NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

ISBN: 978-1-4731-4959-5

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:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Takeda UK**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Anthony Nolan
   b. British Transplantation Society
   c. UK Renal Pharmacy Group

4. **Evidence Review Group critique of company comments on the ACD**

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1		Anthony Nolan	We are concerned that the significant benefit that this treatment could provide to the quality of life of patients has not been adequately accounted for. Patients who have experienced refractory or resistant cytomegalovirus (CMV) infection post-stem cell transplant reported a range of significant challenges as a result of their CMV infection or re-activation. This includes the treatment of CMV, which had a significant physical and psychological impact on many patients. One described the treatment as physically the '*most difficult part of their entire treatment journey*' while others described fearing they would '*never get their lives back',* referring to constant hospital visits and time spent as an inpatient. It was also reported that some had to quit their job, as a result of the significant amount of time they were forced to take off as a result of their CMV treatment and recovery.	Thank you for your comment. The committee acknowledge the issues around the sensitivity of the EQ5D measure, however the committee concluded that the impact on health-related quality of life using utilities had been appropriately captured in the model (see section 3.16 of the final appraisal document [FAD]). The views of clinical experts and patient/carer representatives were considered by the committee when formulating its recommendations.
2		Anthony Nolan	We are concerned that this recommendation does not fully consider the lack of alternative treatment options for some patients with a refractory or resistant cytomeglovirus infection after a transplant. Although the availability of letermovir prophylaxis has benefited patients, those with breakthrough infections that do not respond to gangciclovir, valganciclovir, foscarnet, and cidofovir often have poor outcomes.	Thank you for your comment. The committee acknowledge the unmet need for more effective treatment options that that do not respond to first line antiviral therapies (see section 3.1 of the FAD).
3		Anthony Nolan	We are concerned at the lack of emphasis placed on maribavir having lower toxicity than some other CMV treatments. Both cytomegalovirus infection and treatments, including gangciclovir and valganciclovir, are marrow toxic and can cause cytopenia and neutropenia. The existing toxicity of current treatment such as these can have a direct impact on bone marrow engraftment and may also increase other autoimmune issues including graft versus host disease, a common side effect of a stem cell transplant which can lead to poor recovery and quality of life in both the long and short term.	Thank you for your comment. The committee acknowledged the existing toxicity of current treatment (see section 3.1 and section 3.13 of the FAD).
4		British Transplantation	Thank you for including the British Transplantation Society (BTS) as a consultee in this appraisal.	Thank you for your comment. . Maribavir is recommended,

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		Society	Our expertise and comments relate to the use of Maribavir in patients with a solid organ transplant (SOT), although some are also applicable to patients receiving haematologic stem cell transplants (HSCT). The BTS is surprised that Maribavir has not been recommended for use in patients with resistant or refractory CMV – a group of patients for whom current therapy (Foscarnet or Cidofovir) is poorly effective and toxic. We note that: • Maribavir is approved for this indication in the USA (FDA – November 2021). • In the context of the current NHS – when both in-patient beds and staffing are exceptionally challenged – an effective oral agent such as Maribavir is clearly preferable to treatments that require both hospitalization and intravenous administration. Foscarnet and Cidofovir require both – often for several weeks. Whilst the ERG attempts to address this point in economic models, this approach fails to capture the very real pressures on NHS facilities faced by clinicians every day. We note that the ERG refers to the BTS Guidelines on prevention and management of CMV after solid organ transplantation (2015). These guidelines are out of date and contain recommendations no longer applicable to clinic practice. The updated guidelines (2022) are available on the BTS website: UK GUIDELINE ON PREVENTION AND MANAGEMENT OF CYTOMEGALOVIRUS (CMV) INFECTION AND DISEASE FOLLOWING SOLID ORGAN TRANSPLANTATION - British Transplantation Society (bts.org.uk)	within its marketing authorisation, as an option for treating cytomegalovirus (CMV) infection that is refractory to treatment including cidofovir, foscarnet, ganciclovir or valganciclovir in adults who have had a haematopoietic stem cell transplant or solid organ transplant. See section 1.1 of the FAD.

5		British Transplantation Society	**Section 3.2 – The conduct and design of the SOLSTICE trial could bias the results**. This may be so, but we do not believe it would be possible to a conduct such a trial without the potential biases raised by the ERG and Committee.
			
			• SOLSTICE is an open label trial. This may not be perfect, but there is no way of blinding clinicians or patients to the treatment received. Maribavir is oral and the alternatives (Ganciclovir, Foscarnet or Cidofovir) are all administered intravenously in very different fluid volumes, and at different frequencies. The alternative of a very complex trial design (which would require patients assigned to Maribavir to be admitted to hospital and receive multiple placebo IV infusions) is not practically possible:
			
			  ○ It is very unlikely any ethics committee would consider such a design acceptable given the very invasive nature of the placebo treatment.
			
			  ○ The very distinctive adverse effects of each medication and required monitoring would effectively un-blind most recipients to their clinicians.
			
			• Treatment in the IAT group. The ERG and Committee are concerned that investigators could choose which alternative treatment to use. But this choice is based on patient characteristics and local expertise. Whilst Foscarnet is likely the most frequent second line treatment in the UK, Cidofovir is used in other countries- the SOLSTICE trial was conducted in more than 100 centres in 12 countries. If anything, allowing investigators to select which alternative treatment to use biases the trail towards the IAT group, since investigators are likely to select a treatment they consider most likely to be effective.
				Thank you for your comment. The ERG noted some concerns around the open-label design of the trial and that the rescue arm may introduce bias to some outcomes. The committee therefore concluded that some aspects of the conduct and design of SOLSTICE could bias the results.
				
				The committee's discussions around the conduct and design of the SOLSTICE trial are reported in section 3.2 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• The ERG and Committee are concerned that the investigators were able to modify immunosuppression. However, this is an essential component in managing patients with refractory / resistant CMV, and is necessarily determined by the clinical circumstances of each patient. So for Ganciclovir / Valganciclovir treated patients, the most common intervention would be to reduce or withdraw mycophenolic acid-based medications (MPA). In contrast, both Foscarnet and Cidofovir are nephrotoxic, and some clinicians would aim to reduce calcineurin inhibitors (CNI). Any changes to immunosuppression would have to be considered with regard to recent rejection episodes and rejection risk. Accordingly mandating changes to immunosuppression would not be possible in a trial protocol. • The ERG and Committee are concerned that patients in the IAT group not responding to treatment at 3 weeks could be switched to Maribavir. We accept that such a study design leads to difficulty in performing the detailed analyses required by NICE. Never the less, the ERG and Committee have accepted that current treatments for refractory / resistant CMV are poorly effective and poorly tolerated (section 3.1), so allowing patients to switch from demonstrably ineffective interventions would seem entirely justified.	
6		British Transplantation Society	**Section 3.3 – Results of SOLSTICE may not be generalizable to clinical practice**. We disagree with this statement. In fact the SOT patient population included in the trial very much reflects current clinical practice. • We have discussed points related to immunosuppression and choice of treatment in the IAT arm above. • We note the comment 'the mean and median time since transplant at randomization were longer than would be expected in clinical practice for the SOT subgroup …' However nowhere in the SOLSTICE study or supplementary information is there any data on time since transplant. This issue was raised in several Priority Questions – A2, A4, B7, B8 and more. The company confirmed that the time since transplant was not collected in SOLSTICE. However, page 41 of the ERG report includes the statement 'the mean time since transplant was around [redacted] months for SOT patients'. It would be helpful to know what data 'one of the clinical experts' is referring to? • In any case, the time for transplant to (a) first CMV viraemia and (b) resistant / refractory CMV is inherently very variable in clinical practice. The key determinant is the use of CMV prophylaxis – usually valganciclovir. Whilst >80% of the patients were high risk CMV D+ / R- transplants, only 40% of patients received any prophylaxis. In those that did receive prophylaxis, the duration is not specified but is likely to be either 100 days or 200 days. Accordingly CMV diagnoses will be distributed over the first post-transplant year – this is exactly the reality of clinical practice. • We accept the challenges with regard to the timing of CMV diagnoses and the economic modelling raised by the ERG. • The ERG and Committee observe that some patients in the IAT group were assigned treatments to which they have resistance. Again, this is the current clinical reality. There are two common forms of resistance:	Thank you for your comment. The committee discussed how generalisable SOLSTICE was to clinical practice. The committee concluded that the results from SOLSTICE may not be generalisable to clinical practice. The committee's discussions around the generalisability of SOLSTICE to clinical practice are reported in section 3.3 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			○ Mutations in the UL97 gene – which confer Ganciclovir resistance. These patients are usually treated with Foscarnet / Cidofovir. ○ Mutations in the UL54 gene - which confer resistance to all three medications. • These resistance mutations are determined by genetic polymorphisms of the relevant genes (or which there are many), and resistance is not absolute – so for example some patients with UL97 mutations who do not respond to oral Valganciclovir may respond to IV Ganciclovir. In he case of UL54 mutations, there is no alternative treatment (aside from Maribavir).	
7		British Transplantation Society	**Section 3.4 – SOLSTICE data suggests that Maribavir improved clearance compared with IAT, but the results are highly uncertain.** We strongly disagree with this conclusion. The Committee points to the uncertainties discussed in Sections 3.2 and 3.3. But we argue that these uncertainties represent the reality of clinical practice, and that the highly significant advantage of Maribavir over alternative therapies has been demonstrated in a patient group comparable to those managed in transplant units around the UK.	Thank you for your comment. Please see comment number 5 and 6.
8		British Transplantation Society	**Sections 3.5 onwards – The Company's economic model.** We are not able to comment on detail of the economic modelling – either of the Company or ERG, but would welcome the opportunity to address any clinical uncertainties involved in these models.	Thank you for your comment. No action required.
9		UK Renal Pharmacy Group	We are concerned that this recommendation does not meet the clinical needs of patients with renal dysfunction, including solid organ kidney and kidney-pancreas transplant recipients. Whilst accepting that refractory or resistant CMV infection has a low incidence in this cohort, maribavir does offer a significant treatment option for the following reasons:- a) For renal transplant patients or immunocompromised patients with renal dysfunction foscarnet, as referenced in section 3.1 is nephrotoxic. However the significance of this in clinical practice needs further consideration. When foscarnet is used it can either lead to significant graft dysfunction/loss (this can render a patient in need of renal replacement therapy – haemofiltration or haemodialysis at significant cost to NHS). Transplant function may not recover and long term renal replacement therapy will then be necessary. Or the patient may endure significant side effects due to poor drug clearance which may render a patient with life changing, disabling effects e.g peripheral neuropathy leaving patient unable to walk, physically unable to use their arm(s) to lift any weight, sensory impairment to hot/cold. To improve foscarnet tolerability it needs to be given with increased fluid which for patients with significant renal dysfunction and fluid restriction, this can be further challenging. In clinical practice foscarnet is very poorly tolerated in this cohort. Maribavir, after foscarnet treatment failure or early cessation is therefore the only viable alternative treatment option as cidofovir for many renal patients is contra-indicated (see b) Furthermore cidofovir, referenced as causing neutropenia in section 3.1, is in fact contraindicated in patients	Thank you for your comment Maribavir is recommended, within its marketing authorisation, as an option for treating cytomegalovirus (CMV) infection that is refractory to treatment including cidofovir, foscarnet, ganciclovir or valganciclovir in adults who have had a haematopoietic stem cell transplant or solid organ transplant. See section 1.1 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			with estimated renal function (creatinine clearance) less than 55ml/min ie where renal function is working at less than 55% capacity. Cidofovir for many renal transplant patients is therefore NOT a treatment option as average renal function post-renal transplant is 25-50ml/min, with many patients having transplant renal function less than 25ml/min ie renal function working at less than 25% capacity.	
10		UK Renal Pharmacy Group	It is important for the committee to be aware that usage in renal transplant patients for this indication would be low. In a single centre experience with over 1900 long term renal transplant follow up patients, transplanting over 200 new renal patients per year, refractory CMV disease affects 1 patient every 18-24months. Whilst the drug may be high cost, its usage will be very low in this cohort but it is an essential treatment option for the reasons explained above.	Thank you for your comment. No action required.
11		UK Renal Pharmacy Group	We fully agree with the committee recommendation to include disease complications in the modelling to consider transplant graft loss as a consequence of CMV treatment from foscarnet, a nephrotoxic agent.	Thank you for your comment. The committee noted that the company's revised base case included disease complications in the model (see section 3.12 of the FAD). For further information please see comment number 22.
12	Consultee (company)	Takeda UK Ltd	**The clinical need for maribavir with limited treatment options available** Takeda note that all conventional therapies are used off-label for the treatment of CMV post-transplant. Maribavir offers the first approved treatment for refractory (with or without resistance) CMV infection. Many of the conventional therapies are associated with adverse events (neutropenia and nephrotoxicity) that can lead to the development of viral resistance. Maribavir may reduce treatment burden as an oral therapy and reduce the hospitalisations required for IV therapies. We recognise that CMV infection and conventional strategies for management have negative impacts on both patient and caregiver quality of life, in terms of physical activity and mobility limitations, stress, mental fatigue & inability to work. For caregivers, there is an emotional burden and impact on daily life & work that we are unable to capture in the economic model.	Thank you for your comment. The committee acknowledged the unmet need for more effective treatment options and that maribavir is an oral therapy (see section 3.1-3.3 of the FAD).
13	Consultee (company)	Takeda UK Ltd	**The conduct and design of SOLSTICE could bias the results** Takeda dispute that the SOLSTICE trial results are biased. Extensive sensitivity analysis has been provided throughout technical engagement that demonstrate the robustness of the data. Multiple sensitivity analyses of the primary endpoint demonstrate a consistent efficacy advantage over IAT, regardless of whether the study drug was prematurely discontinued, clearance occurred at any time during the treatment phase, or the IAT patients received alternative anti-CMV treatment. Takeda note that the SOLSTICE trial population was heterogenous, in both solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) patients. The trial design was deemed ethical and sufficient for this patient population, and both the EMA and FDA were consulted on the trial design.	Thank you for your comment. At the first committee meeting, the committee concluded that some aspects of the conduct and design of SOLTICE could bias the results (see section 3.2 of the FAD). The committee noted in the second committee meeting that this issue was difficult to resolve.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Furthermore, we highlight that CHMP opinion was granted on 15th September 2022 based on maribavir demonstrating statistically superior efficacy compared to conventional therapies for the primary endpoint, indicating the regulators confidence in the data package for maribavir.[1] The ERG thought that the rescue arm may introduce bias to some outcomes. The committee considered that 3 weeks of treatment may not be long enough to assess a lack of efficacy. Takeda would like to clarify that the rescue arm was only an option for IAT subjects who, despite a minimum of 3 weeks of therapy with IAT, met stringent and objective criteria for lack of improvement/worsening of CMV infection, namely: • ≥1 log10 increase in CMV DNA from baseline • <1 log10 decrease in CMV DNA from baseline with new, worsening, or no improvement in tissue-invasive disease; or • lack of viremia clearance and demonstrated intolerance to IAT with either >50% increase from baseline in serum creatinine, development of haemorrhagic cystitis, or development of neutropenia (absolute neutrophil count [ANC] <500/mm3). Therefore, the above criteria demonstrated no response within a set timeframe of three weeks, an endpoint that was agreed with the EMA and FDA during the design of the trial. Throughout the ratification of the NICE submission, Takeda spoke with numerous SOT and HSCT clinicians where it was confirmed that if after two weeks of therapy no reduction in viral load was seen, an alternative treatment plan would be considered. This is also aligned to BTS guidelines which states: *Based on knowledge of the viral kinetics with anti-CMV treatment, members agreed to recommend treatment for at least 14 days duration as this has been shown to be associated with a viraemia reduction of approximately 1.0 log10 (90%).*[2]	
14	Consultee (company)	Takeda UK Ltd	**Results of SOLSTICE may not be generalisable to clinical practice** Takeda note the Committee had some concerns about an imbalance in time since transplant between treatment arms. We would like to draw attention to the extensive regression analysis performed during technical engagement which demonstrated 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] and [redacted], respectively. This indicates that the odds of each outcome are almost unchanged by increasing the number of months since transplant, and it is the treatment effect of maribavir that is driving the efficacy. We are pleased to see the sensitivity analysis provided at technical engagement regarding patients in the IAT group having retreatment with anti-CMV therapies to which their infection was resistant has demonstrated the sustained benefit of maribavir, and that the clinical experts confirmed that continuing treatment in these circumstances is plausible when there are no better treatment options available. During technical engagement, extensive missing data analysis was provided to the technical team, and we confirmed that minimal missing data for recurrence was seen. Takeda note the ERG agreed missing data wasn't a significant issue for the ITT population. We agree that the missing data is greater in the IAT arm due to the presence of a rescue arm. Without the rescue arm, the trial would have not met the necessary ethical	Thank you for your comment. At the first committee meeting, the committee concluded that the results from SOLSTICE may not be generalisable to clinical practice (see section 3.3 of the FAD). The committee noted in the second committee meeting that this issue was difficult to resolve.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			standards during the design phase.	
15	Consultee (company)	Takeda UK Ltd	**SOLSTICE data suggests that maribavir improves clearance compared with IAT, but the results are highly uncertain** Takeda note that regulators have agreed that data from the SOLSTICE trial demonstrates the efficacy of maribavir. CHMP opinion was granted on 15th September 2022 and FDA approval on 23 November 2021, based on maribavir demonstrating statistically superior efficacy compared to conventional therapies for the primary endpoint. Regulators agreed during the design of the trial that transplantation patient's level of CMV viremia is considered a validated surrogate endpoint that predicts mortality. Detailed sensitivity and supplemental analyses were prespecified to assess the robustness of the results in the CSR.	Thank you for your comment. No action required.
16	Consultee (company)	Takeda UK Ltd	**Using OTUS data is more robust than using multiple data sources to model outcomes in the stage 1 Markov model** Takeda note the potential uncertainties arising due to the nature of incorporating two separate data sources to inform initial and subsequent episodes in the economic model. However, Takeda maintain that SOLSTICE provides the most reliable data source to estimate the treatment effect of maribavir compared to standard care and also, therefore, that the IAT arm of the SOLSTICE trial represents the most reliable source of data to inform the standard care arm for the initial R/R CMV episodes in which maribavir is being appraised. Despite this, Takeda are willing to acknowledge the Committee's concerns and incorporate this within our revised analyses with the aim of achieving expedited access for patients. Within our revised analyses we have also amended the mortality adjustment that was initially applied to the clearance estimates. This was incorrectly applied previously, and we have now aligned with the Committee's preferred approach.	Thank you for your comment. Section 3.6 of the FAD has been updated to reflect that the company incorporated OTUS data in its revised analyses, with the relative treatment effect of maribavir from SOLSTICE. The committee noted that the ERG queried the company's estimate of probability of clearance for the HSCT population. The committee acknowledged that the company had submitted additional data from OTUS ahead of the second committee meeting. The ERG was satisfied with the company's update. The committee concluded that the data used in the company's model was suitable for decision making.
17	Consultee (company)	Takeda UK Ltd	**Maribavir may increase the likelihood of maintaining CMV clearance, but there is no evidence to support this** Takeda note that the NICE clinical expert agreed with the company approach during the first appraisal committee meeting. We also highlight that in SOLSTICE the durability of the effect of maribavir was demonstrated, the proportion of responders that achieved CMV viremia clearance and CMV infection symptom control at Week 8 and maintained the effect through Weeks 12, 16, and 20 off-treatment was	Thank you for your comment. Section 3.7 of the FAD has been updated to reflect that the company updated its base case and applied treatment independent recurrence risk.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			approximately 2-fold higher for maribavir-treated patients than for the IAT group, regardless of the duration of follow-up. However, in the absence of direct supporting evidence within the SOLTSTICE data for patients treated with maribavir having a lower probability of CMV recurrence than patients treated with IAT, Takeda are willing to accept the Committee's preference.	The committee concluded that using a treatment-independent risk of recurrence is suitable for decision making.
18	Consultee (company)	Takeda UK Ltd	**The number of CMV recurrences is overestimated in the model** Takeda would like to comment that evidence for multiple recurrences has been demonstrated in the OTUS data and was provided to the ERG during technical engagement. The limited number of patients experiencing multiple recurrences reflects the small population of patients who are refractory or resistance to prior anti-CMV therapies. We consider the ERG approach of limiting the number of recurrences in the model is very conservative and merely removes uncertain benefit rather than considers the uncertainty surrounding that benefit in the context of a very rare condition with an important unmet need. Despite this, Takeda are keen for maribavir to be made available to patients as soon as possible and are willing to amend the revised analysis to the conservative scenario where recurrences can only occur up to week 39 as per the ERG's preferred analysis. Importantly, this aspect of the revised economic analyses now aligns with the Committee's preferred assumption and therefore any further modelling to assess the uncertainty surrounding the longer-term recurrence rates beyond week 39 is no longer relevant. This therefore fully addresses the Committee's preferences.	Thank you for your comment. Section 3.8 of the FAD has been updated to reflect that the company updated its base case to 2 CMV recurrences. The committee concluded that restricting the model to 2 recurrences was likely to be conservative, but in the absence of further data, this was the most suitable approach for decision making.
19	Consultee (company)	Takeda UK Ltd	**The duration of the stage 1 Markov model should align with the duration that CMV recurrences can be accurately modelled** Takeda believe the OTUS data is a robust source for modelling recurrences over time. Although the evidence for greater than two recurrences can be observed in the OTUS data, we recognise the number of patients with >2 recurrences diminish over time and is reflective of this population. As there is robust data in OTUS that demonstrate the first and second recurrence occur by 39.2 weeks, we are willing to accept the Committee's preference to limit stage 1 of the Markov model to this length.	Thank you for your comment. Section 3.9 of the FAD has been updated to reflect that the company updated its base case restricting the stage 1 Markov model to 39.2 weeks and 2 CMV recurrences. The committee noted that the company had not provided any scenario analyses as requested at the first meeting. Despite this, the committee concluded that the company's updated model was suitable for decision making.
20	Consultee (company)	Takeda UK Ltd	**Risk of mortality in the stage 1 Markov model should be the same for people having maribavir and IAT** Takeda have aligned the stage 1 mortality in the economic model with the ERG's suggested methodology and therefore the revised results provided in this response document are fully aligned with the ERG's preferred approach.	Thank you for your comment. Section 3.10 of the FAD discusses the company's original assumptions for

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Takeda believe the committee's position to assume that there should be no life year gain in the model is in contradiction not only to the alignment of Takeda and the ERG but also of the published evidence base. Furthermore, it has been acknowledged by clinicians advising both Takeda and the ERG that there is a clear association between CMV and the risk of mortality, and two recent large-scale studies have further substantiated the association between CMV viraemia and mortality.[3, 4] The remainder of this section outlines the key evidence demonstrating this mortality association (including an update from the 12-month extension to SOLSTICE) as well as addressing some corrections to the IPD analysis report highlighted previously by the ERG. In response to the points made by the ERG (Section 2.5, page 14 of the *ERG's review of the company's response to the ERG TE critique*, August 2022) in relation to the cross-over adjusted mortality analyses, Takeda would like to clarify some errors in figure headings that caused misleading conclusions by the ERG. The adjusted KM plot for mortality that the ERG refers to was incorrectly labelled as "adjusted for treatment switch by RPSFTM method". This plot in fact represents *treatment-free* transformed survival i.e., removing the treatment effect (estimated using e.g., the RPSFTM adjustment) and thus compares two groups of patients who are hypothetically untreated with maribavir. This plot should not be interpreted as a lack of treatment effect for maribavir compared to IAT following adjustment. The adjusted KM plots for each method accounting for cross-over are all indistinguishable given the similarity in the estimated HRs. The KM plot given in Figure 1 therefore provides a representation of the impact of adjusting for cross-over for all adjustment methods. *Figure 1. Kaplan-Meier showing cross-over adjusted survival from SOLSTICE*	modelling mortality in the stage 1 model, and why the committee had concluded there was lot of uncertainty in the company's assumptions. It agreed that SOLSTICE had not shown a survival benefit and that risk of mortality in the stage 1 model should be the same for the maribavir and IAT groups. The committee acknowledged the additional information provided by the company and section 3.10 of the FAD has been updated to reflect that the company updated its base case using published data sources to inform mortality risks for people with clinically significant CMV and no clinically significant CMV. The ERG noted that the company's base case represented the best-case scenario for the risk of mortality associated with CMV. To help with decision making, the ERG provided 2 scenarios: a worst-case scenario with no additional risk of mortality from CMV, and a midpoint scenario in which people with CMV were arbitrarily assumed to have twice the risk of mortality than people without CMV. The committee accepted that it was very likely that CMV clearance would have an impact on mortality, but the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 An additional typographical error highlighted by the ERG was in the tabulated results. To clarify, Table B4 (and B5) of the IPD analysis report had incorrect labels that should have stated *"Time to all-cause mortality prior to initiation of alternative anti-CMV treatment use by treatment arm adjusted for treatment switch by RPSFTM method"*. Previously, Table B4 and B5 had the same headings as Table B1 and B2, respectively. The hazard ratio presented previously in Table B1 was correctly reported for the RPSFTM and this is the relevant result to compare to the primary analysis that used the inverse probability of censoring weights (IPCW) method. The conclusions of these analyses showed that the results of the two methods were similar with hazard ratios of [redacted] and [redacted] for the IPCW and RPSFTM methods, respectively. For the IPE method, the hazard ratio	magnitude of the impact was very uncertain. It commented that it was likely that the upper bound of that magnitude was from the published data sources used by the company. The committee concluded that maribavir may have an impact on mortality, but this is highly uncertain and the magnitude of the impact is unknown.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			showed a slightly greater adjusted treatment effect of [redacted]. These analyses show increasing evidence of an effect being demonstrated even within the short follow-up period of the SOLSTICE trial, which was not powered to detect a significant effect for mortality. A corrected version of the IPD report will be supplied alongside this response document for full clarity of the corrections. In addition to this, SOLSTICE provides clear evidence of a difference in survival associated with response to CMV treatment, as shown in the KM plot in Figure 2. This plot shows a statically significant difference in the hazard rate of death between those who achieved clearance at week 8 (in either treatment group) compared to those who failed to achieve clearance. *Figure 2: Kaplan Meier plot of OS by clearance status at week 8* As there are important differences in the mortality rate of the two transplant types, (SOT and HSCT), it is also important to assess the survival of the two subgroups separately. Figure 3 shows KM plots for survival form SOLSTICE split by clearance status at week 8 as well as transplant type. This also clearly demonstrates the impact that achieving clearance has on the risk of death and emphasizes the need for a treatment like maribavir for patients who have R/R CMV. This also supports Takeda's original approach to modelling mortality by health state. 	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 3: Kaplan Meier plot of OS by clearance status at week 8 and transplant type  Furthermore, since technical engagement, the CSR for the 12-month extension study (TAK620-5004) has been made available.[5] TAK620-5004 was a retrospective study to collect follow-up data at 12 months among transplant recipients randomised to the maribavir arm in the SOLSTICE study. The study population for the final analysis consisted of [redacted] patients including [redacted] ([redacted]%) SOT and [redacted] ([redacted]%) HSCT patients. The primary objective was to measure all-cause mortality at 12 months and median overall survival, for the overall population and for HSCT and SOT cohorts, separately. Results demonstrate that the observed overall mortality was numerically lower than published estimates at 12 months following treatment initiation for R/R CMV post-transplant (Figure 4) Overall mortality was [redacted] % at 12 months in the 12-month maribavir extension study. Two published articles report mortality of 31% and 50% after initiation of treatment for CMV in small samples of HSCT and SOT recipients.[6, 7]	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
Figure 4: 1-year mortality estimates and confidence intervals for maribavir and historical published data including HSCT and SOT populations treated for R/R CMV

The mortality trended in the expected direction for both SOT and HSCT, with lower mortality in SOT than HSCT ([redacted]% vs [redacted]%). The one year mortality by transplant in the chart review sample was generally lower than published estimates and real-world (RW) cohort studies (OTUS) in treated resistant/refractory populations reporting mortality by transplant type (Table 1)

Table 1: mortality outcomes by transplant type
<table>
<tr><th>Study</th><th>SOT mortality</th><th>HSCT mortality</th></tr>
<tr><td>TAK620-5004[5]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Avery 2016[6]</td><td>9% (2/22)</td><td>59% (10/17)</td></tr>
<tr><td>Mehta 2020[7]</td><td>37.5% (3/8)</td><td>75% (3/4)</td></tr>
<tr><td>Fisher 2017[8]</td><td>16.2% (6/37)</td><td>n/a</td></tr>
<tr><td>Karantoni 2022[9]</td><td>n/a</td><td>33.3% (~15/46)</td></tr>
<tr><td>OTUS (Takeda study)</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Based on the above, we have maintained a mortality benefit for maribavir in the stage 1 Markov as maintaining the same risk for maribavir and IAT would be in direct contradiction to the evidence base and the ERG's suggested approach.

Given that we have aligned to the ERG's preferred approach of applying published mortality rates to inform
</td><td></td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			stage 1 mortality and all other aspects we have conceded to the Committee's conservative approaches, Takeda hope that the revised analyses demonstrating cost-effectiveness will aid the acceptance of maribavir for access to patients as soon as possible given the clearly outlined need for this treatment as voiced by the patient and clinical communities at the first appraisal committee meeting and also demonstrated in the evidence base.	
21	Consultee (company)	Takeda UK Ltd	**The mean time since transplant should be used at model entry** Takeda acknowledge there is some uncertainty in whether medium or mean time since transplant should be used at model entry given the heterogeneous population. We agree with the Committee's preference to use mean time since transplant	Thank you for your comment. Section 3.11 of the FAD has been updated to reflect that the company used the mean time since transplant in the updated model. The committee concluded that the updated model was suitable for decision making.
22	Consultee (company)	Takeda UK Ltd	**The impact of disease complications should be included in the economic model** ***Graft versus host disease (GvHD)*** Although Takeda considers the link between CMV and GvHD to be uncertain without any supporting evidence that CMV causes GvHD, Takeda are willing to compromise on the inclusion of GvHD within the economic model. However, the analysis provided in the original model had not subsequently been amended to account for time since transplant. Therefore, Takeda have now amended the scenario using the same data sources as the previous scenario but now using the time frame of the published KM plot that aligns to the mean time since transplant from OTUS, and therefore more appropriately aligning to the economic model. The original analysis was based on baseline GvHD rates from Hahn *et al.* 2008[10], which provided probabilities of GvHD from the time of transplant. This estimated that 11% of patients suffered GvHD every 4 weeks since the time of transplant up to 100 days post-transplant. This also was based only on the earlier transplant data (1995-98) that was shown to have increased rates of GvHD compared to more recent data (1999-02). The estimated 4-week probability of GvHD was applied for the non-clinically significant CMV health state in the economic model. To estimate a probability for the clinically significant CMV health state, a hazard ratio of 2.18 reported in Cantoni *et al.* 2010[11] was applied. The updated scenario now estimates the probabilities based on the KM plot from Hahn *et al.* 2008[10] but now only from around the time of the mean time since transplant from OTUS of [redacted] for HSCT. At this time point, Hahn *et al.*2008[10] reports approximately 25% of patients having GvHD at day 40 (based on 1999-02 data), which increases to 30% at day 100, the latest follow-up point. Using these two time points we calculated a more reflective underlying rate of GvHD and subsequently calculated the 4-week probability of 3.2%. Note that given the diminishing rates of GvHD over the time period reported, this is still likely to overestimate the rates of GvHD in the model in the long term. For full transparency, the calculations used to derive the values are as follows: 4-week probability of GvHD (n-csCMV) = 1-EXP(LN((1-0.3)/(1-0.25))*(28/(100-40))) = 3.2%	Thank you for your comment. Section 3.12 of the FAD has been updated to reflect that the company's updated approach included leukaemia recurrence and graft failure and the committee concluded that the model was suitable for decision making. **Graft versus-host disease** Section 3.13 of the FAD has been updated to reflect the company's base case to include graft versus-host disease. The committee noted that although developing graft-versus-host disease had not been directly associated with CMV infection, population data suggests that there is a higher incidence of developing graft-versus-host disease in people who also have CMV. The committee was aware that the clearance

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			4-week probability of GvHD (csCMV) =1-EXP(1-0.032)^2.18 = 6.8% **Leukaemia Recurrence** Takeda considers the assumption that 47% of patients who received HSCT after having leukaemia would experience a recurrence of their underlying disease and subsequently die, to be implausible. This would result in a double counting of the mortality impact given that the mortality estimates used in the model incorporate death by all causes. However, in the interests of achieving expedited access to maribavir for patients at need, Takeda have incorporated this assumption into the revised analyses. **Graft failure** Graft failure was already appropriate captured within our base case analysis, so this is aligned to the Committee's preferred assumptions.	of CMV may not lead to a reduction in developing graft-versus-host disease in the future. The committee concluded that the approach the company took to modelling graft-versus-host disease by CMV status was likely to be reasonable although uncertainty exists meaning that the ERG's scenario was also plausible.
23	Consultee (company)	Takeda UK Ltd	**The model should include different intravenous administration costs for first and subsequent administrations** Takeda note the committee's preference that using first and subsequent IV administration costs are appropriate and have updated the base case to reflect this.	Thank you for your comment. Section 3.14 of the FAD has been updated to reflect that the company updated its base case, amending the administration cost to account for the reduced cost of subsequent attendance. The committee concluded that the company's approach was in line with its preferences.
24	Consultee (company)	Takeda UK Ltd	**The cost of hospitalisation for people with clinically significant CMV is likely to be higher than for people without clinically significant CMV** Takeda are pleased to observe the Committee decided that our approach was considered appropriate and that csCMV would be more costly to manage in hospital than ncsCMV. We have therefore maintained this in our updated base case.	Thank you for your comment. No action required.
25	Consultee (company)	Takeda UK Ltd	**Because of the uncertainty, an acceptable ICER is around £20,000 per QALY gained** Takeda recognise that despite the robust evidence base seen in the SOLSTICE trial for the benefit of maribavir there are elements of uncertainty that reflect the heterogenous and rare population that are refractory to CMV therapies. We have therefore updated our price and base case assumptions to provide an ICER of £19,908 per QALY gained which is below the threshold required from the committee. Below we present our revised analysis and new base case.	Thank you for your comment. The committee considered the company's most recent base-case results in its decision making. This is reported in section 3.18 of the FAD.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td>24</td><td>Consultee (company)</td><td>Takeda UK Ltd</td><td>
Revised analysis and base case
Takeda have provided a revised set of analyses taking on feedback from the committee as well as the ERG. The updated base case analyses are based on a revised patient access scheme discount of [redacted] from list price resulting in a new net cost of [redacted] per 56 x 200mg pack or [redacted] per 8-week treatment cycle.

As discussed throughout this document, we have made changes to our original base case to account for the committee's and ERG's concerns around uncertainty. A summary of the revisions is as follows:

1. Using OTUS as the baseline for the standard care arm and applying relative efficacy from SOLSTICE to derive the mairbavir clearance and recurrence probabilities
2. Applying mean time since transplant rather than median (from OTUS)
3. Limiting the duration of phase 1 of the model to 39.2 weeks despite evidence of CMV risks beyond this time frame
4. Applying treatment independent recurrence probabilities despite evidence of an effect
5. Including leukaemia recurrences despite the potential double counting for mortality
6. Including GvHD but with amended rates accounting for the mean time since transplant in OTUS
7. Amending the administration cost to account for the reduced cost of follow-up attendance;

Furthermore, since technical engagement Takeda noticed the comparator costs of foscarnet have been reduced in the BNF[12], and the price for cidofovir has been published at a price lower than that originally used in the Takeda model.[13] In the interests of full transparency Takeda have updated the economic model to reflect these most recent NHS costs.

Note that this base case aligns with the committee's preferred assumptions with the exception of one issue on which the company's base case aligns with the ERG's suggested approach of applying published relative mortality risks from Hakimi et al.[14] and Camargo et al.[15] to estimate risks for those with csCMV.

The results of the revised base case analysis are given in Table 2, with an ICER of £19,908 per QALY gained, demonstrating the maribavir is clearly a cost-effective use of NHS resource by being under the lower NICE willingness-to-pay threshold.

Table 2. Company's Revised Base Case Results
<table>
<tr><th></th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>Maribavir</td><td rowspan="2">[redacted]</td><td>4.97</td><td rowspan="2">£7,146</td><td rowspan="2">0.359</td><td rowspan="2">£19,908</td></tr>
<tr><td>IAT</td><td>4.61</td></tr>
</table>
A number of scenario analyses given in Table 3 showing the plausible potential that the true ICER is actually even lower than the conservative base case analysis that has been aligned to the Committee's preferred assumptions in the interests of achieving expedited access to maribavir for patients in need.
</td><td>Thank you for your comment. Please see response to comment 25.</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>

Table 3. Scenario Analysis Results

#	Scenario	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
0	*Base case*	*£7,146*	*0.359*	*£19,908*
1	Treatment independent recurrence	£5,745	0.411	£13,964
2	Remove GvHD	£7,198	0.350	£20,590
3	Remove leukaemia recurrence	£7,146	0.452	£15,809

The uncertainty in the various aspects of the model is clearly important to the decision-making process for this appraisal and therefore it is important to assess the impact of the uncertainty of all parameters through a probabilistic sensitivity analysis (PSA) as well as one-way sensitivity analyses (OWSAs).

The results of the PSA are given in Table 4, showing that the ICER actually decreases compared to the deterministic base case results, with an ICER of £16,942 per QALY gained. This demonstrates that the deterministic results are more than robust to the uncertainties with the data sources used and, therefore, Committee can be confident that this revised base case analysis represent a clearly cost-effective use of NHS resources for a small population of patients with a severe unmet need in current clinical practice.

Furthermore, the PSA scatterplot in Figure 5 and the cost-effectiveness acceptability curve (CEAC) in Figure 6 both show the high likelihood of cost-effectiveness even at low willingness-to-pay thresholds. The OWSA plot in Figure 7 show further that the results are robust to changes in the parameters in the revised base case analysis.

Table 4. Company's Revised Probabilistic Sensitivity Analysis Results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Maribavir	[redacted]	4.96	£6,621	0.391	£16,942
IAT	[redacted]	4.57			

Figure 5. Scatterplot showing 10,000 PSA samples on the cost-effectiveness plane

</td><td></td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 *Figure 6. Cost effectiveness Acceptability Curve*	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 *Figure 7. One-way Sensitivity Analyses* 	
26		Takeda UK Ltd	**Summary & References**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Takeda are willing to accept the intrinsic uncertainty within this submission and therefore have provided a base case with an ICER under the £20,000 / QALY willingness to pay threshold. We have aligned to all the Committee's preferences however we cannot accept zero benefit for mortality with maribavir. Additional data has been provided to demonstrate the link between maribavir treatment and mortality benefits and our approach aligns with the ERG's suggested approach. Based on this response (which builds on the evidence in the original company submission and during technical engagement) and a modified base case ICER that is well below the standard cost effectiveness threshold, Takeda requests that NICE adopt a positive final recommendation for maribavir for R/R CMV after transplant, a population with a clear unmet need. 1. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Summary of opinion. Livtencity (maribavir) EMA/CHMP/248091/2022. 2022; Available from: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-opinion-livtencity_en.pdf. 2. British Transplantation Society. UK GUIDELINE ON PREVENTION AND MANAGEMENT OF CYTOMEGALOVIRUS (CMV) INFECTION AND DISEASE FOLLOWING SOLID ORGAN TRANSPLANTATION. 2022; Available from: https://bts.org.uk/uk-guideline-on-prevention-and-management-of-cytomegalovirus-cmv-infection-and-disease-following-solid-organ-transplantation/. 3. Dobrer S, e.a., PRECISION MEDICINE IN TRANSPLANTATION: MAGNITUDE, DURATION, AND IMPACT OF CMV VIREMIA ON GRAFT AND MORTALITY OUTCOMES OP328, in 20th Biennial European Society for Organ Transplantation (ESOT) Congress, Milan, Italy, 29 August – 1 September 2021. 2021. 4. Green, M.L., et al., Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. Lancet Haematol, 2016. 3(3): p. e119-27. 5. International, T.P., CLINICAL STUDY REPORT Retrospective Study to Collect Follow-Up Data at 12 Months Among Transplant Recipients with Refractory or Resistant Cytomegalovirus Infections Randomized to the Maribavir Treatment Arm in the TAK620-303 Open-label Phase III Trial PROTOCOL NUMBER: TAK620-5004. 2022. 6. Avery, R.K., et al., Outcomes in Transplant Recipients Treated With Foscarnet for Ganciclovir-Resistant or Refractory Cytomegalovirus Infection. Transplantation, 2016. 100(10): p. e74-80. 7. Mehta, S.A., et al., Outpatient management of kidney transplant recipients with suspected COVID-19-Single-center experience during the New York City surge. Transpl Infect Dis, 2020. 22(6): p. e13383. 8. Fisher, C.E., et al., Risk Factors and Outcomes of Ganciclovir-Resistant Cytomegalovirus Infection in Solid Organ Transplant Recipients. Clin Infect Dis, 2017. 65(1): p. 57-63. 9. Karantoni, E., et al., Outcomes of Refractory Cytomegalovirus Infection in the First Year after Allogeneic Hematopoietic Cell Transplantation. Transplant Cell Ther, 2022. 28(7): p. 403.e1-403.e7. 10. 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. 11. 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. 12. British National Formulary, Foscarnet sodium. Foscavir 6g/250ml solution for infusion bottles. 2022. 13. British National Formulary. Cidofovir 375mg/5ml concentrate for solution for infusion vials. 2022; Available from: https://bnf.nice.org.uk/drugs/cidofovir/medicinal-forms/.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			14. 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). 15. 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.	

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
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**
Name of commentator person completing form:	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**The clinical need for maribavir with limited treatment options available** Takeda note that all conventional therapies are used off-label for the treatment of CMV post-transplant. Maribavir offers the first approved treatment for refractory (with or without resistance) CMV infection. Many of the conventional therapies are associated with adverse events (neutropenia and nephrotoxicity) that can lead to the development of viral resistance. Maribavir may reduce treatment burden as an oral therapy and reduce the hospitalisations required for IV therapies. We recognise that CMV infection and conventional strategies for management have negative impacts on both patient and caregiver quality of life, in terms of physical activity and mobility limitations, stress, mental fatigue & inability to work. For caregivers, there is an emotional burden and impact on daily life & work that we are unable to capture in the economic model.
2	**The conduct and design of SOLSTICE could bias the results** Takeda dispute that the SOLSTICE trial results are biased. Extensive sensitivity analysis has been provided throughout technical engagement that demonstrate the robustness of the data. Multiple sensitivity analyses of the primary endpoint demonstrate a consistent efficacy advantage over IAT, regardless of whether the study drug was prematurely discontinued, clearance occurred at any time during the treatment phase, or the IAT patients received alternative anti-CMV treatment. Takeda note that the SOLSTICE trial population was heterogenous, in both solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) patients. The trial design was deemed ethical and sufficient for this patient population, and both the EMA and FDA were consulted on the trial design. Furthermore, we highlight that CHMP opinion was granted on 15th September 2022 based on maribavir demonstrating statistically superior efficacy compared to conventional therapies for the primary endpoint, indicating the regulators confidence in the data package for maribavir.[1] The ERG thought that the rescue arm may introduce bias to some outcomes. The committee considered that 3 weeks of treatment may not be long enough to assess a lack of efficacy. Takeda would like to clarify that the rescue arm was only an option for IAT subjects who, despite a minimum of 3 weeks of therapy with IAT, met stringent and objective criteria for lack of improvement/worsening of CMV infection, namely: • ≥1 log10 increase in CMV DNA from baseline • <1 log10 decrease in CMV DNA from baseline with new, worsening, or no improvement in tissue-invasive disease; or • lack of viremia clearance and demonstrated intolerance to IAT with either >50% increase from baseline in serum creatinine, development of haemorrhagic cystitis, or development of neutropenia (absolute neutrophil count [ANC] <500/mm3). Therefore, the above criteria demonstrated no response within a set timeframe of three weeks, an endpoint that was agreed with the EMA and FDA during the design of the trial.

Please return to: **NICE DOCS**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Throughout the ratification of the NICE submission, Takeda spoke with numerous SOT and HSCT clinicians where it was confirmed that if after two weeks of therapy no reduction in viral load was seen, an alternative treatment plan would be considered. This is also aligned to BTS guidelines which states: *Based on knowledge of the viral kinetics with anti-CMV treatment, members agreed to recommend treatment for at least 14 days duration as this has been shown to be associated with a viraemia reduction of approximately 1.0 log10 (90%).*[2]
3	**Results of SOLSTICE may not be generalisable to clinical practice** Takeda note the Committee had some concerns about an imbalance in time since transplant between treatment arms. We would like to draw attention to the extensive regression analysis performed during technical engagement which demonstrated 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] and [redacted], respectively. This indicates that the odds of each outcome are almost unchanged by increasing the number of months since transplant, and it is the treatment effect of maribavir that is driving the efficacy. We are pleased to see the sensitivity analysis provided at technical engagement regarding patients in the IAT group having retreatment with anti-CMV therapies to which their infection was resistant has demonstrated the sustained benefit of maribavir, and that the clinical experts confirmed that continuing treatment in these circumstances is plausible when there are no better treatment options available. During technical engagement, extensive missing data analysis was provided to the technical team, and we confirmed that minimal missing data for recurrence was seen. Takeda note the ERG agreed missing data wasn't a significant issue for the ITT population. We agree that the missing data is greater in the IAT arm due to the presence of a rescue arm. Without the rescue arm, the trial would have not met the necessary ethical standards during the design phase.
4	**SOLSTICE data suggests that maribavir improves clearance compared with IAT, but the results are highly uncertain** Takeda note that regulators have agreed that data from the SOLSTICE trial demonstrates the efficacy of maribavir. CHMP opinion was granted on 15th September 2022 and FDA approval on 23 November 2021, based on maribavir demonstrating statistically superior efficacy compared to conventional therapies for the primary endpoint. Regulators agreed during the design of the trial that transplantation patient's level of CMV viremia is considered a validated surrogate endpoint that predicts mortality. Detailed sensitivity and supplemental analyses were prespecified to assess the robustness of the results in the CSR.
5	**Using OTUS data is more robust than using multiple data sources to model outcomes in the stage 1 Markov model** Takeda note the potential uncertainties arising due to the nature of incorporating two separate data sources to inform initial and subsequent episodes in the economic model. However, Takeda maintain that SOLSTICE provides the most reliable data source to estimate the treatment effect of maribavir compared to standard care and also, therefore, that the IAT arm of the SOLSTICE trial represents the most reliable source of data to inform the standard care arm for the initial R/R CMV episodes in which maribavir is being appraised. Despite this, Takeda are willing to acknowledge the Committee's concerns and incorporate this within our revised analyses with the aim of achieving expedited access for patients. Within our revised analyses we have also amended the mortality adjustment that was initially applied to the clearance estimates. This was incorrectly applied previously, and we have now aligned with the Committee's preferred approach.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

6	**Maribavir may increase the likelihood of maintaining CMV clearance, but there is no evidence to support this** Takeda note that the NICE clinical expert agreed with the company approach during the first appraisal committee meeting. We also highlight that in SOLSTICE the durability of the effect of maribavir was demonstrated, the proportion of responders that achieved CMV viremia clearance and CMV infection symptom control at Week 8 and maintained the effect through Weeks 12, 16, and 20 off-treatment was approximately 2-fold higher for maribavir-treated patients than for the IAT group, regardless of the duration of follow-up. However, in the absence of direct supporting evidence within the SOLTSTICE data for patients treated with maribavir having a lower probability of CMV recurrence than patients treated with IAT, Takeda are willing to accept the Committee's preference.
7	**The number of CMV recurrences is overestimated in the model** Takeda would like to comment that evidence for multiple recurrences has been demonstrated in the OTUS data and was provided to the ERG during technical engagement. The limited number of patients experiencing multiple recurrences reflects the small population of patients who are refractory or resistance to prior anti-CMV therapies. We consider the ERG approach of limiting the number of recurrences in the model is very conservative and merely removes uncertain benefit rather than considers the uncertainty surrounding that benefit in the context of a very rare condition with an important unmet need. Despite this, Takeda are keen for maribavir to be made available to patients as soon as possible and are willing to amend the revised analysis to the conservative scenario where recurrences can only occur up to week 39 as per the ERG's preferred analysis. Importantly, this aspect of the revised economic analyses now aligns with the Committee's preferred assumption and therefore any further modelling to assess the uncertainty surrounding the longer-term recurrence rates beyond week 39 is no longer relevant. This therefore fully addresses the Committee's preferences.
8	**The duration of the stage 1 Markov model should align with the duration that CMV recurrences can be accurately modelled** Takeda believe the OTUS data is a robust source for modelling recurrences over time. Although the evidence for greater than two recurrences can be observed in the OTUS data, we recognise the number of patients with >2 recurrences diminish over time and is reflective of this population. As there is robust data in OTUS that demonstrate the first and second recurrence occur by 39.2 weeks, we are willing to accept the Committee's preference to limit stage 1 of the Markov model to this length.
9	**Risk of mortality in the stage 1 Markov model should be the same for people having maribavir and IAT** Takeda have aligned the stage 1 mortality in the economic model with the ERG's suggested methodology and therefore the revised results provided in this response document are fully aligned with the ERG's preferred approach. Takeda believe the committee's position to assume that there should be no life year gain in the model is in contradiction not only to the alignment of Takeda and the ERG but also of the published evidence base. Furthermore, it has been acknowledged by clinicians advising both Takeda and the ERG that there is a clear association between CMV and the risk of mortality, and two recent large-scale studies have further substantiated the association between CMV viraemia and mortality.[3, 4]

Please return to: **NICE DOCS**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

The remainder of this section outlines the key evidence demonstrating this mortality association (including an update from the 12-month extension to SOLSTICE) as well as addressing some corrections to the IPD analysis report highlighted previously by the ERG.

In response to the points made by the ERG (Section 2.5, page 14 of the *ERG's review of the company's response to the ERG TE critique*, August 2022) in relation to the cross-over adjusted mortality analyses, Takeda would like to clarify some errors in figure headings that caused misleading conclusions by the ERG.

The adjusted KM plot for mortality that the ERG refers to was incorrectly labelled as "adjusted for treatment switch by RPSFTM method". This plot in fact represents *treatment-free* transformed survival i.e., removing the treatment effect (estimated using e.g., the RPSFTM adjustment) and thus compares two groups of patients who are hypothetically untreated with maribavir. This plot should not be interpreted as a lack of treatment effect for maribavir compared to IAT following adjustment.

The adjusted KM plots for each method accounting for cross-over are all indistinguishable given the similarity in the estimated HRs. The KM plot given in Figure 1 therefore provides a representation of the impact of adjusting for cross-over for all adjustment methods.

Figure 1. Kaplan-Meier showing cross-over adjusted survival from SOLSTICE

An additional typographical error highlighted by the ERG was in the tabulated results. To clarify, Table B4 (and B5) of the IPD analysis report had incorrect labels that should have stated *"Time to all-cause mortality prior to initiation of alternative anti-CMV treatment use by treatment arm adjusted for treatment switch by RPSFTM method"*. Previously, Table B4 and B5 had the same

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

headings as Table B1 and B2, respectively. The hazard ratio presented previously in Table B1 was correctly reported for the RPSFTM and this is the relevant result to compare to the primary analysis that used the inverse probability of censoring weights (IPCW) method.

The conclusions of these analyses showed that the results of the two methods were similar with hazard ratios of [redacted] and [redacted] for the IPCW and RPSFTM methods, respectively. For the IPE method, the hazard ratio showed a slightly greater adjusted treatment effect of [redacted]. These analyses show increasing evidence of an effect being demonstrated even within the short follow-up period of the SOLSTICE trial, which was not powered to detect a significant effect for mortality. A corrected version of the IPD report will be supplied alongside this response document for full clarity of the corrections.

In addition to this, SOLSTICE provides clear evidence of a difference in survival associated with response to CMV treatment, as shown in the KM plot in Figure 2. This plot shows a statically significant difference in the hazard rate of death between those who achieved clearance at week 8 (in either treatment group) compared to those who failed to achieve clearance.

Figure 2: Kaplan Meier plot of OS by clearance status at week 8

As there are important differences in the mortality rate of the two transplant types, (SOT and HSCT), it is also important to assess the survival of the two subgroups separately. Figure 3 shows KM plots for survival form SOLSTICE split by clearance status at week 8 as well as transplant type. This also clearly demonstrates the impact that achieving clearance has on the risk of death and emphasizes the need for a treatment like maribavir for patients who have R/R CMV. This also supports Takeda's original approach to modelling mortality by health state.

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

Figure 3: Kaplan Meier plot of OS by clearance status at week 8 and transplant type

Furthermore, since technical engagement, the CSR for the 12-month extension study (TAK620-5004) has been made available.[5] TAK620-5004 was a retrospective study to collect follow-up data at 12 months among transplant recipients randomised to the maribavir arm in the SOLSTICE study. The study population for the final analysis consisted of [redacted] patients including [redacted] ([redacted]%) SOT and [redacted] ([redacted]%) HSCT patients. The primary objective was to measure all-cause mortality at 12 months and median overall survival, for the overall population and for HSCT and SOT cohorts, separately.

Results demonstrate that the observed overall mortality was numerically lower than published estimates at 12 months following treatment initiation for R/R CMV post-transplant (Figure 4) Overall mortality was [redacted] % at 12 months in the 12-month maribavir extension study. Two published articles report mortality of 31% and 50% after initiation of treatment for CMV in small samples of HSCT and SOT recipients.[6, 7]

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

Figure 4: 1-year mortality estimates and confidence intervals for maribavir and historical published data including HSCT and SOT populations treated for R/R CMV

The mortality trended in the expected direction for both SOT and HSCT, with lower mortality in SOT than HSCT ([redacted]% vs [redacted]%). The one year mortality by transplant in the chart review sample was generally lower than published estimates and real-world (RW) cohort studies (OTUS) in treated resistant/refractory populations reporting mortality by transplant type (Table 1)

Table 1: mortality outcomes by transplant type

Study	SOT mortality	HSCT mortality
TAK620-5004[5]	[redacted]	[redacted]
Avery 2016[6]	9% (2/22)	59% (10/17)
Mehta 2020[7]	37.5% (3/8)	75% (3/4)
Fisher 2017[8]	16.2% (6/37)	n/a
Karantoni 2022[9]	n/a	33.3% (~15/46)
OTUS (Takeda study)	[redacted]	[redacted]

Based on the above, we have maintained a mortality benefit for maribavir in the stage 1 Markov as maintaining the same risk for maribavir and IAT would be in direct contradiction to the evidence base and the ERG's suggested approach.

Given that we have aligned to the ERG's preferred approach of applying published mortality rates to inform stage 1 mortality and all other aspects we have conceded to the Committee's conservative approaches, Takeda hope that the revised analyses demonstrating cost-effectiveness will aid the acceptance of maribavir for access to patients as soon as possible given the clearly outlined need for this treatment as voiced by the patient and clinical communities at the first appraisal committee meeting and also demonstrated in the evidence base.

10 **The mean time since transplant should be used at model entry**

Takeda acknowledge there is some uncertainty in whether medium or mean time since transplant should be used at model entry given the heterogeneous population. We agree with the Committee's preference to use mean time since transplant

11 **The impact of disease complications should be included in the economic model**

Graft versus host disease (GvHD)

Although Takeda considers the link between CMV and GvHD to be uncertain without any supporting evidence that CMV causes GvHD, Takeda are willing to compromise on the inclusion of

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	GvHD within the economic model. However, the analysis provided in the original model had not subsequently been amended to account for time since transplant. Therefore, Takeda have now amended the scenario using the same data sources as the previous scenario but now using the time frame of the published KM plot that aligns to the mean time since transplant from OTUS, and therefore more appropriately aligning to the economic model. The original analysis was based on baseline GvHD rates from Hahn *et al.* 2008[10], which provided probabilities of GvHD from the time of transplant. This estimated that 11% of patients suffered GvHD every 4 weeks since the time of transplant up to 100 days post-transplant. This also was based only on the earlier transplant data (1995-98) that was shown to have increased rates of GvHD compared to more recent data (1999-02). The estimated 4-week probability of GvHD was applied for the non-clinically significant CMV health state in the economic model. To estimate a probability for the clinically significant CMV health state, a hazard ratio of 2.18 reported in Cantoni *et al.* 2010[11] was applied. The updated scenario now estimates the probabilities based on the KM plot from Hahn *et al.* 2008[10] but now only from around the time of the mean time since transplant from OTUS of [redacted] for HSCT. At this time point, Hahn *et al.*2008[10] reports approximately 25% of patients having GvHD at day 40 (based on 1999-02 data), which increases to 30% at day 100, the latest follow-up point. Using these two time points we calculated a more reflective underlying rate of GvHD and subsequently calculated the 4-week probability of 3.2%. Note that given the diminishing rates of GvHD over the time period reported, this is still likely to overestimate the rates of GvHD in the model in the long term. For full transparency, the calculations used to derive the values are as follows: 4-week probability of GvHD (n-csCMV) = 1-EXP(LN((1-0.3)/(1-0.25))*(28/(100-40))) = 3.2% 4-week probability of GvHD (csCMV) =1-EXP(1-0.032)^2.18 = 6.8% **Leukaemia Recurrence** Takeda considers the assumption that 47% of patients who received HSCT after having leukaemia would experience a recurrence of their underlying disease and subsequently die, to be implausible. This would result in a double counting of the mortality impact given that the mortality estimates used in the model incorporate death by all causes. However, in the interests of achieving expedited access to maribavir for patients at need, Takeda have incorporated this assumption into the revised analyses. **Graft failure** Graft failure was already appropriate captured within our base case analysis, so this is aligned to the Committee's preferred assumptions.
12	**The model should include different intravenous administration costs for first and subsequent administrations** Takeda note the committee's preference that using first and subsequent IV administration costs are appropriate and have updated the base case to reflect this.
13	**The cost of hospitalisation for people with clinically significant CMV is likely to be higher than for people without clinically significant CMV** Takeda are pleased to observe the Committee decided that our approach was considered appropriate and that csCMV would be more costly to manage in hospital than ncsCMV. We have therefore maintained this in our updated base case.

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

14 **Because of the uncertainty, an acceptable ICER is around £20,000 per QALY gained**

Takeda recognise that despite the robust evidence base seen in the SOLSTICE trial for the benefit of maribavir there are elements of uncertainty that reflect the heterogenous and rare population that are refractory to CMV therapies. We have therefore updated our price and base case assumptions to provide an ICER of £19,908 per QALY gained which is below the threshold required from the committee. Below we present our revised analysis and new base case.

15 **Revised analysis and base case**

Takeda have provided a revised set of analyses taking on feedback from the committee as well as the ERG. The updated base case analyses are based on a revised patient access scheme discount of [redacted] from list price resulting in a new net cost of [redacted] per 56 x 200mg pack or [redacted] per 8-week treatment cycle.

As discussed throughout this document, we have made changes to our original base case to account for the committee's and ERG's concerns around uncertainty. A summary of the revisions is as follows:

1. Using OTUS as the baseline for the standard care arm and applying relative efficacy from SOLSTICE to derive the mairbavir clearance and recurrence probabilities
2. Applying mean time since transplant rather than median (from OTUS)
3. Limiting the duration of phase 1 of the model to 39.2 weeks despite evidence of CMV risks beyond this time frame
4. Applying treatment independent recurrence probabilities despite evidence of an effect
5. Including leukaemia recurrences despite the potential double counting for mortality
6. Including GvHD but with amended rates accounting for the mean time since transplant in OTUS
7. Amending the administration cost to account for the reduced cost of follow-up attendance;

Furthermore, since technical engagement Takeda noticed the comparator costs of foscarnet have been reduced in the BNF[12], and the price for cidofovir has been published at a price lower than that originally used in the Takeda model.[13] In the interests of full transparency Takeda have updated the economic model to reflect these most recent NHS costs.

Note that this base case aligns with the committee's preferred assumptions with the exception of one issue on which the company's base case aligns with the ERG's suggested approach of applying published relative mortality risks from Hakimi *et al.*[14] and Camargo *et al.*[15] to estimate risks for those with csCMV.

The results of the revised base case analysis are given in Table 2, with an ICER of £19,908 per QALY gained, demonstrating the maribavir is clearly a cost-effective use of NHS resource by being under the lower NICE willingness-to-pay threshold.

Table 2. Company's Revised Base Case Results

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER incremental (£/QALY)**
Maribavir	[redacted]	4.97	£7,146	0.359	£19,908

Please return to: **NICE DOCS**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

IAT	[redacted]	4.61			

A number of scenario analyses given in Table 3 showing the plausible potential that the true ICER is actually even lower than the conservative base case analysis that has been aligned to the Committee's preferred assumptions in the interests of achieving expedited access to maribavir for patients in need.

Table 3. Scenario Analysis Results

#	Scenario	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
0	*Base case*	*£7,146*	*0.359*	*£19,908*
1	Treatment independent recurrence	£5,745	0.411	£13,964
2	Remove GvHD	£7,198	0.350	£20,590
3	Remove leukaemia recurrence	£7,146	0.452	£15,809

The uncertainty in the various aspects of the model is clearly important to the decision-making process for this appraisal and therefore it is important to assess the impact of the uncertainty of all parameters through a probabilistic sensitivity analysis (PSA) as well as one-way sensitivity analyses (OWSAs).

The results of the PSA are given in Table 4, showing that the ICER actually decreases compared to the deterministic base case results, with an ICER of £16,942 per QALY gained. This demonstrates that the deterministic results are more than robust to the uncertainties with the data sources used and, therefore, Committee can be confident that this revised base case analysis represent a clearly cost-effective use of NHS resources for a small population of patients with a severe unmet need in current clinical practice.

Furthermore, the PSA scatterplot in Figure 5 and the cost-effectiveness acceptability curve (CEAC) in Figure 6 both show the high likelihood of cost-effectiveness even at low willingness-to-pay thresholds. The OWSA plot in Figure 7 show further that the results are robust to changes in the parameters in the revised base case analysis.

Table 4. Company's Revised Probabilistic Sensitivity Analysis Results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Maribavir	[redacted]	4.96	£6,621	0.391	£16,942
IAT		4.57			

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

Figure 5. Scatterplot showing 10,000 PSA samples on the cost-effectiveness plane

Figure 6. Cost effectiveness Acceptability Curve

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Figure 7. One-way Sensitivity Analyses 
16	**Summary & References** Takeda are willing to accept the intrinsic uncertainty within this submission and therefore have provided a base case with an ICER under the £20,000 / QALY willingness to pay threshold. We have aligned to all the Committee's preferences however we cannot accept zero benefit for mortality with maribavir. Additional data has been provided to demonstrate the link between maribavir treatment and mortality benefits and our approach aligns with the ERG's suggested approach. Based on this response (which builds on the evidence in the original company submission and during technical engagement) and a modified base case ICER that is well below the standard cost effectiveness threshold, Takeda requests that NICE adopt a positive final recommendation for maribavir for R/R CMV after transplant, a population with a clear unmet need. 1. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Summary of opinion. Livtencity (maribavir) EMA/CHMP/248091/2022. 2022; Available from: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-opinion-livtencity_en.pdf. 2. British Transplantation Society. UK GUIDELINE ON PREVENTION AND MANAGEMENT OF CYTOMEGALOVIRUS (CMV) INFECTION AND DISEASE FOLLOWING SOLID ORGAN TRANSPLANTATION. 2022; Available from: https://bts.org.uk/uk-guideline-on-prevention-and-management-of-cytomegalovirus-cmv-infection-and-disease-following-solid-organ-transplantation/. 3. Dobrer S, e.a., PRECISION MEDICINE IN TRANSPLANTATION: MAGNITUDE, DURATION, AND IMPACT OF CMV VIREMIA ON GRAFT AND MORTALITY OUTCOMES OP328, in 20th Biennial European Society for Organ Transplantation (ESOT) Congress, Milan, Italy, 29 August – 1 September 2021. 2021. 4. Green, M.L., et al., Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. Lancet Haematol, 2016. 3(3): p. e119-27. 5. International, T.P., CLINICAL STUDY REPORT Retrospective Study to Collect Follow-Up Data at 12 Months Among Transplant Recipients with Refractory or Resistant Cytomegalovirus Infections Randomized to the Maribavir Treatment Arm in the TAK620-303 Open-label Phase III Trial PROTOCOL NUMBER: TAK620-5004. 2022. 6. Avery, R.K., et al., Outcomes in Transplant Recipients Treated With Foscarnet for Ganciclovir-Resistant or Refractory Cytomegalovirus Infection. Transplantation, 2016. 100(10): p. e74-80. 7. Mehta, S.A., et al., Outpatient management of kidney transplant recipients with suspected COVID-19-Single-center experience during the New York City surge. Transpl Infect Dis, 2020. 22(6): p. e13383. 8. Fisher, C.E., et al., Risk Factors and Outcomes of Ganciclovir-Resistant Cytomegalovirus Infection in Solid Organ Transplant Recipients. Clin Infect Dis, 2017. 65(1): p. 57-63. 9. Karantoni, E., et al., Outcomes of Refractory Cytomegalovirus Infection in the First Year after Allogeneic Hematopoietic Cell Transplantation. Transplant Cell Ther, 2022. 28(7): p. 403.e1-403.e7. 10. 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.

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	11. 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. 12. British National Formulary, Foscarnet sodium. Foscavir 6g/250ml solution for infusion bottles. 2022. 13. British National Formulary. Cidofovir 375mg/5ml concentrate for solution for infusion vials. 2022; Available from: https://bnf.nice.org.uk/drugs/cidofovir/medicinal-forms/. 14. 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). 15. 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.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

Please return to: **NICE DOCS**

Addendum following the ERG's review of the company's response to the ACD

31st October 2022

1. Clearance data from OTUS HSCT.

The clinical study reports for both OTUS SOT and OTUS HSCT have now been finalised and they are attached alongside this document.

The clearance estimates including both SOT and HSCT have now be re-estimated and the impact on the cost-effectiveness results when applied in the model is minimal.

Firstly, it should be clarified that previous estimates based on only the SOT data were incorrectly reported. We previously stated that there were [redacted] clearance events 8 weeks after treatment initiation in the [redacted] patients with an index CMV episode. However, the [redacted] events were actually based on all [redacted] CMV episodes and not just the [redacted] index episodes. Therefore, the estimate of clearance for the SOT population should have been [redacted] out of [redacted] or approximately [redacted]. See page 49 of the OTUS SOT CSR for the reporting of these values.

For the HSCT population, the OTUS study reports [redacted] clearances at 8 weeks after treatment initiation from a total of [redacted] CMV episodes. This results in a clearance estimate for the HSCT population alone of [redacted]. See page 52 of the OTUS HSCT CSR for the reporting of these values.

Combining these data and weighting them according to the distribution of transplant types in the economic model (i.e. 59.9% SOT, 40.1% HSCT), gives an estimate of [redacted] for the OTUS standard care clearance estimate at week 8. When applying this in the model, the company's base case results have a very minor change with an ICER of £19,770 per QALY.

2. Mortality for stage 1.

Follow-up period for parameter estimates

In terms of the time period over which the OTUS mortality risks in the model are estimated, the ERG has incorrectly determined that data were only used up to week 20. Kaplan-Meier estimates from OTUS SOT and HSCT provided probabilities of death at day 56 (week 8), 140 (week 20) and 365 (week 52). Each of these time points were used to estimate the risk of mortality at relevant time points in the model i.e., for the week 8 to 20 parameter in the model, the rate is estimated based on the deaths that occurred between day 56, and day 140; and for the parameter in the model informing the risk of death after 20 weeks, the rate was based on the deaths that occurred between day 140 and day 365. The model, therefore, appropriately accounts for the changing risk of mortality between week 20 and week 39 in the model.

CMV event inclusion for n-csCMV

The mortality data from OTUS used to estimate the risks for the n-csCMV health state are based on all-cause mortality data given that health-state specific data were not pre-specified for the OTUS study, and therefore were not available when the CSRs were recently finalised.

These data will therefore theoretically include mortality events that occurred in patients with CMV and thus is likely to overestimate the baseline risk of mortality. However, the ERG's scenario

analyses did not address this issue as they varied the *relative* risk of mortality between health states and not the *baseline* absolute risk for the n-csCMV health state on which the relative risk was applied to estimate the csCMV risk.

The ERG stated that the relationship between CMV and mortality as reported in the published literature was robust and therefore their scenario that applied an arbitrary alternative value is not meaningful. The relative risk is the key driver of mortality, and this estimate is robust. The baseline risk estimate can never be perfectly attributed to n-csCMV given the cyclical nature of CMV; however, this is likely to be a minor issue with baseline risk estimates already very low and the key driver therefore being the relative risk.

3. GvHD

The approach of applying equivalent GvHD risks by health state results in the maribavir group having a greater incidence of GvHD due to a small overall survival benefit. However, there is no clinical rationale for a maribavir-treated population to have a greater incidence of GvHD in comparison to standard of care. There is some evidence to suggest the plausibility of it potentially reducing the risk of GvHD through the improved chance of achieving clearance, however, we acknowledge the uncertainty of causality.

GvHD should, therefore, either be modelled as a potential benefit for maribavir or conservatively excluded from the model to remove any benefit. A detrimental effect for the maribavir group is clinically implausible, has no evidence to support and should not be modelled as such.

Furthermore, considering a potential greater risk of mortality on top of that already accounted for in the model would compound this issue and would introduce double counting as mortality for all causes has already been factored into the model.

A final overarching point regarding the uncertainties around GvHD is that due to the introduction of letermovir for prophylaxis, we expect the HSCT R/R population to be very limited. We now estimate the expected annual uptake for maribavir to include approximately [redacted] patients following HSCT and [redacted] patients following SOT. Therefore, the population is likely to be weighted much more towards the SOT population with only around [redacted] of patients in the post-HSCT population, and thus, the true ICER for the population as a whole is much closer to that for the SOT population.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Anthony Nolan
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the significant benefit that this treatment could provide to the quality of life of patients has not been adequately accounted for. Patients who have experienced refractory or resistant cytomegalovirus (CMV) infection post-stem cell transplant reported a range of significant challenges as a result of their CMV infection or re-activation. This includes the treatment of CMV, which had a significant physical and psychological impact on many patients. One described the treatment as physically the '*most difficult part of their entire treatment journey*' while others described fearing they would '*never get their lives back',* referring to constant hospital visits and time spent as an inpatient. It was also reported that some had to quit their job, as a result of the significant amount of time they were forced to take off as a result of their CMV treatment and recovery.
2	We are concerned that this recommendation does not fully consider the lack of alternative treatment options for some patients with a refractory or resistant cytomeglovirus infection after a transplant. Although the availability of letermovir prophylaxis has benefited patients, those with breakthrough infections that do not respond to gangciclovir, valganciclovir, foscarnet, and cidofovir often have poor outcomes.
3	We are concerned at the lack of emphasis placed on maribavir having lower toxicity than some other CMV treatments. Both cytomegalovirus infection and treatments, including gangciclovir and valganciclovir, are marrow toxic and can cause cytopenia and neutropenia. The existing toxicity of current treatment such as these can have a direct impact on bone marrow engraftment and may also increase other autoimmune issues including graft versus host disease, a common side effect of a stem cell transplant which can lead to poor recovery and quality of life in both the long and short term.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright

Please return to: **NICE DOCS**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Transplantation Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Thank you for including the British Transplantation Society (BTS) as a consultee in this appraisal. Our expertise and comments relate to the use of Maribavir in patients with a solid organ transplant (SOT), although some are also applicable to patients receiving haematologic stem cell transplants (HSCT). The BTS is surprised that Maribavir has not been recommended for use in patients with resistant or refractory CMV – a group of patients for whom current therapy (Foscarnet or Cidofovir) is poorly effective and toxic. We note that: • Maribavir is approved for this indication in the USA (FDA – November 2021). • In the context of the current NHS – when both in-patient beds and staffing are exceptionally challenged – an effective oral agent such as Maribavir is clearly preferable to treatments that require both hospitalization and intravenous administration. Foscarnet and Cidofovir require both – often for several weeks. Whilst the ERG attempts to address this point in economic models, this approach fails to capture the very real pressures on NHS facilities faced by clinicians every day. We note that the ERG refers to the BTS Guidelines on prevention and management of CMV after solid organ transplantation (2015). These guidelines are out of date and contain recommendations no longer applicable to clinic practice. The updated guidelines (2022) are available on the BTS website: UK GUIDELINE ON PREVENTION AND MANAGEMENT OF CYTOMEGALOVIRUS (CMV) INFECTION AND DISEASE FOLLOWING SOLID ORGAN TRANSPLANTATION - British Transplantation Society (bts.org.uk)

2	**Section 3.2 – The conduct and design of the SOLSTICE trial could bias the results**. This may be so, but we do not believe it would be possible to a conduct such a trial without the potential biases raised by the ERG and Committee.
	
	• SOLSTICE is an open label trial. This may not be perfect, but there is no way of blinding clinicians or patients to the treatment received. Maribavir is oral and the alternatives (Ganciclovir, Foscarnet or Cidofovir) are all administered intravenously in very different fluid volumes, and at different frequencies. The alternative of a very complex trial design (which would require patients assigned to Maribavir to be admitted to hospital and receive multiple placebo IV infusions) is not practically possible:
	
	  ○ It is very unlikely any ethics committee would consider such a design acceptable given the very invasive nature of the placebo treatment.
	
	  ○ The very distinctive adverse effects of each medication and required monitoring would effectively un-blind most recipients to their clinicians.

Please return to: **NICE DOCS**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	• Treatment in the IAT group. The ERG and Committee are concerned that investigators could choose which alternative treatment to use. But this choice is based on patient characteristics and local expertise. Whilst Foscarnet is likely the most frequent second line treatment in the UK, Cidofovir is used in other countries- the SOLSTICE trial was conducted in more than 100 centres in 12 countries. If anything, allowing investigators to select which alternative treatment to use biases the trail towards the IAT group, since investigators are likely to select a treatment they consider most likely to be effective. • The ERG and Committee are concerned that the investigators were able to modify immunosuppression. However, this is an essential component in managing patients with refractory / resistant CMV, and is necessarily determined by the clinical circumstances of each patient. So for Ganciclovir / Valganciclovir treated patients, the most common intervention would be to reduce or withdraw mycophenolic acid- based medications (MPA). In contrast, both Foscarnet and Cidofovir are nephrotoxic, and some clinicians would aim to reduce calcineurin inhibitors (CNI). Any changes to immunosuppression would have to be considered with regard to recent rejection episodes and rejection risk. Accordingly mandating changes to immunosuppression would not be possible in a trial protocol. • The ERG and Committee are concerned that patients in the IAT group not responding to treatment at 3 weeks could be switched to Maribavir. We accept that such a study design leads to difficulty in performing the detailed analyses required by NICE. Never the less, the ERG and Committee have accepted that current treatments for refractory / resistant CMV are poorly effective and poorly tolerated (section 3.1), so allowing patients to switch from demonstrably ineffective interventions would seem entirely justified.
3	**Section 3.3 – Results of SOLSTICE may not be generalizable to clinical practice**. We disagree with this statement. In fact the SOT patient population included in the trial very much reflects current clinical practice. • We have discussed points related to immunosuppression and choice of treatment in the IAT arm above. • We note the comment ‘the mean and median time since transplant at randomization were longer than would be expected in clinical practice for the SOT subgroup …’ However nowhere in the SOLSTICE study or supplementary information is there any data on time since transplant. This issue was raised in several Priority Questions – A2, A4, B7, B8 and more. The company confirmed that the time since transplant was not collected in SOLSTICE. However, page 41 of the ERG report includes the statement ’the mean time since transplant was around [redacted] months for SOT patients’. It would be helpful to know what data ‘one of the clinical experts’ is referring to? • In any case, the time for transplant to (a) first CMV viraemia and (b) resistant / refractory CMV is inherently very variable in clinical practice. The key determinant is the use of CMV prophylaxis – usually valganciclovir. Whilst >80% of the patients were high risk CMV D+ / R- transplants, only 40% of patients received any prophylaxis. In those that

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	did receive prophylaxis, the duration is not specified but is likely to be either 100 days or 200 days. Accordingly CMV diagnoses will be distributed over the first post-transplant year – this is exactly the reality of clinical practice. • We accept the challenges with regard to the timing of CMV diagnoses and the economic modelling raised by the ERG. • The ERG and Committee observe that some patients in the IAT group were assigned treatments to which they have resistance. Again, this is the current clinical reality. There are two common forms of resistance: o Mutations in the UL97 gene – which confer Ganciclovir resistance. These patients are usually treated with Foscarnet / Cidofovir. o Mutations in the UL54 gene - which confer resistance to all three medications. • These resistance mutations are determined by genetic polymorphisms of the relevant genes (or which there are many), and resistance is not absolute – so for example some patients with UL97 mutations who do not respond to oral Valganciclovir may respond to IV Ganciclovir. In he case of UL54 mutations, there is no alternative treatment (aside from Maribavir).
4	**Section 3.4 – SOLSTICE data suggests that Maribavir improved clearance compared with IAT, but the results are highly uncertain.** We strongly disagree with this conclusion. The Committee points to the uncertainties discussed in Sections 3.2 and 3.3. But we argue that these uncertainties represent the reality of clinical practice, and that the highly significant advantage of Maribavir over alternative therapies has been demonstrated in a patient group comparable to those managed in transplant units around the UK.
5	**Sections 3.5 onwards – The Company's economic model.** We are not able to comment on detail of the economic modelling – either of the Company or ERG, but would welcome the opportunity to address any clinical uncertainties involved in these models.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Renal Pharmacy Group
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Name of commentator person completing form:	[redacted]

Comment number	Comments

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this recommendation does not meet the clinical needs of patients with renal dysfunction, including solid organ kidney and kidney-pancreas transplant recipients. Whilst accepting that refractory or resistant CMV infection has a low incidence in this cohort, maribavir does offer a significant treatment option for the following reasons:- a) For renal transplant patients or immunocompromised patients with renal dysfunction foscarnet, as referenced in section 3.1 is nephrotoxic. However the significance of this in clinical practice needs further consideration. When foscarnet is used it can either lead to significant graft dysfunction/loss (this can render a patient in need of renal replacement therapy – haemofiltration or haemodialysis at significant cost to NHS). Transplant function may not recover and long term renal replacement therapy will then be necessary. Or the patient may endure significant side effects due to poor drug clearance which may render a patient with life changing, disabling effects e.g peripheral neuropathy leaving patient unable to walk, physically unable to use their arm(s) to lift any weight, sensory impairment to hot/cold. To improve foscarnet tolerability it needs to be given with increased fluid which for patients with significant renal dysfunction and fluid restriction, this can be further challenging. In clinical practice foscarnet is very poorly tolerated in this cohort. Maribavir, after foscarnet treatment failure or early cessation is therefore the only viable alternative treatment option as cidofovir for many renal patients is contra-indicated (see b) b) Furthermore cidofovir, referenced as causing neutropenia in section 3.1, is in fact contraindicated in patients with estimated renal function (creatinine clearance) less than 55ml/min ie where renal function is working at less than 55% capacity. Cidofovir for many renal transplant patients is therefore NOT a treatment option as average renal function post-renal transplant is 25-50ml/min, with many patients having transplant renal function less than 25ml/min ie renal function working at less than 25% capacity.
2	It is important for the committee to be aware that usage in renal transplant patients for this indication would be low. In a single centre experience with over 1900 long term renal transplant follow up patients, transplanting over 200 new renal patients per year, refractory CMV disease affects 1 patient every 18-24months. Whilst the drug may be high cost, its usage will be very low in this cohort but it is an essential treatment option for the reasons explained above.
3	We fully agree with the committee recommendation to include disease complications in the modelling to consider transplant graft loss as a consequence of CMV treatment from foscarnet, a nephrotoxic agent.
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted,

Please return to: **NICE DOCS**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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

ERG review of company's response to the ERG TE critique

October 2022

Source of funding

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 in response to the ACD.

2 ERG review of comments

2.1 Issue 5 in company's response: Use of OTUS data in the model

In response to the committee's conclusions, the company accepted to use the OTUS data to model treatment effectiveness in the IAT arm of the model, with the maribavir relative treatment effect being taken from SOLSTICE.

The company used the [redacted] probability of clearance from the SOT population in OTUS at 8 weeks ([redacted] clearance events, out of [redacted] patients with R/R CMV). 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 both the SOT and the HSCT populations in the model.

The following concerns raised by the ERG (after TE) regarding the company's approach to using OTUS data remain unaddressed by the company:

1. The [redacted]% estimate does not include HSCT clearances (as the company reported that these are not available). The ERG remains concerned with the company's approach given that the company provided KM data on clearance for HSCT patients in OTUS. The KM data provided by the company suggest that clearances for HSCT patients at 8 weeks might have been higher ([redacted]) than those observed in the KM estimates for SOT patients at the same point [redacted]. Therefore, the company's approach is likely to underestimate clearances for the HSCT population in both arms of the model.
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.

The ERG, therefore, 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) before the second committee meeting.

2.2 Issue 9 in company's response: Modelling of mortality in stage 1 Markov

Before the first ACM, the company provided a scenario analysis using the OTUS mortality data for both arms of the model. In this scenario, mortality differed only by CMV status, where published literature was used 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 1).

The ERG had three concerns regarding the company's analysis before the ACM:

1) The company's methodology implied that the KM data from OTUS captured deaths for patients without CMV (given that a HR from literature was applied to estimate CMV deaths).
2) The company did not provide the analysis recommended by the ERG during TE, 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, where a HR for mortality for CMV vs nCMV could have potentially been derived from the study.
3) The ERG was unclear why only 20 weeks of mortality data from OTUS were used in the model, 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, recommended that the company clarified if the KM mortality data from OTUS only included patients without CMV recurrence, and asked that the company included the longer-term data from the study for time points beyond 20 weeks in the model.

Crucially, the ERG noted that the OTUS; the Hakimi and the Camargo data all showed 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 ERG noted that the company's approach was likely to overestimate CMV-related mortality.

Table 1. 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]

The committee recognised that there is a lot of uncertainty in the assumptions for mortality in the stage 1 model, but that SOLSTICE had not shown a survival benefit. It considered that mortality should not differ for people based on treatment, so there should be no life year gain with maribavir in the model. It concluded that risk of mortality in the stage 1 model should be the same for the maribavir and IAT groups.

After the ACM, the company maintained its view that an indirect mortality benefit for maribavir (through CMV status) should be included in the stage 1 Markov as maintaining the same risk for maribavir and IAT would be in direct contradiction to the evidence base and the ERG's suggested approach.

The ERG maintains its view that that the Hakimi *et al*. 2017 and the Camargo *et al.* 2018 studies show a robust relationship between CMV presence and an increased risk of death (vs nCMV). Therefore, the ERG's view remains that assuming a survival benefit for nCMV in the model is a more clinically plausible approach. However, the ERG remains in disagreement with the company's implementation of this in the model:

1. For nCMV patients - The ERG has previously requested that the company used the long follow-up mortality data from OTUS, instead of only using the 20 weeks of data from the study. However, this impact of this issue is reduced in the company's updated analysis given the fact that the stage 1 Markov was reduced from 78 to 39 weeks, after which patients are assumed to have the same mortality in the model (as there are no more CMV events).
2. For nCMV patients - 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. The latter would have been the preferred option (if available).
3. Finally, the ERG asked that the company clarified if the KM data from OTUS used in the analysis only included patients without CMV (given that a HR from literature was applied to estimate CMV deaths). The company also failed to clarify the latter.

Given the ERG's assessment that the company's current approach is likely to overestimate survival, and the company's failure to address the ERG's concerns, the ERG produced a scenario analysis as per the committee's preferred view of no survival associated with nCMV. Nonetheless, the ERG notes that this scenario is intended to provide a range of ICERs between no survival benefit associated with nCMV, and the survival benefit estimated in the company's model post-ACM. The ERG reiterates its view that the "true" ICER is likely to be somewhere in this range, as the ERG considers that modelling a survival benefit associated with nCMV is clinically valid.

2.3 Issue 11 in company's response: Modelling of GvHD

Clinical expert opinion originally provided to the ERG indicated that HSCT patients with chronic GvHD (i.e., unresolved GvHD at 100 days post-surgery) have a higher probability of death. However, as also acknowledged by the company at submission, the experts stated that 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 chronic GvHD independent of CMV status was included in the model. Furthermore, the ERG asked that the company included the increase in mortality associated with GvHD in the analysis.

After TE, the company included the ERG-suggested scenario analysis where GvHD was assumed to be independent from CMV. The company chose to assume a 4-weekly probability of 24% in the model, for both CMV and nCMV states. However, at that point, the ERG also noted that the company had not assumed GvHD patients to have a higher mortality risk in the model. Therefore, the ERG recommended that the company added this latter assumption to their scenario analysis. Furthermore, the ERG also noted that if GvHD events (independent of CMV status) were 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 was likely that the ICER associated with maribavir would have increased.

The committee concluded that, although a causal relationship between CMV presence and GvHD could not be identified, the effects on overall mortality could have a large impact on the cost-effectiveness estimates. The committee also accepted the ERG's approach to modelling GvHD (i.e., based on the company's scenario analysis after TE where the rate of GvHD was the same for CMV and nCMV events).

The company's updated approach after the ACM consisted of:

1. Changing the rate of GvHD in the model – the company used the same source (Hahn *et al.* 2008)[10] as before but changed the rate of GvHD to reflect TST in OTUS ([redacted]) instead of SOLSTICE ([redacted]).
2. Applying a HR in order to estimate a differential of GvHD for CMV and nCMV patients - the company used a HR of 2.18 taken from Cantoni *et al*. 2010[11]. The HR of 2.18 included in the study was in reference to the risk of patients developing any grade of acute GvHD during episodes of CMV replication (95% confidence interval of 1.30 to 3.65, p-value<0.01). The company's approach resulted in applying a 4-weekly probability of GvHD for CMV patients of 6.8% and of 3.2% for nCMV patients.

The ERG acknowledges the complexity of including GvHD in the model, particularly due to the fact that the change in mean TST from SOLSTICE to OTUS for HSCT patients in the model means that the initial inclusion of only chronic GvHD (i.e., unresolved GvHD at 100 days post-surgery) might be less appropriate when the mean TST from OTUS is used at baseline in the model.

The EAG disagrees with the company's estimation of the probability of GvHD in the model. This was estimated based on the cumulative incidence of acute GvHD from Hahn *et al*. 2008 for patients with and without CMV. To this, the company then applied the Cantoni *et al.* HR, in order to estimate the proportion of patients with GvHD without CMV. This is inappropriate, as the baseline estimate of GvHD included patients with and without CMV. Alternatively, the Cantoni *et al.* study reported the cumulative incidence for patients with CMV replication at 100 days post-transplant (n=86), who also developed GvHD during CMV replication (n=17), therefore translating to a probability of 20% for CMV patients developing GvHD. This translates into a 4-weekly probability of 6% and a probability of 2.7% for patients without CMV if the HR from the same study is applied. When the ERG replaced the company's probabilities of 6.8% and 3.2% with the 6% and 2.7% probabilities, the impact on the final ICER was negligible.

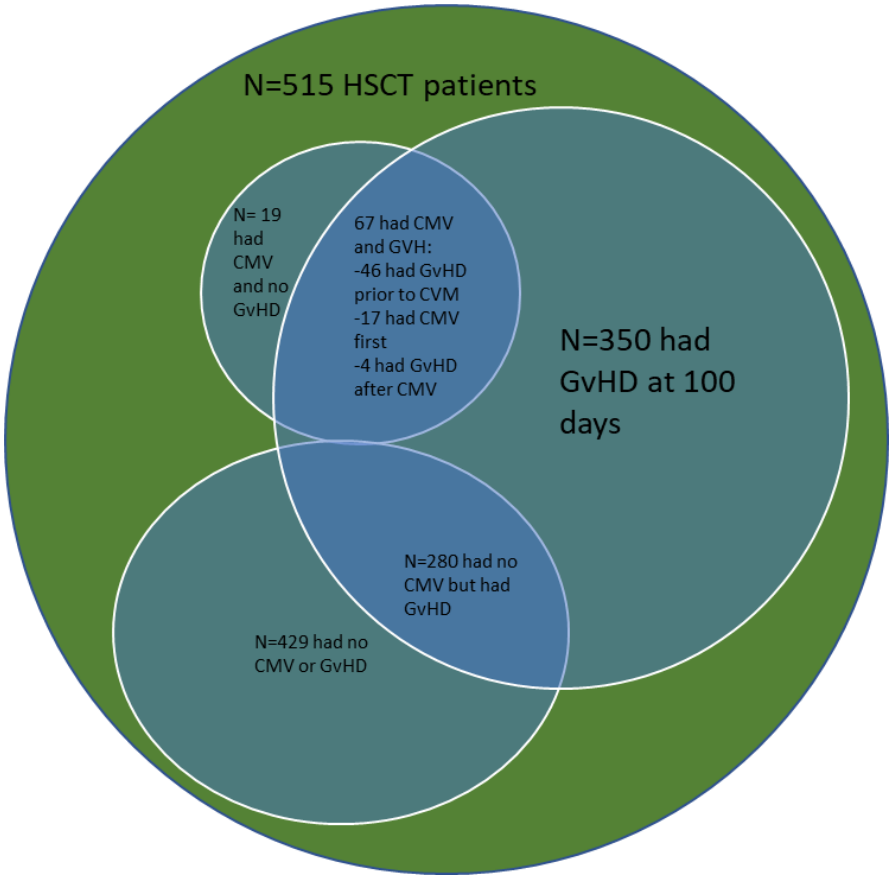
With regards to modelling a differential in GvHD for CMV vs nCMV patients, the ERG cannot be certain on the clinical plausibility of this approach but notes that the source used by the company provides a generally robust source of evidence for the impact of having CMV on GvHD, albeit acute GvHD. Given clinical expert view, the committee's view, and the company's own original assessment that the causal relationship between chronic GvHD and CMV presence is not well established, the ERG is wary of the inclusion of this benefit for maribavir in the economic analysis at this stage in the process.

For inclusiveness, and to aid the committee discussion, the ERG reported the rates of GvHD in the study population from Cantoni *et al.* in Figure 1. The ERG notes that even though the percentage of patients with GvHD in the study was very high (68%), the R/R CMV population in the model eligible for maribavir means that only patients with a CMV event post-HSCT are relevant for the analysis.

The Cantoni *et al.* study also reported that 4 patients, out of the 86 with CMV replication had GvHD after CMV resolution. Therefore, overall, out of all patients with a CMV event after HSCT, 21 patients had GvHD either during a CMV event or after, amounting to 24% of patients with GvHD regardless of CMV status. This equates to a 4-weekly probability of 7.5%. This considerably differs from the company's estimate of 24% (4-weekly) included in the scenario analysis of CMV-agnostic GvHD rates. As a scenario analysis the ERG assumed that both CMV and nCMV patients had the same probability of 7.5% of GvHD in the model and presents the results in Section 2.6.

The company failed to include the impact of GvHD on survival as requested by the committee.

Figure 1. Disposition of GvHD in the Cantoni *et al.* study



Overall, the ERG advises that the inclusion of GvHD events in the model is further discussed at a second ACM, in particular with a view to reach a conclusion on the following questions:

1. Is it appropriate to include acute GvHD in the model or should this be restricted to cases of chronic GvHD?
2. Does the company have an update on the OTUS GvHD data, as this was meant to be available before the end of the year?
3. Is it appropriate to assume that patients with CMV have a higher probability of GvHD? And is this true for both acute and chronic GvHD?
4. Does acute GvHD increase patients' mortality? Is this the same as chronic GvHD?

The ERG presents cost-effectiveness results with and without a CMV effect on GvHD in Section 2.6.

2.4 Additional changes made by the company

The company has updated the costs of foscarnet and cidofovir to reflect the decrease in reported costs since the ACM. The ERG agrees with the company's approach.

The company has also updated the patient access scheme (PAS) discount from [redacted], resulting in a new net cost of [redacted] per 56 x 200mg pack or [redacted] per 8-week treatment cycle.

All the results reported in the following sections include the updated prices.

2.5 Company's updated cost-effectiveness results

The deterministic and probabilistic results of the company's revised base case are reported in Table 2 and Table 3, respectively. The deterministic ICER for maribavir is £19,908 per QALY gained. According to the company's analysis, maribavir is expected to increase patients' life expectancy by 0.714 years compared with IATs, at a higher cost and incremental QALYs. The company's probabilistic results are 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 are £15,628 and £27,537 per QALY gained, respectively.

Table 2. Company's updated base case deterministic results

Interventions	Total Costs (£)	Total LYG (undiscounted)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Maribavir	[redacted]	10.54	4.97	-	-	-	-
IAT	[redacted]	9.83	4.61	£7,146	0.714	0.359	£19,908

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 3. Company's updated base case probabilistic results

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Maribavir	[redacted]	4.96	-	-	-
IAT	[redacted]	4.57	£6,621	0.391	£16,942

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

2.6 ERG scenario analysis

The exploratory analyses undertaken by the ERG are explained throughout the report. The results of the analysis are reported in Table 5. The assumptions explored are the following:

1. Assuming that CMV status does not affect the risk of GvHD (and assuming a 4-weekly probability of 7.5%);
2. Assuming no mortality risk associated with CMV vs nCMV.

The results in Table 5 show that the model key driver is the assumption of a mortality benefit associated with nCMV. Nonetheless, given the uncertainty around GvHD, the ERG recommends that the committee validates the GvHD probabilities used in both ERG's scenarios, as increasing the rates (in both scenarios) could lead to a considerable increase in the final ICER.

Table 6 reports the impact of combining the ERG's scenarios. When CMV is assumed to have an impact on the probability of GvHD, the ERG's scenarios range from £19,908 to £111,516, depending on assuming that CMV has an impact on patients' mortality.

When CMV is assumed to not have an impact on the probability of GvHD, the ERG's scenarios range from £22,814 to £313,939, depending on assuming that CMV has an impact on patients' mortality.

The ERG acknowledges that the ranges provided still reflect a paramount level of uncertainty. To aid the decision making-making process, the ERG provided a scenario where CMV is assumed to have an impact on patients' mortality; however, where CMV patients were assumed to have a lower survival benefit than that assumed by the company (but still twice as much as the probability of death for nCMV patients – see Table 4).

When the ERG's scenarios are combined, and CMV patients are assumed to have twice the probability of death as nCMV patients (which resulted in a lower survival benefit than that assumed by the company), the ICERs range from £36,653 to £47,294, depending on assuming that CMV has an impact on GvHD or not, respectively (see Table 6).

Table 4. Probability of all-cause mortality in ERG's scenarios

	Company's base case		No benefit assumed (mortality data pooled from OTUS)		CMV patients assumed to have twice the probability of death as nCMV patients	
Input	SOT	HSCT	SOT	HSCT	SOT	HSCT
nCMV (weeks 8 to 20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CMV (weeks 8 to 20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nCMV (week 20 onwards)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CMV (week 20 onwards)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5. Deterministic results for ERG's exploratory analysis (incremental)

		Incremental costs	Incremental QALYs	ICER
0	Company's updated base case	£7,146	0.36	£19,908
1	Assuming no CMV effect on the risk of GvHD	£7,352	0.32	£22,814
2	Assuming no mortality risk associated with CMV vs nCMV	£5,255	0.05	£111,516

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 6. Deterministic results (cumulative)

		Incremental costs	Incremental QALYs	ICER
0	Company's updated base case: Assuming CMV increases the probability of GvHD	£7,146	0.36	£19,908

	Assuming CVM patients have higher mortality			
1	Assuming CMV increases the probability of GvHD Assuming CVM has no impact on mortality	£5,255	0.05	£111,516
2	Assuming CMV does not increase the probability of GvHD Assuming CVM patients have higher mortality	£7,352	0.32	£22,814
3	Assuming CMV does not increase the probability of GvHD Assuming CVM has no impact on mortality	£5,422	0.02	£313,939
4	Assuming CMV increases the probability of GvHD Assuming CMV patients have twice the probability of death as nCMV patients	£6,025	0.16	£36,653
5	Assuming CMV does not increase the probability of GvHD Assuming CMV patients have twice the probability of death as nCMV patients	£6,211	0.13	£47,294

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

2.7 Conclusions and list of ERG's recommendations

The ERG maintains its view that that the Hakimi *et al*. 2017 and the Camargo *et al.* 2018 studies show a robust relationship between CMV presence and an increased risk of death (vs nCMV). Therefore, and as validated by clinical expert opinion provided to the ERG, assuming a survival benefit for nCMV in the model seems to be the more clinically plausible approach. However, the ERG remains in disagreement with some of the aspects around the company's implementation of this benefit in the model. The ERG remains particularly interested in understanding if there was a statistically significant CMV-related increase in mortality in OTUS, and how comparable this estimate would be to the ones reported in the Hakimi *et al*. 2017 and the Camargo *et al.* 2018 studies, for SOT and HSCT patients, respectively.

Given the ERG's concerns around the company's current approach, the ERG produced a scenario analysis as per the committee's preference of no survival associated with nCMV. Nonetheless, given the ERG's disagreement with the clinical plausibility of the latter, the ERG also provided an additional scenario analysis where the increase in CMV-related mortality in relation to nCMV was decreased compared to the company's base case. The respective ICERs for this additional scenario range from

£36,653 to £47,294, per QALY gained, depending on assuming that CMV has an impact on GvHD or not, respectively.

With regards to modelling a differential in GvHD for CMV vs nCMV patients, the ERG cannot be certain on the clinical plausibility of this approach but notes that the source used by the company provides a generally robust source of evidence for the impact of having CMV on GvHD, albeit only for acute GvHD. Given the uncertainty around the inclusion of GvHD in the model, the ERG recommends that the committee obtains clinical expert opinion to validate the GvHD probabilities used in both ERG's scenarios, as increasing the rates (in both scenarios) could lead to a considerable increase in the final ICER.

Additionally, the ERG recommends that the company:

1. Provides the clearance data used to estimate the [redacted] probability of clearance for SOT at 8 weeks, available from OTUS (for all time points);
2. Provides the clearance available for HSCT patients in OTUS and incorporates it into the clearance estimates used in the updated model.
3. Uses the long follow-up mortality data from OTUS in the model up to week 39, instead of only using the 20 weeks of data from the study. Nonetheless, the ERG notes that this impact of this issue is reduced in the company's updated analysis given the fact that the stage 1 Markov was reduced from 78 to 39 weeks. Therefore, if the company can demonstrate that the mortality in OTUS from week 20 to week 39 remained the same, this scenario might not be necessary.
4. Investigates the statistical significance of CMV vs nCMV mortality in OTUS, and consequently, the possibility of using these data instead of external literature to capture the CMV-related increase in mortality in the model.
5. Clarifies if the KM data from OTUS used in the analysis only included patients without CMV (given that a HR from literature was applied to estimate CMV deaths).
6. Includes the impact of GvHD on survival in the model.

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.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
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**
Name of commentator person completing form:	**Mark Robinson**

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.	ERG comment
1	**The clinical need for maribavir with limited treatment options available** Takeda note that all conventional therapies are used off-label for the treatment of CMV post-transplant. Maribavir offers the first approved treatment for refractory (with or without resistance) CMV infection. Many of the conventional therapies are associated with adverse events (neutropenia and nephrotoxicity) that can lead to the development of viral resistance. Maribavir may reduce treatment burden as an oral therapy and reduce the hospitalisations required for IV therapies. We recognise that CMV infection and conventional strategies for management have negative impacts on both patient and caregiver quality of life, in terms of physical activity and mobility limitations, stress, mental fatigue & inability to work. For caregivers, there is an emotional burden and impact on daily life & work that we are unable to capture in the economic model.	The ERG agrees with the company that there is an unmet need in the treatment of CMV post-implant for a cost-effective option compared to conventional therapies.
2	**The conduct and design of SOLSTICE could bias the results** Takeda dispute that the SOLSTICE trial results are biased. Extensive sensitivity analysis has been provided throughout technical engagement that demonstrate the robustness of the data. Multiple sensitivity analyses of the primary endpoint demonstrate a consistent efficacy advantage over IAT, regardless of whether the study drug was prematurely discontinued, clearance occurred at any time during the treatment phase, or the IAT patients received alternative anti-CMV treatment. Takeda note that the SOLSTICE trial population was heterogenous, in both solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) patients. The trial design was deemed ethical and sufficient for this patient population, and both the EMA and FDA were consulted on the trial design.	The ERG's concerns remain that the conduct and design of SOLSTCE may bias the results of clearance and recurrence requiring treatment. The sensitivity analyses provided do not address the potential biases introduced by the open label trial design: that patients in the IAT arm may not have been treated long enough before considered non-responders and offered rescue therapy with maribavir, and similarly that the need for alternative anti-CMV treatment for recurrences were at the discretion of the investigator. This is discussed in Section 3.2.1 of the ERG report

Please return to: **NICE DOCS**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Furthermore, we highlight that CHMP opinion was granted on 15th September 2022 based on maribavir demonstrating statistically superior efficacy compared to conventional therapies for the primary endpoint, indicating the regulators confidence in the data package for maribavir.[1] The ERG thought that the rescue arm may introduce bias to some outcomes. The committee considered that 3 weeks of treatment may not be long enough to assess a lack of efficacy. Takeda would like to clarify that the rescue arm was only an option for IAT subjects who, despite a minimum of 3 weeks of therapy with IAT, met stringent and objective criteria for lack of improvement/worsening of CMV infection, namely: • ≥1 log10 increase in CMV DNA from baseline • <1 log10 decrease in CMV DNA from baseline with new, worsening, or no improvement in tissue-invasive disease; or • lack of viremia clearance and demonstrated intolerance to IAT with either >50% increase from baseline in serum creatinine, development of haemorrhagic cystitis, or development of neutropenia (absolute neutrophil count [ANC] <500/mm3). Therefore, the above criteria demonstrated no response within a set timeframe of three weeks, an endpoint that was agreed with the EMA and FDA during the design of the trial. Throughout the ratification of the NICE submission, Takeda spoke with numerous SOT and HSCT clinicians where it was confirmed that if after two weeks of therapy no reduction in viral load was seen, an alternative treatment plan would be considered. This is also aligned to BTS guidelines which states: *Based on knowledge of the viral kinetics with anti-CMV treatment, members agreed to recommend treatment for at least 14 days duration as this has been shown to be associated with a viraemia reduction of approximately 1.0 log10 (90%).*[2]	
3	**Results of SOLSTICE may not be generalisable to clinical practice** Takeda note the Committee had some concerns about an imbalance in time since transplant between treatment arms. We would like to draw attention to the extensive regression analysis performed during technical engagement which demonstrated 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] and [redacted], respectively. This indicates that the odds of each outcome are almost unchanged by increasing the number of months since transplant, and it is the treatment effect of maribavir that is driving the efficacy.	The ERG highlights that the results of SOLSTICE may not be generalisable to clinical practice because the time since transplant was considerably longer in SOLSTICE than would be expected in practice (based on input from the ERG's and NICE's clinical experts). The risk of recurrence and mortality are likely to be substantially higher in clinical practice than were observed in the trial.

Please return to: **NICE DOCS**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	We are pleased to see the sensitivity analysis provided at technical engagement regarding patients in the IAT group having retreatment with anti-CMV therapies to which their infection was resistant has demonstrated the sustained benefit of maribavir, and that the clinical experts confirmed that continuing treatment in these circumstances is plausible when there are no better treatment options available. During technical engagement, extensive missing data analysis was provided to the technical team, and we confirmed that minimal missing data for recurrence was seen. Takeda note the ERG agreed missing data wasn't a significant issue for the ITT population. We agree that the missing data is greater in the IAT arm due to the presence of a rescue arm. Without the rescue arm, the trial would have not met the necessary ethical standards during the design phase.	The ERG agrees with the company that there were minimal missing data for recurrence and missing data for clearance were explored adequately.
4	**SOLSTICE data suggests that maribavir improves clearance compared with IAT, but the results are highly uncertain** Takeda note that regulators have agreed that data from the SOLSTICE trial demonstrates the efficacy of maribavir. CHMP opinion was granted on 15th September 2022 and FDA approval on 23 November 2021, based on maribavir demonstrating statistically superior efficacy compared to conventional therapies for the primary endpoint. Regulators agreed during the design of the trial that transplantation patient's level of CMV viremia is considered a validated surrogate endpoint that predicts mortality. Detailed sensitivity and supplemental analyses were prespecified to assess the robustness of the results in the CSR.	The ERG agrees that data from SOLSTICE demonstrate that maribavir is effective in terms of achieving clearance but the uncertainty around the estimates of clearance and recurrence requiring treatment remains high.
5	**Using OTUS data is more robust than using multiple data sources to model outcomes in the stage 1 Markov model** Takeda note the potential uncertainties arising due to the nature of incorporating two separate data sources to inform initial and subsequent episodes in the economic model. However, Takeda maintain that SOLSTICE provides the most reliable data source to estimate the treatment effect of maribavir compared to standard care and also, therefore, that the IAT arm of the SOLSTICE trial represents the most reliable source of data to inform the standard care arm for the initial R/R CMV episodes in which maribavir is being appraised. Despite this, Takeda are willing to acknowledge the Committee's concerns and incorporate this within our revised analyses with the aim of achieving expedited access for patients.	The ERG agrees that the company's approach is in line with the committee's preference; however, notes that some of the ERG's previously raised concerns were not fully addressed - please see ERG's review of company's response to ACD.

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Within our revised analyses we have also amended the mortality adjustment that was initially applied to the clearance estimates. This was incorrectly applied previously, and we have now aligned with the Committee's preferred approach.	
6	**Maribavir may increase the likelihood of maintaining CMV clearance, but there is no evidence to support this** Takeda note that the NICE clinical expert agreed with the company approach during the first appraisal committee meeting. We also highlight that in SOLSTICE the durability of the effect of maribavir was demonstrated, the proportion of responders that achieved CMV viremia clearance and CMV infection symptom control at Week 8 and maintained the effect through Weeks 12, 16, and 20 off-treatment was approximately 2-fold higher for maribavir-treated patients than for the IAT group, regardless of the duration of follow-up. However, in the absence of direct supporting evidence within the SOLTSTICE data for patients treated with maribavir having a lower probability of CMV recurrence than patients treated with IAT, Takeda are willing to accept the Committee's preference.	The ERG agrees that the company's approach is in line with the committee's preference.
7	**The number of CMV recurrences is overestimated in the model** Takeda would like to comment that evidence for multiple recurrences has been demonstrated in the OTUS data and was provided to the ERG during technical engagement. The limited number of patients experiencing multiple recurrences reflects the small population of patients who are refractory or resistance to prior anti-CMV therapies. We consider the ERG approach of limiting the number of recurrences in the model is very conservative and merely removes uncertain benefit rather than considers the uncertainty surrounding that benefit in the context of a very rare condition with an important unmet need. Despite this, Takeda are keen for maribavir to be made available to patients as soon as possible and are willing to amend the revised analysis to the conservative scenario where recurrences can only occur up to week 39 as per the ERG's preferred analysis. Importantly, this aspect of the revised economic analyses now aligns with the Committee's preferred assumption and therefore any further modelling to assess the uncertainty surrounding the longer-term recurrence rates beyond week 39 is no longer relevant. This therefore fully addresses the Committee's preferences.	The ERG agrees that the company's approach is in line with the committee's preference.

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

8	**The duration of the stage 1 Markov model should align with the duration that CMV recurrences can be accurately modelled** Takeda believe the OTUS data is a robust source for modelling recurrences over time. Although the evidence for greater than two recurrences can be observed in the OTUS data, we recognise the number of patients with >2 recurrences diminish over time and is reflective of this population. As there is robust data in OTUS that demonstrate the first and second recurrence occur by 39.2 weeks, we are willing to accept the Committee's preference to limit stage 1 of the Markov model to this length.	The ERG agrees that the company's approach is in line with the committee's preference.
9	**Risk of mortality in the stage 1 Markov model should be the same for people having maribavir and IAT** Takeda have aligned the stage 1 mortality in the economic model with the ERG's suggested methodology and therefore the revised results provided in this response document are fully aligned with the ERG's preferred approach. Takeda believe the committee's position to assume that there should be no life year gain in the model is in contradiction not only to the alignment of Takeda and the ERG but also of the published evidence base. Furthermore, it has been acknowledged by clinicians advising both Takeda and the ERG that there is a clear association between CMV and the risk of mortality, and two recent large-scale studies have further substantiated the association between CMV viraemia and mortality.[3, 4] The remainder of this section outlines the key evidence demonstrating this mortality association (including an update from the 12-month extension to SOLSTICE) as well as addressing some corrections to the IPD analysis report highlighted previously by the ERG. In response to the points made by the ERG (Section 2.5, page 14 of the *ERG's review of the company's response to the ERG TE critique*, August 2022) in relation to the cross-over adjusted mortality analyses, Takeda would like to clarify some errors in figure headings that caused misleading conclusions by the ERG. The adjusted KM plot for mortality that the ERG refers to was incorrectly labelled as "adjusted for treatment switch by RPSFTM method". This plot in fact represents *treatment-free* transformed survival i.e., removing the treatment effect (estimated using e.g., the RPSFTM adjustment) and thus	The ERG disagrees with the approach of removing a survival benefit for nCMV patients vs nCMV patients (and, therefore, removing the indirect survival benefit for maribavir patients) as suggested by the committee. However, the company has not addressed some of the issues raised by the ERG before the ACM in relation to the implementation of a nCMV-related survival benefit in the model - please see ERG's review of company's response to ACD.

	compares two groups of patients who are hypothetically untreated with maribavir. This plot should not be interpreted as a lack of treatment effect for maribavir compared to IAT following adjustment. The adjusted KM plots for each method accounting for cross-over are all indistinguishable given the similarity in the estimated HRs. The KM plot given in Figure 1 therefore provides a representation of the impact of adjusting for cross-over for all adjustment methods. *Figure 1. Kaplan-Meier showing cross-over adjusted survival from SOLSTICE*	

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	[redacted] An additional typographical error highlighted by the ERG was in the tabulated results. To clarify, Table B4 (and B5) of the IPD analysis report had incorrect labels that should have stated *"Time to all-cause mortality prior to initiation of alternative anti-CMV treatment use by treatment arm adjusted for treatment switch by RPSFTM method"*. Previously, Table B4 and B5 had the same headings as Table B1 and B2, respectively. The hazard ratio presented previously in Table B1 was correctly reported for the RPSFTM and this is the relevant result to compare to the primary analysis that used the inverse probability of censoring weights (IPCW) method.		

	The conclusions of these analyses showed that the results of the two methods were similar with hazard ratios of [redacted] and [redacted] for the IPCW and RPSFTM methods, respectively. For the IPE method, the hazard ratio showed a slightly greater adjusted treatment effect of [redacted]. These analyses show increasing evidence of an effect being demonstrated even within the short follow-up period of the SOLSTICE trial, which was not powered to detect a significant effect for mortality. A corrected version of the IPD report will be supplied alongside this response document for full clarity of the corrections. In addition to this, SOLSTICE provides clear evidence of a difference in survival associated with response to CMV treatment, as shown in the KM plot in Figure 2. This plot shows a statically significant difference in the hazard rate of death between those who achieved clearance at week 8 (in either treatment group) compared to those who failed to achieve clearance. *Figure 2: Kaplan Meier plot of OS by clearance status at week 8* 	

	As there are important differences in the mortality rate of the two transplant types, (SOT and HSCT), it is also important to assess the survival of the two subgroups separately. Figure 3 shows KM plots for survival form SOLSTICE split by clearance status at week 8 as well as transplant type. This also clearly demonstrates the impact that achieving clearance has on the risk of death and emphasizes the need for a treatment like maribavir for patients who have R/R CMV. This also supports Takeda's original approach to modelling mortality by health state. *Figure 3: Kaplan Meier plot of OS by clearance status at week 8 and transplant type*	

Furthermore, since technical engagement, the CSR for the 12-month extension study (TAK620-5004) has been made available.[5] TAK620-5004 was a retrospective study to collect follow-up data at 12 months among transplant recipients randomised to the maribavir arm in the SOLSTICE study. The study population for the final analysis consisted of [redacted] patients including [redacted] ([redacted]%) SOT and [redacted] ([redacted]%) HSCT patients. The primary objective was to measure all-cause mortality at 12 months and median overall survival, for the overall population and for HSCT and SOT cohorts, separately. Results demonstrate that the observed overall mortality was numerically lower than published estimates at 12 months following treatment initiation for R/R CMV post-transplant (Figure 4) Overall mortality was [redacted]% at 12 months in the 12-month maribavir extension study. Two published articles report mortality of 31% and 50% after initiation of treatment for CMV in small samples of HSCT and SOT recipients.[6, 7]

Figure 4: 1-year mortality estimates and confidence intervals for maribavir and historical published data including HSCT and SOT populations treated for R/R CMV

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

[redacted]

The mortality trended in the expected direction for both SOT and HSCT, with lower mortality in SOT than HSCT ([redacted]% vs [redacted]%). The one year mortality by transplant in the chart review sample was generally lower than published estimates and real-world (RW) cohort studies (OTUS) in treated resistant/refractory populations reporting mortality by transplant type (Table 1)

Table 1: mortality outcomes by transplant type

Study	SOT mortality	HSCT mortality
TAK620-5004[5]	[redacted]	[redacted]
Avery 2016[6]	9% (2/22)	59% (10/17)
Mehta 2020[7]	37.5% (3/8)	75% (3/4)
Fisher 2017[8]	16.2% (6/37)	n/a
Karantoni 2022[9]	n/a	33.3% (~15/46)
OTUS (Takeda study)	[redacted]	[redacted]

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Based on the above, we have maintained a mortality benefit for maribavir in the stage 1 Markov as maintaining the same risk for maribavir and IAT would be in direct contradiction to the evidence base and the ERG's suggested approach. Given that we have aligned to the ERG's preferred approach of applying published mortality rates to inform stage 1 mortality and all other aspects we have conceded to the Committee's conservative approaches, Takeda hope that the revised analyses demonstrating cost-effectiveness will aid the acceptance of maribavir for access to patients as soon as possible given the clearly outlined need for this treatment as voiced by the patient and clinical communities at the first appraisal committee meeting and also demonstrated in the evidence base.	
10	**The mean time since transplant should be used at model entry** Takeda acknowledge there is some uncertainty in whether medium or mean time since transplant should be used at model entry given the heterogeneous population. We agree with the Committee's preference to use mean time since transplant	The ERG agrees that the company's approach is in line with the committee's preference.
11	**The impact of disease complications should be included in the economic model** ***Graft versus host disease (GvHD)*** Although Takeda considers the link between CMV and GvHD to be uncertain without any supporting evidence that CMV causes GvHD, Takeda are willing to compromise on the inclusion of GvHD within the economic model. However, the analysis provided in the original model had not subsequently been amended to account for time since transplant. Therefore, Takeda have now amended the scenario using the same data sources as the previous scenario but now using the time frame of the published KM plot that aligns to the mean time since transplant from OTUS, and therefore more appropriately aligning to the economic model. The original analysis was based on baseline GvHD rates from Hahn *et al.* 2008[10], which provided probabilities of GvHD from the time of transplant. This estimated that 11% of patients suffered GvHD every 4 weeks since the time of transplant up to 100 days post-transplant. This also was based only on the earlier transplant data (1995-98) that was shown to have increased rates of GvHD compared to more recent data (1999-02). The estimated 4-week probability of GvHD was applied for the non-clinically significant CMV health state in the economic model. To estimate a probability for the clinically significant CMV health state, a hazard ratio of 2.18 reported in Cantoni *et al.* 2010[11] was applied.	The ERG agrees that the company's approach is in line with the committee's preference for leukaemia recurrence and graft failure. For the modelling of GvHD, the ERG does not consider that the company has fully addressed the committee's concerns - please see ERG's review of company's response to ACD.

Please return to: **NICE DOCS**

	The updated scenario now estimates the probabilities based on the KM plot from Hahn *et al.* 2008[10] but now only from around the time of the mean time since transplant from OTUS of [redacted] for HSCT. At this time point, Hahn *et al.*2008[10] reports approximately 25% of patients having GvHD at day 40 (based on 1999-02 data), which increases to 30% at day 100, the latest follow-up point. Using these two time points we calculated a more reflective underlying rate of GvHD and subsequently calculated the 4-week probability of 3.2%. Note that given the diminishing rates of GvHD over the time period reported, this is still likely to overestimate the rates of GvHD in the model in the long term. For full transparency, the calculations used to derive the values are as follows: 4-week probability of GvHD (n-csCMV) = 1-EXP(LN((1-0.3)/(1-0.25))*(28/(100-40))) = 3.2% 4-week probability of GvHD (csCMV) =1-EXP(1-0.032)^2.18 = 6.8% **Leukaemia Recurrence** Takeda considers the assumption that 47% of patients who received HSCT after having leukaemia would experience a recurrence of their underlying disease and subsequently die, to be implausible. This would result in a double counting of the mortality impact given that the mortality estimates used in the model incorporate death by all causes. However, in the interests of achieving expedited access to maribavir for patients at need, Takeda have incorporated this assumption into the revised analyses. **Graft failure** Graft failure was already appropriate captured within our base case analysis, so this is aligned to the Committee's preferred assumptions.	
12	**The model should include different intravenous administration costs for first and subsequent administrations** Takeda note the committee's preference that using first and subsequent IV administration costs are appropriate and have updated the base case to reflect this.	The ERG agrees that the company's approach is in line with the committee's preference.
13	**The cost of hospitalisation for people with clinically significant CMV is likely to be higher than for people without clinically significant CMV**	The ERG agrees that the company's approach is in line with the committee's preference.

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Takeda are pleased to observe the Committee decided that our approach was considered appropriate and that csCMV would be more costly to manage in hospital than ncsCMV. We have therefore maintained this in our updated base case.	
14	**Because of the uncertainty, an acceptable ICER is around £20,000 per QALY gained** Takeda recognise that despite the robust evidence base seen in the SOLSTICE trial for the benefit of maribavir there are elements of uncertainty that reflect the heterogenous and rare population that are refractory to CMV therapies. We have therefore updated our price and base case assumptions to provide an ICER of £19,908 per QALY gained which is below the threshold required from the committee. Below we present our revised analysis and new base case.	The ERG conducted scenario analysis with the company updated PAS and presents the results in its review of the company's response to ACD.
15	**Revised analysis and base case** Takeda have provided a revised set of analyses taking on feedback from the committee as well as the ERG. The updated base case analyses are based on a revised patient access scheme discount of [redacted] from list price resulting in a new net cost of [redacted] per 56 x 200mg pack or [redacted] per 8-week treatment cycle. As discussed throughout this document, we have made changes to our original base case to account for the committee's and ERG's concerns around uncertainty. A summary of the revisions is as follows: 1. Using OTUS as the baseline for the standard care arm and applying relative efficacy from SOLSTICE to derive the mairbavir clearance and recurrence probabilities 2. Applying mean time since transplant rather than median (from OTUS) 3. Limiting the duration of phase 1 of the model to 39.2 weeks despite evidence of CMV risks beyond this time frame 4. Applying treatment independent recurrence probabilities despite evidence of an effect 5. Including leukaemia recurrences despite the potential double counting for mortality	The ERG agrees that the company's approach is in line with most of the committee's preferences, with the exception of the modelling of GvHD. The ERG also notes that some of the ERG's previously raised concerns about clearance rates from OTUS and about the implementation of a nCMV-related survival benefit in the model were not fully addressed by the company- please see ERG's review of company's response to ACD.

6. Including GvHD but with amended rates accounting for the mean time since transplant in OTUS

7. Amending the administration cost to account for the reduced cost of follow-up attendance;

Furthermore, since technical engagement Takeda noticed the comparator costs of foscarnet have been reduced in the BNF[12], and the price for cidofovir has been published at a price lower than that originally used in the Takeda model.[13] In the interests of full transparency Takeda have updated the economic model to reflect these most recent NHS costs.

Note that this base case aligns with the committee's preferred assumptions with the exception of one issue on which the company's base case aligns with the ERG's suggested approach of applying published relative mortality risks from Hakimi *et al.*[14] and Camargo *et al.*[15] to estimate risks for those with csCMV.

The results of the revised base case analysis are given in Table 2, with an ICER of £19,908 per QALY gained, demonstrating the maribavir is clearly a cost-effective use of NHS resource by being under the lower NICE willingness-to-pay threshold.

Table 2. Company's Revised Base Case Results

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER incremental (£/QALY)**
Maribavir	[redacted]	4.97	£7,146	0.359	£19,908
IAT		4.61			

A number of scenario analyses given in Table 3 showing the plausible potential that the true ICER is actually even lower than the conservative base case analysis that has been aligned to the Committee's preferred assumptions in the interests of achieving expedited access to maribavir for patients in need.

Table 3. Scenario Analysis Results

#	Scenario	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
0	*Base case*	*£7,146*	*0.359*	*£19,908*
1	Treatment independent recurrence	£5,745	0.411	£13,964
2	Remove GvHD	£7,198	0.350	£20,590
3	Remove leukaemia recurrence	£7,146	0.452	£15,809

The uncertainty in the various aspects of the model is clearly important to the decision-making process for this appraisal and therefore it is important to assess the impact of the uncertainty of all parameters through a probabilistic sensitivity analysis (PSA) as well as one-way sensitivity analyses (OWSAs).

The results of the PSA are given in Table 4, showing that the ICER actually decreases compared to the deterministic base case results, with an ICER of £16,942 per QALY gained. This demonstrates that the deterministic results are more than robust to the uncertainties with the data sources used and, therefore, Committee can be confident that this revised base case analysis represent a clearly cost-effective use of NHS resources for a small population of patients with a severe unmet need in current clinical practice.

Furthermore, the PSA scatterplot in Figure 5 and the cost-effectiveness acceptability curve (CEAC) in Figure 6 both show the high likelihood of cost-effectiveness even at low willingness-to-pay thresholds. The OWSA plot in Figure 7 show further that the results are robust to changes in the parameters in the revised base case analysis.

Table 4. Company's Revised Probabilistic Sensitivity Analysis Results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Maribavir	[redacted]	4.96	£6,621	0.391	£16,942
IAT		4.57			

	Figure 5. Scatterplot showing 10,000 PSA samples on the cost-effectiveness plane  *Figure 6. Cost effectiveness Acceptability Curve*	

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	[redacted]	

Please return to: **NICE DOCS**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

	Figure 7. One-way Sensitivity Analyses 	
16	**Summary & References** Takeda are willing to accept the intrinsic uncertainty within this submission and therefore have provided a base case with an ICER under the £20,000 / QALY willingness to pay threshold. We have aligned to all the Committee's preferences however we cannot accept zero benefit for mortality with maribavir. Additional data has been provided to demonstrate the link between maribavir treatment and mortality benefits and our approach aligns with the ERG's suggested approach. Based on this response (which builds on the evidence in the original company submission and during technical engagement) and a modified base case ICER that is well below the standard cost effectiveness threshold, Takeda requests that NICE adopt a positive final recommendation for maribavir for R/R CMV after transplant, a population with a clear unmet need. 1. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Summary of opinion. Livtencity (maribavir) EMA/CHMP/248091/2022. 2022; Available from: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-opinion-livtencity_en.pdf. 2. British Transplantation Society. UK GUIDELINE ON PREVENTION AND MANAGEMENT OF CYTOMEGALOVIRUS (CMV) INFECTION AND DISEASE FOLLOWING SOLID ORGAN TRANSPLANTATION. 2022; Available from:	N/A

https://bts.org.uk/uk-guideline-on-prevention-and-management-of-cytomegalovirus-cmv-infection-and-disease-following-solid-organ-transplantation/.

3. Dobrer S, e.a., PRECISION MEDICINE IN TRANSPLANTATION: MAGNITUDE, DURATION, AND IMPACT OF CMV VIREMIA ON GRAFT AND MORTALITY OUTCOMES OP328, in 20th Biennial European Society for Organ Transplantation (ESOT) Congress, Milan, Italy, 29 August – 1 September 2021. 2021.
4. Green, M.L., et al., Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. Lancet Haematol, 2016. 3(3): p. e119-27.
5. International, T.P., CLINICAL STUDY REPORT Retrospective Study to Collect Follow-Up Data at 12 Months Among Transplant Recipients with Refractory or Resistant Cytomegalovirus Infections Randomized to the Maribavir Treatment Arm in the TAK620-303 Open-label Phase III Trial PROTOCOL NUMBER: TAK620-5004. 2022.
6. Avery, R.K., et al., Outcomes in Transplant Recipients Treated With Foscarnet for Ganciclovir-Resistant or Refractory Cytomegalovirus Infection. Transplantation, 2016. 100(10): p. e74-80.
7. Mehta, S.A., et al., Outpatient management of kidney transplant recipients with suspected COVID-19-Single-center experience during the New York City surge. Transpl Infect Dis, 2020. 22(6): p. e13383.
8. Fisher, C.E., et al., Risk Factors and Outcomes of Ganciclovir-Resistant Cytomegalovirus Infection in Solid Organ Transplant Recipients. Clin Infect Dis, 2017. 65(1): p. 57-63.
9. Karantoni, E., et al., Outcomes of Refractory Cytomegalovirus Infection in the First Year after Allogeneic Hematopoietic Cell Transplantation. Transplant Cell Ther, 2022. 28(7): p. 403.e1-403.e7.
10. 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.
11. 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.
12. British National Formulary, Foscarnet sodium. Foscavir 6g/250ml solution for infusion bottles. 2022.
13. British National Formulary. Cidofovir 375mg/5ml concentrate for solution for infusion vials. 2022; Available from: https://bnf.nice.org.uk/drugs/cidofovir/medicinal-forms/.
14. 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).
15. 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.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 19 October 2022. Please submit via NICE Docs.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

Please return to: **NICE DOCS**

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

ERG review of company's response to the ERG TE critique - addendum

October 2022

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135439.

1 Introduction

This document provides an addendum to the Evidence Review Group's (ERG's) review of the company's comments and additional data presented in response to the ACD. The exploratory analysis conducted by the ERG assesses the impact of increasing the clearance rate in the model for HSCT patients, in accordance with the analysis requested by NICE.

2 Exploratory analysis

2.1 Issue 5 in company's response: Use of OTUS data in the model

The company used the [redacted] probability of clearance from the SOT population in OTUS at 8 weeks ([redacted] clearance events, out of [redacted] patients with R/R CMV). 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 both the SOT and the HSCT populations in the model.

The ERG was concerned with the company's approach given that the company provided KM data on clearance for HSCT patients in OTUS, which suggest that clearances for HSCT patients at 8 weeks might have been higher ([redacted]) than those observed in the KM estimates for SOT patients at the same point [redacted]. Therefore, the company's approach is likely to underestimate clearances for the HSCT population in both arms of the model.

Given that the company was not able to provide the additional clearance data for HSCT patients as requested by the ERG, the relative difference in KM estimates at week 8 was used ([redacted] increase in the probability of recurrence for HSCT vs SOT patients) to estimate the overall probability of clearance for HSCT patients in exploratory analysis. The ERG's scenario therefore used a probability of clearance of [redacted]% for SOT patients and of [redacted] for HSCT patients in the IAT arm, and applied the same odds ratio as the company ([redacted]) to obtain the probability of clearance for HSCT patients in the maribavir arm.

The ERG caveats its analysis by the fact that KM estimates are not directly comparable to absolute clearances probabilities given that the former include the impact of censored events. However, the ERG did not have alternative data available to conduct the exploratory analysis requested by NICE in order to assess the impact of assuming a higher clearance rate for HSCT patients in the model.

The other exploratory analyses undertaken by the ERG are explained throughout the ERG's review of the company's response to ACD. The results of the additional analysis are reported in Table 1, whereas Table 2 reports the impact of combining the all the ERG's scenarios.

Table 1. Deterministic results for ERG's exploratory analysis (incremental)

	Incremental costs	Incremental QALYs	ICER
Company's updated base case	£7,146	0.36	£19,908
Assuming a higher probability of clearance for HSCT patients	£7,161	0.36	£20,012

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 2. Deterministic results (cumulative)

		Incremental costs	Incremental QALYs	ICER
0	Company's updated base case: Assuming CMV increases the probability of GvHD Assuming CVM patients have higher mortality Assuming a higher probability of clearance for HSCT patients	£7,161	0.36	£20,012
1	Assuming CMV increases the probability of GvHD Assuming CVM has no impact on mortality Assuming a higher probability of clearance for HSCT patients	£5,279	0.05	£112,701
2	Assuming CMV does not increase the probability of GvHD Assuming CVM patients have higher mortality Assuming a higher probability of clearance for HSCT patients	£7,365	0.32	£22,912
3	Assuming CMV does not increase the probability of GvHD Assuming CVM has no impact on mortality Assuming a higher probability of clearance for HSCT patients	£5,445	0.02	£315,732
4	Assuming CMV increases the probability of GvHD Assuming CMV patients have twice the probability of death as nCMV patients	£6,045	0.16	£36,930

	Assuming a higher probability of clearance for HSCT patients			
5	Assuming CMV does not increase the probability of GvHD Assuming CMV patients have twice the probability of death as nCMV patients Assuming a higher probability of clearance for HSCT patients	£6,229	0.13	£47,582
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year				