were around the company's use of the SB14Z NHS reference cost as a daily IV administration cost. In their second response to TE, the company clarified that the justification for using this specific NHS reference cost is the precedent set in TA591, where the ERG to TA591 undertook a scenario analysis using the SB14Z NHS code - "Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance" to estimate the daily cost of IV treatment with pre-emptive therapy infusion.

The ERG appreciates the company's clarification around the rationale for choosing the NHS reference cost, however, notes that this does not change the ERG's view that subsequent

administration cycles (after first treatment) should be associated with a lower cost. As explained in the ERG's original report, the 2020/21 National cost collection guidance document notes that the SBZ14 cost applies to only the first administration of a chemotherapy cycle and that another lower reference cost for subsequent elements of a chemotherapy cycle (SB15Z) should be used for "*delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance*." Furthermore, as also discussed in the ERG's report, feedback from the ERG's clinical experts suggested that administration of the IV treatments for CMV (ganciclovir, foscarnet, cidofovir) would utilise an existing central line and that approximately 4 hours of ICU nurse time would be required per administration of these IV drugs. As such, the use of a complex chemotherapy at first attendance cost throughout subsequent administrations means that costs associated with inserting catheters to facilitate IV treatment would be applied every day for the duration on treatment – this is inconsistent with the ERG's clinical expert feedback.

After TE, the ERG conducted two alternative scenario analyses to address the issue:

1. The SB14Z and SB15Z NHS reference cost codes were used as intended by the 2020/21 National cost collection guidance document – SB14Z was used for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle. Due to model structure constraints this was implemented as a weighted average of the two costs (by the number of administrations in each IAT treatment cycle). This scenario resulted in a daily administration IV cost of £343.
2. The daily administration costs for IV treatments were estimated based on the PSSRU hourly cost of a critical care nurse based on the ERG's clinical expert estimates that administration for 2 patients concurrently occupied 4 hours of a nurse's time (Guidelines for Provision of Intensive Care Services [FICM/ICS] outline a 2:1 patient to nurse ratio for level 2 patients). The cost of 15 minutes of hospital pharmacist time was also added. This scenario resulted in a daily administration IV cost of £180.

The ERG considers that both of these scenarios remain relevant, therefore conducted these on the company's updated model. Results of these analyses are provided and discussed in Section 2.12.

Hospitalisation costs

During the clarification stage, the company explained that evidence from the SOLSTICE trial indicates that a proportion of patients both in the nCMV state and CMV state are likely to be hospitalised

([redacted]).

In order to cost hospitalisations for CMV patients, the company used non-elective long stay costs for major infectious diseases with interventions, whereas the nCMV hospitalisation cost corresponded to a non-elective long stay costs for major infectious diseases without interventions.

The ERG remains unclear on the specific reasons for hospitalisation of nCMV patients, and what the "interventions" in the cost codes refer to. However, it is plausible that the only difference in hospitalisation costs between patients with and without CMV disease is based on treatment acquisition and administration costs, which are already separately costed in the company's model. As such, the ERG preference is to apply an equal unit hospitalisation cost to both CMV and nCMV patients. Namely, the cost of non-elective long stay for major infectious diseases without interventions (£1,969.53) as this reflects hospitalisations due to a variety of infectious diseases of varying duration.

The company stated that the ERG's preferred scenario is inappropriate because CMV patients would require additional care and incur greater costs compared with patients in the nCMV state (beyond treatment costs). The ERG remains uncertain on the company's assertion and advises that more details are provided with regards to the nature of the additional costs required by CMV patients beyond treatment costs, in comparison with hospitalised nCMV patients.

The ERG has produced a scenario analysis investigating the impact of this change and presents the results in Section 2.14.

Cost of IAT retreatment

Given the ERG's consideration that recurrences are still likely to be overestimated in the model (see Section 2.4), the costs associated with IAT retreatment are also likely to continue to be overestimated in the model.

During TE the ERG recommended that the company conducted a scenario analysis where the first line IAT treatment consisted of the cost of foscarnet only, with the other IATs being a retreatment option for further lines. This reflects the ERG's clinical experts' opinion that foscarnet is the most relevant comparator to maribavir and could potentially decrease the overall costs of retreatment (even though it would have increased the cost associated with the initial round of IAT treatment)

given that foscarnet is the most expensive treatment in the IAT basket. The company included the scenario analysis in their updated model and not only did maribavir [redacted] but the incremental costs associated with IAT increased, given the difference in price in foscarnet compared with other IATs, and the fact that 100% of IAT patients in this scenario receive first line foscarnet.

2.11 Company's updated cost-effectiveness results

The company's deterministic and probabilistic results remained the same. The ERG reproduced the results in Table 7 and Table 8, respectively.

According to the company's analysis maribavir is expected to increase patients' life expectancy by [redacted] years compared with IATs, at a lower cost and incremental QALYs, resulting in the dominance of maribavir. The company's probabilistic results also show dominance and are closely aligned with the deterministic values. The company did not provide life years gained results in its probabilistic results.

The ERG notes that the company's separate ICERs for SOT and HSCT patients (provided in the company's response to TE document) also show dominance of maribavir. Nonetheless, the HSCT population remains the one where the benefit of maribavir is smaller.

Table 7. Company's base case deterministic results using SOLSTICE

Interventions	Total Costs (£)	Total LYG (undiscounted)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Maribavir	[redacted]	[redacted]	[redacted]	-	-	-	-
IAT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 8. Company's base case probabilistic results using SOLSTICE

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Maribavir	73,296	6.58	-	-	-
IAT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

2.12 ERG scenario analysis

The scenario analyses undertaken by the ERG are explained throughout the report. The ERG conducted two sets of analyses: 1) SOLSTICE data were used to estimate treatment effectiveness in the IAT arm of the model (Table 9 and Table 10); and 2) OTUS data were used to estimate treatment effectiveness in the IAT arm of the model (The impact of varying the same assumptions when the OTUS data are used in the model is smaller than when the SOLSTICE data are used (see results in Table 11). Even though all the scenarios using OTUS data result in maribavir being incrementally more costly than IATs (compared to the scenarios using SOLSTICE), these also result in maribavir being associated with higher incremental QALYs than IATs (compared to when SOLTICE data are used). This is related to the base case results for OTUS yielding higher incremental costs ([redacted]) when compared to SOLSTICE and considerably higher QALYs ([redacted]).

The difference in using OTUS or SOLSTICE on the final ICER is driven by the SOT population (given that it represents 60% of the entire model population) and by the fact that survival and nCMV events increase both in absolute and in incremental terms when OTUS data are used. Due to the mortality rates for SOT patients at week 8 are very similar between SOSTICE and OTUS ([redacted] respectively), the number of patients alive at the end of week 8 is very similar across both scenarios (because everyone has CMV for the initial 8 weeks of the model). However, the clearance rate for SOT patients in OTUS at week 8 is higher than in SOLSTICE ([redacted], respectively, for unadjusted clearance for IATs and [redacted], respectively, for maribavir). Therefore, the proportion of SOT patients without CMV at week 12 in the model is higher when OTUS data are used, and the higher proportion of nCMV cases leads, in its turn, to a positive incremental impact on survival, and this benefit is propagated throughout the model (at the end of the stage 1 Markov, there are [redacted] of SOT patients alive, respectively, in the maribavir arm and in the IAT arm when SOLSTICE is used and, and [redacted] of SOT patients alive in the maribavir arm and in the IAT arm, respectively, when OTUS is used). Conversely, even though clearance at week 8 in OTUS for HSCT patients in higher than in SOLSTICE (the unadjusted clearance rates from SOSLTICE and OTUS are the same for SOT and HSCT patients), the increase in mortality observed for HSCT patients in the first 8 weeks of OTUS ([redacted], respectively for SOLSTICE and OTUS) is such that the decrease in overall survival for HSCT patients also leads to an absolute decrease in the number of patients with and without CMV.

Overall, and as discussed in the next paragraphs, using OTUS data accentuates the differences in the results for the SOT and HSCT populations even further (when compared to SOLSTICE). As discussed in Section 2.5, the ERG notes that the company analysis of the OTUS mortality data is likely to overestimate CMV-related mortality and recommends that the company clarifies if the KM mortality data from OTUS only included patients without CMV recurrence, and asks that the company includes the longer-term data from the study for time points beyond 20 weeks in the model.

The results in Table 11 show that the model key drivers when the OTUS data are used remain the length of the stage 1 Markov; the IV administration costs associated with IATs; and the assumption that maribavir patients have a lower probability of recurrence regardless of being off treatment (for the first 12 weeks after stopping treatment).

Decreasing the length of time over which patients can experience CMV recurrences from 78 weeks to 39.2 weeks after baseline increases the ICER from [redacted] to [redacted], where OTUS data are used to model up to 2 episodes of disease recurrence after the index CMV event.

The assumptions made to estimate the IV administration costs of IATs in the model also have a considerable impact on the final ICER, where using the SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle increases the ICER from [redacted] to [redacted]. Alternatively, when the ERG estimated the cost of IV administration using clinical expert input that administration for 2 patients concurrently occupied 4 hours of a nurse's time, with an addition of the cost of 15 minutes of a hospital pharmacist time increased the ICER to [redacted]. The ERG's first IV cost scenario yields a higher IV administration cost, which is why the ICER in the first scenario is lower than the ICER in the second cost scenario.

Finally, assuming that maribavir patients have a higher probability of clearance at week 8 (and therefore a lower probability of graft loss and other CMV-related complications) but have the same probability of recurrence as IAT patients (who have achieved clearance on IATs) increases the ICER from [redacted] to [redacted].

When the ERG's scenarios are combined, the final ICERs range between [redacted] and [redacted] per QALY gained, depending on the assumption used to estimate the IV administration treatment costs and, on the assumption made for the maribavir treatment effectiveness (Table 12).

When the ERG disaggregated the results by type of transplant, the ICERs are [redacted] and [redacted] for SOT and HSCT patients, respectively, at the "best-case scenario" end of the ERG's range (i.e., the equivalent to the [redacted] "combined" ICER). At the more conservative end of the ERG's range, ([redacted]), the disaggregated ICERs are [redacted] and [redacted] for SOT and HSCT patients, respectively.

Table 11 and Table 12). The common assumptions in both of these scenarios are the following:

1. Assuming that the probability of maintaining clearance is independent of the treatment received by patients, and only dependent on time spent in clearance (i.e., the probability of maintaining clearance in the model is the same in both treatment arms and sourced from the IAT arm).
2. Including leukaemia recurrence in the model and correcting the costs of disease to reflect 6 months of survival.
3. Including GvHD as a disease complication in the model.
4. Using the SB14Z and SB15Z NHS reference cost codes for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle. Due to model structure constraints this was implemented as a weighted average of the two costs (by the number of administrations in each IAT treatment cycle). This scenario resulted in a daily administration IV cost of £343.
5. Estimating the daily administration costs for IV treatments based on the PSSRU hourly cost of a critical care nurse, based on the ERG's clinical expert estimates that administration for 2 patients concurrently occupied 4 hours of a nurse's time (Guidelines for Provision of Intensive Care Services [FICM/ICS] outline a 2:1 patient to nurse ratio for level 2 patients). The cost of 15 minutes of hospital pharmacist time was also added. This scenario resulted in a daily administration IV cost of £180.
6. Applying an equal unit hospitalisation cost to both CMV and nCMV patients. Namely, the weighted average of all WJ02C-WJ02E service costs (£1,969.53) as this reflects hospitalisations due to a variety of infectious diseases of varying duration.

When SOLSTICE data are used to estimate treatment effectiveness in the IAT arm of the model:

   a. Using mean TST from SOLSTICE instead of median TST at baseline for SOT and HSCT patients.

b. Limiting the stage 1 Markov to 20 weeks.

When OTUS data are used to estimate treatment effectiveness in the IAT arm of the model:

a. Using mean TST from OTUS.
b. Limiting the stage 1 Markov to 39.2 weeks.

When OTUS data are used to estimate treatment effectiveness in the IAT arm of the model:

a. Using mean TST from OTUS.
b. Limiting the stage 1 Markov to 39.2 weeks.
c. When the ERG used the OTUS clearance data in the model, it discovered that the company used clearance rates from OTUS adjusted for 8-week mortality from OTUS (to which the company then applied a treatment effect to estimate clearance for maribavir). The ERG has not seen any justification for why this adjustment was necessary, or any details on how clearance outcomes were captured from OTUS. Therefore, the ERG removed this adjustment from the company's analysis and presents the results of the ERGs exploratory analysis conducted with the unadjusted clearance rates (reported in Section 2.3); however, the ERG advises that the company provides additional details and justifies why this adjustment might be needed. The ERG provides results using the company's adjustment in Appendix 4.1.

The results in Table 9 show that the model key drivers remain the length of the stage 1 Markov, followed by the IV administration costs associated with IATs, and finally the assumption that maribavir patients have a lower probability of recurrence regardless of being off treatment (for the first 12 weeks after stopping treatment).

Decreasing the length of time over which patients can experience CMV recurrences from 78 weeks to 20 weeks after baseline increases the ICER from dominant to [redacted]. The ERG notes that SOLSTICE provided data for CMV clearance and recurrence 20 weeks after patients' index events, after which the company "plugged" OTUS data to estimate recurrences and clearances in the model which relies on the company's flawed assumptions that: 1) the populations in SOLSTICE and OTUS are directly comparable and 2) that third and further recurrences in the model happen at the same rate as second recurrences in OTUS, which has not been demonstrated by the OTUS data.

The assumptions made to estimate the IV administration costs of IATs in the model also have a considerable impact on the final ICER, where using the SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle increases the ICER from dominant to [redacted]. Alternatively, when the ERG estimated the cost of IV administration using clinical expert input that administration for 2 patients concurrently occupied 4 hours of a nurse's time, with an addition of the cost of 15 minutes of a hospital pharmacist time increased the ICER to [redacted]. The ERG's first IV cost scenario yields a higher IV administration cost, which is why the ICER in the first scenario is lower than the ICER in the second cost scenario.

Finally, assuming that maribavir patients have a higher probability of clearance at week 8 (and therefore a lower probability of graft loss and other CMV-related complications) but have the same probability of recurrence as IAT patients (who have achieved clearance on IATs) increases the ICER from dominant to [redacted].

When the ERG's scenarios are combined, the final ICERs range between [redacted] and [redacted] per QALY gained, depending on the assumption used to estimate the IV administration treatment costs and, on the assumption made for the maribavir treatment effectiveness (Table 10).

When the ERG disaggregated the results by type of transplant, the ICERs are [redacted] and [redacted] for SOT and HSCT patients, respectively, at the "best-case scenario" end of the ERG's range (i.e., the equivalent to the [redacted] "combined" ICER). At the more conservative end of the ERG's range, ([redacted]), the disaggregated ICERs are [redacted] and [redacted] for SOT and HSCT patients, respectively.

The ERG notes that all the scenarios reported are using the SOLSTICE data as the main source of clinical outcomes in the model.

Table 9. Deterministic results when SOLSTICE data are used to estimate effectiveness in the IAT arm

		Incremental costs	Incremental QALYs	ICER
0	Company's base case	[redacted]	[redacted]	[redacted]
1	Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)	[redacted]	[redacted]	[redacted]

2	Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival	[redacted]	[redacted]	[redacted]
3	Including GvHD in the model	[redacted]	[redacted]	[redacted]
4	Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle	[redacted]	[redacted]	[redacted]
5	Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time	[redacted]	[redacted]	[redacted]
6	Applying an equal unit hospitalisation cost to both CMV and nCMV patients	[redacted]	[redacted]	[redacted]
a	Using mean TST	[redacted]	[redacted]	[redacted]
b	Limiting the stage 1 Markov to 20 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 10. Deterministic results (incremental) when SOLSTICE data are used to estimate effectiveness in the IAT arm

		Incremental costs	Incremental QALYs	ICER
0	Company's base case	[redacted]	[redacted]	[redacted]
a	Using mean TST	[redacted]	[redacted]	[redacted]
a+b	Using mean TST Limiting the stage 1 Markov to 20 weeks	[redacted]	[redacted]	[redacted]
a+b+2	Using mean TST Limiting the stage 1 Markov to 20 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival	[redacted]	[redacted]	[redacted]
a+b+2+3	Using mean TST Limiting the stage 1 Markov to 20 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model	[redacted]	[redacted]	[redacted]

a+b+3+6	Using mean TST Limiting the stage 1 Markov to 20 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients	[redacted]	[redacted]	[redacted]
a+b+3+6+4	Using mean TST Limiting the stage 1 Markov to 20 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle	[redacted]	[redacted]	[redacted]
a+b+3+6+5	Using mean TST Limiting the stage 1 Markov to 20 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time	[redacted]	[redacted]	[redacted]
a+b+3+6+4+1	Using mean TST Limiting the stage 1 Markov to 20 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle	[redacted]	[redacted]	[redacted]

	Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)			
a+b+3+6+5+1	Using mean TST Limiting the stage 1 Markov to 20 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

The impact of varying the same assumptions when the OTUS data are used in the model is smaller than when the SOLSTICE data are used (see results in Table 11). Even though all the scenarios using OTUS data result in maribavir being incrementally more costly than IATs (compared to the scenarios using SOLSTICE), these also result in maribavir being associated with higher incremental QALYs than IATs (compared to when SOLTICE data are used). This is related to the base case results for OTUS yielding higher incremental costs ([redacted]) when compared to SOLSTICE and considerably higher QALYs ([redacted]).

The difference in using OTUS or SOLSTICE on the final ICER is driven by the SOT population (given that it represents 60% of the entire model population) and by the fact that survival and nCMV events increase both in absolute and in incremental terms when OTUS data are used. Due to the mortality rates for SOT patients at week 8 are very similar between SOSTICE and OTUS ([redacted] respectively), the number of patients alive at the end of week 8 is very similar across both scenarios (because everyone has CMV for the initial 8 weeks of the model). However, the clearance rate for SOT patients in OTUS at week 8 is higher than in SOLSTICE ([redacted], respectively, for unadjusted clearance for IATs and [redacted], respectively, for maribavir). Therefore, the proportion of SOT patients without CMV at week 12 in the model is higher when OTUS data are used, and the higher proportion of nCMV cases leads, in its turn, to a positive incremental impact on survival, and this benefit is propagated throughout the model (at the end of the stage 1 Markov, there are

[redacted] of SOT patients alive, respectively, in the maribavir arm and in the IAT arm when SOLSTICE is used and, and [redacted] of SOT patients alive in the maribavir arm and in the IAT arm, respectively, when OTUS is used). Conversely, even though clearance at week 8 in OTUS for HSCT patients in higher than in SOLSTICE (the unadjusted clearance rates from SOSLTICE and OTUS are the same for SOT and HSCT patients), the increase in mortality observed for HSCT patients in the first 8 weeks of OTUS ([redacted], respectively for SOLSTICE and OTUS) is such that the decrease in overall survival for HSCT patients also leads to an absolute decrease in the number of patients with and without CMV.

Overall, and as discussed in the next paragraphs, using OTUS data accentuates the differences in the results for the SOT and HSCT populations even further (when compared to SOLSTICE). As discussed in Section 2.5, the ERG notes that the company analysis of the OTUS mortality data is likely to overestimate CMV-related mortality and recommends that the company clarifies if the KM mortality data from OTUS only included patients without CMV recurrence, and asks that the company includes the longer-term data from the study for time points beyond 20 weeks in the model.

The results in Table 11 show that the model key drivers when the OTUS data are used remain the length of the stage 1 Markov; the IV administration costs associated with IATs; and the assumption that maribavir patients have a lower probability of recurrence regardless of being off treatment (for the first 12 weeks after stopping treatment).

Decreasing the length of time over which patients can experience CMV recurrences from 78 weeks to 39.2 weeks after baseline increases the ICER from [redacted] to [redacted], where OTUS data are used to model up to 2 episodes of disease recurrence after the index CMV event.

The assumptions made to estimate the IV administration costs of IATs in the model also have a considerable impact on the final ICER, where using the SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle increases the ICER from [redacted] to [redacted]. Alternatively, when the ERG estimated the cost of IV administration using clinical expert input that administration for 2 patients concurrently occupied 4 hours of a nurse's time, with an addition of the cost of 15 minutes of a hospital pharmacist time increased the ICER to [redacted]. The ERG's first IV cost scenario yields a higher IV administration cost, which is why the ICER in the first scenario is lower than the ICER in the second cost scenario.

Finally, assuming that maribavir patients have a higher probability of clearance at week 8 (and therefore a lower probability of graft loss and other CMV-related complications) but have the same probability of recurrence as IAT patients (who have achieved clearance on IATs) increases the ICER from [redacted] to [redacted].

When the ERG's scenarios are combined, the final ICERs range between [redacted] and [redacted] per QALY gained, depending on the assumption used to estimate the IV administration treatment costs and, on the assumption made for the maribavir treatment effectiveness (Table 12).

When the ERG disaggregated the results by type of transplant, the ICERs are [redacted] and [redacted] for SOT and HSCT patients, respectively, at the "best-case scenario" end of the ERG's range (i.e., the equivalent to the [redacted] "combined" ICER). At the more conservative end of the ERG's range, ([redacted]), the disaggregated ICERs are [redacted] and [redacted] for SOT and HSCT patients, respectively.

Table 11. Deterministic results when OTUS data are used to estimate effectiveness in the IAT arm

		Incremental costs	Incremental QALYs	ICER
0	Company's base case using OTUS data	[redacted]	[redacted]	[redacted]
1	Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)	[redacted]	[redacted]	[redacted]
2	Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival	[redacted]	[redacted]	[redacted]
3	Including GvHD in the model	[redacted]	[redacted]	[redacted]
4	Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle	[redacted]	[redacted]	[redacted]
5	Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time	[redacted]	[redacted]	[redacted]
6	Applying an equal unit hospitalisation cost to both CMV and nCMV patients	[redacted]	[redacted]	[redacted]
a	Using mean TST	[redacted]	[redacted]	[redacted]

b	Limiting the stage 1 Markov to 39.2 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 12. Deterministic results (incremental) when OTUS data are used to estimate effectiveness in the IAT arm

		Incremental costs	Incremental QALYs	ICER
0	Company's base case using OTUS data	[redacted]	[redacted]	[redacted]
a	Using mean TST in OTUS	[redacted]	[redacted]	[redacted]
a+b	Using mean TST in OTUS Limiting the stage 1 Markov 39.2 weeks	[redacted]	[redacted]	[redacted]
a+b+2	Using mean TST in OTUS Limiting the stage 1 Markov 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival	[redacted]	[redacted]	[redacted]
a+b+2+3	Using mean TST in OTUS Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model	[redacted]	[redacted]	[redacted]
a+b+3+6	Using mean TST in OTUS Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients	[redacted]	[redacted]	[redacted]
a+b+3+6+4	Using mean TST in OTUS Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients	[redacted]	[redacted]	[redacted]

	Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle			
a+b+3+6+5	Using mean TST in OTUS Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time	[redacted]	[redacted]	[redacted]
a+b+3+6+4+1	Using mean TST in OTUS Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)	[redacted]	[redacted]	[redacted]
a+b+3+6+5+1	Using mean TST in OTUS Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

2.13 Conclusions and list of ERG's recommendations

The ERG considers that the more robust approach to estimating the probability of clearance and recurrence for IAT in the stage 1 Markov model is based on using the OTUS data. Applying the relative risk of recurrence and clearance observed for maribavir compared to IAT from SOLSTICE to the IAT OTUS data allows the relative treatment effectiveness to be sourced from the pivotal maribavir trial while still using OTUS. The latter provides a longer follow up period for IAT patients than SOLSTICE, and as a real-world data source, provides outcome data likely to be more generalisable to UK clinical practice.

The ERG maintains its view that the company's use of the OTUS data in their base case is inappropriate for decision making. By using OTUS recurrence data to model subsequent CMV events after first events modelled with SOLSTICE data (and particularly by assuming that the probability of second clearance could be estimated from SOLTICE while the probability of remaining in the second clearance state was estimated from OTUS), the company assumed that not only the populations, but also clearance and recurrence in both studies are directly comparable and interchangeable. The company's approach relies on a naïve comparison of the SOLSTICE and OTUS data, a method which has been highly criticized for its lack of robustness in previous NICE appraisals. The fact that the available data from both studies suggest that the study populations are not comparable only aggravates the inappropriateness around the use of a naïve comparison method further.

In order to maintain consistency in the clinical outcomes used in the model, the ERG agrees with the company's approach of using OTUS data to model mortality and mean TST. However, the ERG notes that the company analysis of mortality data from OTUS is likely to overestimate CMV-related mortality in the OTUS scenario analysis, which has a considerable impact on the results of these analyses.

The ERG disagrees with the company's chosen duration of a "full cycle" of events and considers that this should match the time to second events in OTUS, which is 39.3 weeks. This would alleviate the ERG's concern around the overestimation of recurrences in the model given the company's assumption that the rate of third and further recurrences in the model is the same as that observed for second recurrences in OTUS, which is not supported by the observed recurrence rate from OTUS, where the rates of subsequent recurrences were much lower after second recurrence.

Additionally, the ERG recommends that the company clarifies/investigates the following issues:

1. The ERG recommends the company presents data on the mean time since clearance (at week 8) to clinically relevant recurrence (from week 8 to week 20), which could provide some support of the suggested correlation between maribavir treatment and time since clearance.
2. The ERG recommends that the company provides the additional clearance data used to estimate the [redacted] probability of clearance for SOT 8 weeks, available from OTUS (for all time points and for HSCT patients if possible).
3. The ERG considers that the cyclical nature of CMV pointed out by the company is an issue in any type of analysis, including the company's base case approach where number of deaths was estimated by CMV status. The ERG is unware how the company attributed deaths to CMV events in the latter analysis, therefore, requests that the company clarifies this (i.e., how the company determined the relevant factor for survial - present CMV; past CMV; duration of CMV, etc.).
4. The ERG requests that the company provides KM survival data by transplant type and by CMV status (as per the first point) from SOLSTICE.
5. The ERG recommends that the company clarifies if the KM mortality data from OTUS only included patients without CMV recurrence, and asks that the company includes the longer-term data from the study for time points beyond 20 weeks in the model.
6. The ERG recommends that the company investigates the OTUS KM mortality data, separated by HSCT and SOT, to assess if mortality by CMV status (within each population) is statistically significantly different for CMV and nCMV IAT patients. If this is the case, then the company would not have to use external literature to estimate CMV-related mortality, and the maribavir treatment effect derived from SOLSTICE leading to the difference in CMV events in the maribavir and IAT arms would generate the survival benefit associated with maribavir.
7. The ERG-suggested scenario analysis including GvHD independent from CMV (from SOLSTICE) has been included in the company's updated model; however, it appears to the ERG that the company has not assumed GvHD patients to have a higher mortality in the model. Therefore, the ERG recommends that the company adds this assumption to their scenario analysis.
8. With regards to GvHD from OTUS, the company replied that the full OTUS HSCT report is not yet available but that it is expected that the latter will be ready within two months of their

second response to TE. Therefore, the ERG recommends that the company provides these data when available.

3 References

Hakimi Z, Aballéa S, Ferchichi S, et al. Burden of cytomegalovirus disease in solid organ transplant recipients: a national matched cohort study in an inpatient setting. *Transplant Infectious Disease* 2017;19(5):e12732.

NHS Blood and Transplant. Organ and Tissue Donation and Transplantation Annual Activity Report 2020/2021 2021 [Available from: https://www.odt.nhs.uk/statistics-and-reports/annual-activity-report/].

Camargo, J.F., 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, 2018. 24(4): p. 806-814.

Martin, P.J., et al., Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. J Clin Oncol, 2010. 28(6): p. 1011-6.

Ara, R. and J.E. Brazier, Populating an economic model with health state utility values: moving toward better practice. Value Health, 2010. 13(5): p. 509-18.

Hahn, T., 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. 26(35): p. 5728-34.

4 Appendix

4.1 ERG's exploratory analysis using OTUS results and the company's mortality adjustment of clearance estimates

The impact of varying the same assumptions when the OTUS data are used in the model is smaller than when the SOLSTICE data are used (see results in Table 13). Even though all the scenarios using OTUS data result in maribavir being incrementally more costly than IATs (compared to the scenarios using SOLSTICE), these also result in maribavir being associated with higher incremental QALYs than IATs (compared to when SOLTICE data are used). This is related to the base case results for OTUS yielding higher incremental costs ([redacted]) when compared to SOLSTICE and considerably higher QALYs ([redacted]).

The difference in using OTUS or SOLSTICE on the final ICER is driven by the SOT population (given that it represents 60% of the entire model population) and by the fact that survival and nCMV events increase both in absolute and in incremental terms when OTUS data are used. Due to the mortality rates for SOT patients at week 8 being very similar between SOSTICE and OTUS ([redacted] respectively), the number of patients alive at the end of week 8 is very similar across both scenarios (because everyone has CMV for the initial 8 weeks of the model). However, the clearance rate in OTUS for SOT patients at week 8 (adjusted for mortality) is higher than in SOLSTICE ([redacted], respectively, for IATs and [redacted], respectively, for maribavir). Therefore, the proportion of patients without CMV at week 12 in the model is higher when OTUS data are used ([redacted] in SOLSTICE vs [redacted] in OTUS). The higher proportion of nCMV cases leads, in its turn, to a positive impact on survival, and this benefit is propagated throughout the model. Conversely, even though HSCT patients also have a higher clearance at week 8 (adjusted for mortality) in OTUS than in SOLSTICE ([redacted], respectively, for IATs and [redacted], respectively, for maribavir), the increase in mortality observed for HSCT patients in the first 8 weeks of OTUS ([redacted] respectively for SOLSTICE and OTUS) is such that the decrease in overall survival for HSCT patients also leads to an absolute decrease in the number of patients with and without CMV.

Overall, and as discussed in the next paragraphs, using OTUS data accentuates the differences in the results for the SOT and HSCT populations even further (when compared to SOLSTICE). As discussed in Section 2.5, the ERG notes that the company analysis of the OTUS mortality data is likely to overestimate CMV-related mortality and recommends that the company clarifies if the KM mortality

data from OTUS only included patients without CMV recurrence, and asks that the company includes the longer-term data from the study for time points beyond 20 weeks in the model.

The results in Table 13 show that the model key drivers when the OTUS data are used remain the length of the stage 1 Markov; the IV administration costs associated with IATs; and the assumption that maribavir patients have a lower probability of recurrence regardless of being off treatment (for the first 12 weeks after stopping treatment).

Decreasing the length of time over which patients can experience CMV recurrences from 78 weeks to 39.2 weeks after baseline increases the ICER from [redacted] to [redacted], where OTUS data are used to model up to 2 episodes of disease recurrence after the index CMV event.

The assumptions made to estimate the IV administration costs of IATs in the model also have a considerable impact on the final ICER, where using the SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle increases the ICER from [redacted] to [redacted]. Alternatively, when the ERG estimated the cost of IV administration using clinical expert input that administration for 2 patients concurrently occupied 4 hours of a nurse's time, with an addition of the cost of 15 minutes of a hospital pharmacist time increased the ICER to [redacted]. The ERG's first IV cost scenario yields a higher IV administration cost, which is why the ICER in the first scenario is lower than the ICER in the second cost scenario.

Finally, assuming that maribavir patients have a higher probability of clearance at week 8 (and therefore a lower probability of graft loss and other CMV-related complications) but have the same probability of recurrence as IAT patients (who have achieved clearance on IATs) increases the ICER from [redacted] to [redacted].

When the ERG's scenarios are combined, the final ICERs range between [redacted] and [redacted] per QALY gained, depending on the assumption used to estimate the IV administration treatment costs and, on the assumption made for the maribavir treatment effectiveness (Table 14).

When the ERG disaggregated the results by type of transplant, the ICERs are [redacted] and [redacted] for SOT and HSCT patients, respectively, at the "best-case scenario" end of the ERG's range (i.e., the equivalent to the [redacted] "combined" ICER). At the more conservative end of the ERG's range, ([redacted]), the disaggregated ICERs are [redacted] and [redacted] for SOT and HSCT patients, respectively.

Table 13. Deterministic results when OTUS data are used to estimate effectiveness in the IAT arm

		Incremental costs	Incremental QALYs	ICER
0	Company's base case using OTUS data	[redacted]	[redacted]	[redacted]
1	Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)	[redacted]	[redacted]	[redacted]
2	Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival	[redacted]	[redacted]	[redacted]
3	Including GvHD in the model	[redacted]	[redacted]	[redacted]
4	Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle	[redacted]	[redacted]	[redacted]
5	Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time	[redacted]	[redacted]	[redacted]
6	Applying an equal unit hospitalisation cost to both CMV and nCMV patients	[redacted]	[redacted]	[redacted]
a	Using mean TST	[redacted]	[redacted]	[redacted]
b	Limiting the stage 1 Markov to 39.2 weeks	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 14. Deterministic results (incremental) when OTUS data are used to estimate effectiveness in the IAT arm

		Incremental costs	Incremental QALYs	ICER
0	Company's base case using OTUS data	[redacted]	[redacted]	[redacted]
a	Using mean TST in OTUS	[redacted]	[redacted]	[redacted]
a+b	Using mean TST in OTUS Limiting the stage 1 Markov 39.2 weeks	[redacted]	[redacted]	[redacted]
a+b+2	Using mean TST in OTUS Limiting the stage 1 Markov 39.2 weeks	[redacted]	[redacted]	[redacted]

	Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival			
a+b+2+3	Using mean TST in OTUS Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model	[redacted]	[redacted]	[redacted]
a+b+3+6	Using mean TST in OTUS Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients	[redacted]	[redacted]	[redacted]
a+b+3+6+4	Using mean TST in OTUS Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle	[redacted]	[redacted]	[redacted]
a+b+3+6+5	Using mean TST in OTUS Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time	[redacted]	[redacted]	[redacted]
a+b+3+6+4+1	Using mean TST in OTUS Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival	[redacted]	[redacted]	[redacted]

	Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)			
a+b+3+6+5+1	Using mean TST in OTUS Limiting the stage 1 Markov to 39.2 weeks Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival Including GvHD in the model Applying an equal unit hospitalisation cost to both CMV and nCMV patients Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year