NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Letermovir prophylaxis for cytomegalovirus disease after allogeneic stem cell transplant [ID1153]

The following documents are made available to the consultees and commentators:

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

2. **Appraisal Consultation Document (ACD) comments from Merck Sharp & Dohme**
   - Initial response
   - Updated response

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Anthony Nolan
   - Royal College of Physicians

4. **Comments on the Appraisal Consultation Document from experts:**
   - Karl Peggs, Clinical Expert, nominated by NHS England

   There were no comments received through the NICE website consultation

5. **Addendum of new evidence –** submitted by Merck Sharp & Dohme

6. **Evidence Review Group critique of company response** – prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

7. **Evidence Review Group critique of company response addendum** - prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

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

Letermovir for preventing cytomegalovirus disease after a stem cell transplant [ID1153]

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 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 determination (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, 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	Expert	K Peggs	I read with interest the appraisal consultation document. I was glad to see that a number of the expert recommendations had been incorporated following the meeting at NICE in Manchester. However, I was disappointed by a number of inaccurate statements and with the final outcome, and would raise a number of points, specifically regarding conclusions that were made that I consider being incorrect.	Thank you for your response. Please see the responses to each issue below.
2	Expert	K Peggs	***Generalizability:*** The committee agreed that it was a well-conducted trial but were concerned that the results were not generalizable to UK populations. As an expert in the field I believe this to be wrong. It is stated that the maximum treatment duration was 100 days but that this was 'inappropriate in clinical practice' because some people 'may need longer prophylaxis'. Firstly, it is unclear how they reach this conclusion. The trial was well designed and demonstrated the impact of 100 days prophylaxis, with appropriate collection of data through a washout period. Some patients did experience CMV events during this later phase. However, it is not clear that they would 'need longer prophylaxis'. This is conjecture. Patients may or may not benefit from longer prophylaxis, but there is no data that speaks to this. Furthermore, limitation of duration of therapy in commissioning would prevent this use, which is off license in any case. Whether or not this is the case, I cannot see why this is relevant to UK use as opposed to other countries. The high risk of CMV reactivation with T cell depletion is an early event. Late events associated with graft versus host disease and steroid use. These would be less likely in the UK patient population because of T cell depletion, so this argument is flawed, especially if it is used to speak to lack of generalizability. Much of what follows in terms of argument for lack of generalizability does not suggest a lesser therapeutic impact in the UK population, but rather a larger one. It is therefore disappointing that the argument has been used in this inverted way. Regarding threshold levels of viraemia for intervention – as noted on the day, the clinical	Comment noted. The committee considered the trial results from PN001 were sufficiently generalisable to clinical practice in England. See FAD section 3.4.

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			difference between a level of 150-300 copies, and 400-700 copies is negligible. Less than 3% of patients in our practice who have detectable DNA would clear this spontaneously. The trial absolutely does not 'overestimate CMV infection rate' – this is defined by detection of circulating DNS, not by a threshold. The committee suggests these uncertainties could overestimate or underestimate efficacy - but should be taken into account. All the expert comment suggests if anything an underestimation of efficacy, and this is what should be taken into account rather than a more general stated issue re lack of generalizability and level of uncertainty.	
3	Expert	K Peggs	***Mortality data from HMRN:*** The report states that clinical experts agreed that mortality in year 2 would be 'much higher' than in year 3, more in line with 19% vs company reported 3%. I do not recall the experts being specifically asked re absolute numbers. The ERG highlight that the data in Wingard is old, and contains >40% paediatric data. This is therefore not relevant to current NHS adult transplantation practice. The way we perform transplants has evolved significantly over the past decade, and I do not think the Wingard data is relevant.	Comment noted. The committee considered that mortality data from Wingard et al was less relevant to clinical practice than that from HMRN. See FAD section 3.11.
4	Expert	K Peggs	***Duration of therapy:*** This is particularly difficult, as I suspect it has a significant impact on cost utility, and anything beyond the trial data is guess work. If prophylaxis is started at day 0, then the patients who would reactivate within the first 11 days will be included. In the trial a number were excluded because they were deemed screen failures if they became PCR positive prior to planned initiation of drug. Early reactivators may be at higher risk of failing prophylactic therapy – in which case treatment duration would be curtailed. A simplistic approach of adding 72.1 to 10.9 = 83 likely overestimates real world mean duration. I would suggest this is reduced to somewhere between 72 and 83. Finally, even if these issues remain unaltered, it appears that the uncertainty re the true ICER cost puts it in a range of £20000-£30200. I would assume that the methods guide referring to decision where the most plausible ICER was above £20000 but uncertain is largely to deal with larger variances where uncertainty puts the possible true ICER significantly higher than the £30000 threshold. Using this method guide as an argument	Comment noted. The committee acknowledged that real-world estimates of treatment duration were not available. However, following input from the clinical experts it agreed that it would consider a range of treatment duration between 72.1 and 83 days from PN001. See FAD section 3.14.

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			against commissioning a drug where the uncertainty barely stretches above £30000 at all seems particularly inappropriate to me, and will result in many patients failing to receive a truly transformative medicine which is already available in the USA,, Germany, and Scotland.	
5	Professional organisation	Royal College of Physicians	The RCP is grateful for the opportunity to comment on this ACD. We have liaised with the Intercollegiate Committee on Haematology and would like to make the following comments	Thank you for your response. Please see the responses to each issue below.
6	Professional organisation	Royal College of Physicians/ Anthony Nolan	We are concerned that too much emphasis is being placed on mortality in this submission (and the consequent decision made by the committee); mortality was only an exploratory endpoint in the company's trial. Cytomegalovirus (CMV) reactivation itself is only linked to mortality if it is able to progress to CMV disease. However, this has become largely uncommon thanks to pre-emptive therapies. Therefore, letermovir is unlikely to reduce mortality, and consequently distort the true QALY.	Comment noted. The committee heard from the clinical experts that a mortality benefit with letermovir is plausible. See FAD section 3.6.
7	Professional organisation	Royal College of Physicians/ Anthony Nolan	We are concerned that the significant benefit in patient quality of life is not adequately taken into account.	Comment noted. The committee considered that not all health-related quality of life benefits were captured in the trial and took account of this in its decision making. See FAD sections 3.8 and 3.19.
8	Professional organisation	Royal College of Physicians/ Anthony Nolan	The ACD acknowledges that trial PN001 did not prove that there was a health-related quality of life compared to placebo. However, this could not be demonstrated by the trial, as the quality of life diminishments described by patients are not a result of the CMV reactivation, but of the pre-emptive therapies which are used to stop progression to CMV disease.	Comment noted. The committee considered that not all health-related quality of life benefits were captured in the trial and took account

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				of this in its decision making. See FAD sections 3.8 and 3.19.
9	Professional organisation	Royal College of Physicians/ Anthony Nolan	As well as causing severe physical side effects, pre-emptive therapies such as valganciclovir are cited on the UK's electronic Medicines Compendium as causing neutropenia. For patients after transplant, neutropenia increases the chance of potentially fatal infections. Prophylaxis (letermovir) would reduce the need for pre-emptive therapy and lower this risk.	Comment noted. The committee recognised that there was an unmet need for an effective and tolerable treatment. See FAD section 3.2.
10	Professional organisation	Royal College of Physicians/ Anthony Nolan	Indeed, section 3.2 of the ACD reads that the committee concludes that "an effective treatment that specifically acts to prevent CMV reactivation would benefit people who are seropositive for CMV who have had an allogeneic HSCT", whilst the ACD also accepts that "letermovir is effective in reducing CMV infection", "reduces the need for pre-emptive therapy", and "has a better safety profile than pre-emptive therapy".	Comment noted. No action required.
11	Professional organisation	Royal College of Physicians/ Anthony Nolan	Given that this has been recognised, we believe that patients should have access to letermovir in order to prevent the reduced quality of life associated with pre-emptive therapy. Stem cell transplant is one of the most difficult pathways for a patient, and anything which can be done to reduce the burden would be greatly beneficial to patients.	Comment noted. The committee recognised the unmet need for an effective and tolerable treatment. See FAD section 3.2.
12	Professional organisation	Anthony Nolan	Although clinically effective, patients have told us that the side effects of pre-emptive therapy significantly lower their quality of life (see Anthony Nolan original submission). Although the psychological effect is taken into account, the physical side effects are not mentioned.	Comment noted. The committee understood that pre-emptive therapies for CMV can have serious side effects. See FAD sections 3.1 and 3.2.
13	Company	MSD (July 2018 response)	The title of the ACD "*Letermovir for preventing cytomegalovirus disease after a stem cell transplant*" is not currently aligned to the submission made to NICE (ID1153). At the time of submission, ID1153 was titled "*Letermovir for the prophylaxis of cytomegalovirus*	Comment noted. Please note that the title of the ACD has

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			reactivation or disease in people with seropositive-cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant [ID1153]"; however, MSD has previously proposed that this title should be amended to "*Letermovir for the prophylaxis of cytomegalovirus reactivation* ***and*** *disease in people with seropositive-cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant [ID1153]*", in order to be consistent with the marketing authorisation.	been shortened to be in line with NICE style. Details of the appraisal population are specified in the recommendation section. See FAD section 1.
14	Company	MSD (July 2018 response)	On Page 8 of the ACD document in line five, the ACD states "*In the trial, a viral load threshold between 150 and 300 copies/ml was used"*. In PN001 the viral load threshold of 150-300 copies/ml was not a stipulation but was merely guidance based on the risk groups characterised in the study as well as consideration of standard practice at the Fred-Hutchinson Cancer Research Centre (FHCRC). It should also be noted that the viral threshold suggested for initiating pre-emptive therapy in low-risk patients may be as high as 1,000 copies/ml according to the assay used by the FHCRC, which corresponds to a level of ~300 copies/ml using the Roche CAP/CTM assay. The Roche CAP/CTM assay was used in PN001.	Comment noted. The committee recognised that there is variation in the viral load threshold used to define a clinically significant CMV infection and subsequently initiate pre-emptive therapy. See FAD section 3.4.
15	Company	MSD (July 2018 response)	On Page 18, for the second bullet point the ACD states "*The committee considered that the company's preferred approach in the efficacy analyses to account for missing data was the most plausible approach (both the company and the ERG's base-case used the 'data as observed' approach). It acknowledged that this would increase the ICER from the ERG's preferred analysis from £27,536 to £30,179 per QALY gained".* MSD would like to clarify that when applying the data as observed (DAO) approach for missing data, the ICER remained at the threshold of £27,536. Only when applying the non-completer equals failure (NC=F) missing data approach did the ICER increase from the ERG's preferred base-case of £27,536 to £30,179. The NC=F missing data approach was neither MSD's nor the ERG's base-case approach, as MSD felt the DAO missing data approach best reflected the likely magnitude of health care resource use.	Comment noted. The FAD has been updated to reflect the committee's considerations of the company's and ERG's updated analyses. Reference to the sensitivity of the ICER to different approaches to handling missing data has now been omitted.
16	Company	MSD (July 2018	MSD has identified a further error in the ERG model. The administration costs of oral pre-emptive therapy had been applied incorrectly to ganciclovir (an IV-administered treatment)	Comment noted. The committee

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		response)	instead of valganciclovir (an orally-administered treatment). In the model provided, and base-case results, MSD have therefore amended the oral pre-emptive therapy administration costs to apply to valganciclovir; this marginally reduces the ICER.	considered these analyses in making its recommendation.
17	Company	MSD (July 2018 response)	***Mortality data*** MSD acknowledges the Committee's comments around the uncertainty associated with the mortality benefit demonstrated in the pivotal PhIII trial for letermovir (PN001). MSD do, however, reiterate that the primary aim of this study was to demonstrate prevention of reactivation of CMV viraemia and disease in patients at high risk of CMV reactivation. The positive trial for letermovir in this setting and patient population was preceded by a number of PhIII trial failures with other anti-CMV drug candidates. This warranted consideration of alternative endpoints to CMV disease and related mortality. Mortality was therefore an exploratory endpoint for which the study was not designed or powered to demonstrate a benefit. The rationale for this endpoint is highlighted below: • Currently, with most centres using CMV preventive strategies including pre-emptive therapy, the overall incidence of CMV disease in HSCT patients has declined to around 5% in the first 3 months post-transplant, from 20-30% prior to the routine use of preventive measures. Accordingly, sample sizes required to show efficacy of novel anti-CMV drugs for antiviral prophylaxis using the incidence of CMV disease alone would be high and unrealistic in the transplantation setting. Marty and Boeckh (2011) reported that to reduce CMV disease at day 100 from 2.5% to 1.25%, approximately 1900 patients would be needed. Yet, proper and systematic use of rescue anti-CMV pre-emptive therapy on patients in the study who develop CMV infection is likely to eliminate any difference in CMV disease occurrence[2]. This approach has been further endorsed by Snydman (2011) stating that sample sizes necessary to show even a 50% reduction in disease makes studies in stem-cell transplantation extremely difficult from a drug development standpoint and in the present era of effective CMV disease prevention, to allow patients to proceed to a CMV disease endpoint is unethical[3]. • It was also suggested that virologic endpoints such as the CMV viral load, whether or not they are linked to the need for pre-emptive therapy, should be strongly considered in future efficacy trials. Thus, the primary endpoint of PN001 in addition to CMV disease also included the incidence of anti-CMV pre-emptive therapy initiation	Comment noted. The committee understood that mortality was not a primary outcome of PN001 and acknowledged that ad hoc analyses from the trial could suggest that there is a mortality benefit with letermovir. It also noted that the magnitude of any benefit was uncertain because of limitations with the trial data. See FAD section 3.6.

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			based on detection of CMV viraemia and the clinical condition of the patient. • As detection of CMV in plasma or blood is associated with an increased risk of CMV disease, CMV viral DNA as a measure of CMV infection is already used routinely in clinical practice to initiate and monitor pre-emptive therapy. Patients with high viral loads or with cumulative high viral loads are at an increased risk of developing disease than those with lower viral loads. It must also be considered that letermovir was granted orphan drug status not only on the basis of the low numbers in the population at risk as per EMA and FDA definitions, but also on the basis of the serious unmet need in this patient population due to severe limitations of existing therapies as well as a demonstrable potential for letermovir to delay the use of pre-emptive therapy[4]. PN001 suggests that CMV reactivation is associated with increased levels of mortality with current standard of care (SoC). As displayed in Table 1 below, after adjusting for age and treating clinically-significant CMV reactivation (cs-CMV reactivation) as a time-varying variable, the hazard ratio (HR) (95% CI) of mortality for cs-CMV reactivation versus no cs-CMV reactivation in the placebo group (SoC) through week 24 is [redacted] This analysis informs that cs-CMV reactivation increases the hazard of mortality through week 24 by [redacted] times for SoC. Notably, the HR (95% CI) of mortality with respect to cs-CMV reactivation versus no cs-CMV reactivation in the letermovir group is [redacted] with nominal [redacted] after adjusting for baseline age. This demonstrates that cs-CMV reactivation was not associated with increasing hazard of mortality in the letermovir group. The HR was reduced by [redacted] with the intervention of letermovir, indicating that it is an effect-modifier for cs-CMV reactivation effect on mortality[5].	

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Table 1: All-cause mortality through week 24 post-transplant among patients with or without cs-CMV reactivation through week 24 post-transplant (FAS population) [5]

	Letermovir (N=325)			Placebo (N=170)		
	n/N (%)	HR† (95% CI)	P-value	n/N (%)	HR† (95% CI)	P-value
CS-CMVi (time-varying)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No CS-CMVi (time-varying)	[redacted]			[redacted]		

† HR is adjusted for baseline age.

Note: Death includes all-cause mortality through Week 24 post-transplant. Week 24 post-transplant is defined as 182 days post-transplant (2 weeks post Week 24 visit). Any death <=182 days post-transplant was counted as death, and any death >182 days post-transplant was counted as alive at Week 24 post-transplant. Clinically significant CMV infection is defined through Week 24 post-transplant. Denominator in the first row only includes subjects with Clinically significant CMV infection and does not include subjects who discontinued early and had missing data.

Every subject is counted a single time for each applicable row and column.

n (%) = Number (percent) of patients in each sub-category.

CS-CMVi = Clinically Significant CMV infection

In response to the identified difficulties of CMV disease/mortality and using these as end points in clinical studies, investigators sought to define a suitable surrogate endpoint for CMV disease using viraemia (a principle that has been universally accepted in the HIV therapy area). Green at al (2016) demonstrated that even when adjusted for the use of pre-emptive therapy, CMV viraemia was indeed a suitable surrogate endpoint for mortality as CMV viraemia after allogeneic haematopoietic stem cell transplantation (HSCT) is associated with overall and non-relapse mortality, independent of pre-emptive therapy to prevent CMV and end-organ disease and other relevant risk factors. A CMV viral load of 250

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			IU/mL or greater was associated with increased risk of early (day 0–60 post-transplantation) death (adjusted HR 19·8, 95% CI 9·6–41·1)[6]. In addition to the data from Green highlighting that viraemia is a suitable surrogate end point through negative post-transplant outcomes, evidence from numerous other studies suggests that CMV reactivation is associated with increased mortality, independent of CMV disease, which can manifest as a decrease in non-relapse mortality (NRM) and/or increased overall survival (Table 2).	

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Table 2: CMV and relapse, non-relapse mortality and overall survival outcomes [7]

Table 1
CMV and relapse, NRM, and OS outcomes.

Reference (author, yr)	No. subjects	Primary disease	CMV status	Relapse outcomes	Survival outcomes
Teira, 2016	9469	AML	Reactivation	–	27% relative decrease OS ($P < 0.0001$)
		ALL	Reactivation	–	95% relative increase NRM ($P < 0.0001$)
					46% relative decrease OS ($P < 0.0001$)
		CML	Reactivation	–	49% relative decrease OS ($P = 0.0005$)
		MDS	Reactivation	–	61% relative increase NRM ($P = 0.0002$)
					31% relative decrease OS ($P = 0.003$)
		AML	Seropositive	24% increase ($P = 0.007$) at 6mos	–
Inagaki, 2016	143	Ped. AML Ped. ALL	Reactivation	14.3% absolute decrease ($P = 0.041$)	22.6% absolute increase NRM ($P < 0.01$)
Takenaka, 2015	3539	AML	Reactivation	23% relative decrease ($P = 0.04$)	60% relative increase NRM ($P < 0.01$)
				7.2% absolute decrease ($P < 0.01$)	37% relative decrease OS ($P < 0.01$)
					11.1% absolute decrease OS ($P < 0.01$)
		ALL	Reactivation	Decreased (NS)	74% relative increase NRM ($P = 0.02$)
					8.2% absolute decrease OS($P < 0.01$)
		CML	Reactivation	Increased (NS)	Increased NRM (NS)
					8.2% absolute decrease OS ($P < 0.01$)
		MDS	Reactivation	6.9% absolute decrease ($P < 0.05$)	Increased NRM (NS)
					Decreased OS (NS)
		Combined	Reactivation	18% relative decrease ($P = 0.01$)	66% relative increase NRM ($P < 0.01$)
				5.8% absolute decrease ($P < 0.01$)	30% relative decrease OS ($P < 0.01$)
					8.8% absolute decrease OS ($P < 0.01$)
		Combined	Seropositive	65% relative increase ($P < 0.01$)	34% relative decrease NRM ($P = 0.02$)
Manjappa, 2014	264	AML	Reactivation	7.6% absolute decrease ($P = 0.03$)	Increased NRM (NS)
				35.8% relative decrease ($P = 0.0242$)	Increased OS (NS)
		MAC	Reactivation	11.4% absolute decrease ($P = 0.01$)	Increased NRM (NS)
				47.5% relative decrease ($P = 0.0061$)	Decreased OS (NS)
		RIC	Reactivation	NS	NS
Green, 2013	2342	AML	Reactivation	44% relative decrease in 100d CIR ($P = 0.02$)	46% relative increase NRM ($P = 0.02$)
		ALL	Reactivation	Decreased (NS)	Increased NRM (NS)
					Increased OS (NS)
		CML	Reactivation	Decreased (NS)	68% relative increase NRM ($P = 0.01$)
					51% relative decrease OS ($P = 0.02$)
		MDS	Reactivation	Decreased (NS)	Increased NRM (NS)
					Increased OS (NS)
		Lymphoma	Reactivation	Decreased (NS)	Increased NRM (NS)
					Increased OS (NS)
		Combined	Reactivation	32% relative decrease ($P < 0.001$)	31% relative increase NRM ($P = 0.02$)
					Decreased OS (NS)
		Combined	Seropositive	31% relative decrease ($P = 0.004$)	–
Elmaagacli, 2011	266	AML	Seropositive	18% absolute decrease ($P < 0.0001$)	24% increase OS ($P < 0.005$)
				160% relative decrease ($P < 0.0001$)	
			Reactivation	33% absolute decrease ($P < 0.0001$)	22% absolute increase OS ($P < 0.002$)
				460% relative decrease ($P < 0.0001$)	
Behrendt, 2009	140	Ped. AML, ALL, MDS	Seropositive	315% decrease ($P = 0.003$)	–

Abbreviations: ALL = acute lymphoblastic leukemia AML = acute myelogenous leukemia, CIR = cumulative incidence of relapse, CML = chronic myelogenous leukemia, MA = myeloablative, MDS = myelodysplastic syndrome, mos = months, NRM = non-relapse mortality, NS = not significant, Ped = pediatric, RIC = reduced intensity conditioning, OS = overall survival, yr = year.

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			Although pre-emptive management strategies have reduced the incidence of CMV disease, this solution remains unsatisfactory, both because CMV disease still occurs in some patients, and because currently-utilised pre-emptive therapies may contribute directly to morbidity in HSCT recipients. In addition to the effects of CMV disease and side effects of anti-CMV therapy, CMV infection continues to influence a broad range of transplant outcomes, particularly the incidence of NRM, with which CMV has a clear relationship[7] . Given the limitations described above and the fact that letermovir met its pre-defined primary endpoint, this coupled with the complex and not fully understood effects of CMV in this setting, lends further credence to a fully plausible benefit of letermovir in reducing mortality due to prevention of CMV reactivation.	
18	Company	MSD (July 2018 response)	***Adverse event profile similar to pre-emptive therapy*** As noted in the ACD "*the ERG commented that the adverse events results were difficult to interpret because of the underlying conditions and treatments as well as toxicity associated with various pre-emptive therapy regimens".* In PN001, patients were randomised to letermovir or placebo at week 0. Once a threshold of CMV viral DNA is reached, pre-emptive therapy is administered irrespective of the treatment allocation in the trial. MSD would like to clarify that adverse events in PN001 were collected relative to the allocated study therapy, i.e. letermovir or placebo, and not when patients had met the primary endpoint and were receiving pre-emptive therapy. Therefore, the safety profile of letermovir is similar to placebo (no letermovir).	Comment noted. The committee agreed that the safety profile of letermovir was acceptable. See FAD section 3.7.
19	Company	MSD (July 2018 response)	***Utility values and collection of utility endpoints*** The ACD states that the "*Committee agreed that there could plausibly be a health-related quality-of-life benefit associated with preventing CMV reactivation"*. Despite the Committee acknowledging that the letermovir is effective in reducing CMV reactivation and the need for pre-emptive therapy, the ACD goes on to state that *"the health-related quality-of-life results of PN001 are therefore difficult to interpret"*.	Comment noted. The committee acknowledged that in PN001 assessment of health-related quality of life was made before starting pre-emptive therapy,

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			The ACD states that "*at randomisation, the mean values for EQ-5D-3L and FACT-BMT scores represent a mixture of those who have had CMV reactivation and started pre-emptive therapy and those who have not. The direct effect of letermovir on health-related quality of life was therefore confounded".* MSD would like to provide clarification around this point. During the trial the health-related quality of life (HRQoL) assessments were measured at baseline (i.e. week 0), week 14, week 24 and week 48. HRQoL was also measured at the study discontinuation visit, i.e. when a patient met the primary endpoint of cs-CMV infection. The HRQoL assessment was made prior to a patient initiating pre-emptive therapy, and therefore the expected disutility associated with the (as noted in the ACD) "*severe side effects"* of pre-emptive therapy, was not reflected. Please also note that HRQoL was a pre-defined exploratory endpoint and was not powered to detect statistically significant differences in QoL scores between the treatment groups.	therefore the disutility associated with toxicities from these therapies was not captured. It took this into account when interpreting its preferred ICER. See FAD sections 3.8 and 3.19.
20	Company	MSD (July 2018 response)	***Treatment duration*** As noted in the ACD, in the ERG's base-case "*the mean duration of treatment was assumed to be 83 days. This was based on the duration of therapy in the full analysis set population (72.1 days) plus an additional 10.9 days from the delayed start of prophylaxis".* As a point of clarification, the mean duration of treatment applied from PN001 of 72.1 days for the FAS population includes patients who delayed initiating prophylaxis, and to include an additional 10.9 days would risk an element of double counting. As such, it would be inappropriate to use 83 days as the treatment duration. Additionally, the model does not take into account the delay in starting letermovir prophylaxis as patients enter the model at the time they initiate either letermovir or placebo (i.e. at randomisation). As such, increasing the duration by 10.9 days would not be reflective of what is expected in current practice, based on the clinical trial data. MSD acknowledges that the clinical experts stated "*the duration treatment is likely to be longer than 69.4 days*" and are therefore including an extended treatment duration for letermovir of 72.1 days to reflect the FAS population from PN001.	Comment noted. The committee acknowledged that real-world estimates of treatment duration were not available. However, following input from the clinical experts it agreed that it would consider a range of treatment duration between 72.1 and 83 days from PN001. See FAD section 3.14.
21	Company	MSD (July 2018 response)	***The use of the 24 week data endpoints versus the 48 week endpoints*** The Committee have deemed that the base-case for the cost effectiveness modelling	Comment noted. The committee noted

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
			provided was "*not appropriate for decision-making because of concerns about…the use of 24-week data over 48-week data*", which was supported by the ERG who questioned the relevance of 24-week data "*when 48-week data were available for most outcomes"*. MSD disagrees with this approach and considers the 24-week data to be more appropriate than the 48-week data for the base-case position. Below, MSD UK questions the reliability and appropriateness of applying the 48-week data to the base-case as considered by the ERG and Committee. The summary of our position is as follows: • The indication of interest in the submission and the primary endpoint of the PN001, cs-CMV reactivation, was collected up until the week 24 timepoint, and was not collected during the safety follow-up period of the study (weeks 24-48). The ACD states "*letermovir statistically significantly reduced the rate of clinically significantly CMV reactivation at week 24 compared with placebo*" providing support that the Committee accepts the evidence that letermovir meets the primary endpoint of PN001. • Without observed data it would be difficult to predict the rate of cs-CMV infection to the extended time point of week 48. The rate of change of cs-CMV infection would be expected to decline between week 24 and week 48 timepoints as the immune system strengthens; however without observed data this would be difficult to infer. • Letermovir prophylaxis was administered until the week 14 time period, with follow-up until week 24. This is supported by the British Society of Haematology guidelines which state "*Monitoring of CMV load should be undertaken at least weekly for the first 3 months post-HSCT*" [8]. • To fully investigate the long-term effect of letermovir a further follow-up phase was agreed between regulatory bodies (EMA and FDA) and MSD, to week 48 to investigate the long-term safety of letermovir. • Using the week 48 data endpoints would not be appropriate to assess the effect of letermovir prophylaxis, as prophylactic treatment would have been stopped for approximately 34 weeks.	these justifications for using 24 week data but considered that it preferred to use the 48 week data because it was available and more complete. See FAD section 3.10.

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
			• For the reasons above, MSD does not agree that the analyses on week 48 data endpoints should be the basis of the Committee's decision.	
22	Company	MSD (July 2018 response)	***Additional analyses (updated base-case)*** The company provided additional analyses including an updated base-case in their updated response to the ACD. These analyses are not reproduced here, please see the company's ACD response document for further detail.	Comment noted. The committee considered the company's updated base-case analysis in making its recommendation. See FAD section 3.17.
22	Company	MSD (January 2019 response)	***Updated patient access scheme*** As stated in the ACD "*the [cost-effectiveness] estimates are affected by small changes in letermovir's mortality benefit, the magnitude of which is uncertain. Because of this letermovir cannot be recommended*". MSD acknowledges the Committee's comments around the uncertainty associated with the mortality benefit demonstrated in the pivotal PhIII trial for letermovir (PN001). MSD do, however, reiterate that the primary aim of this study was to demonstrate prevention of reactivation of CMV viraemia and disease in patients at high risk of CMV reactivation. Based on the draft negative recommendation in the ACD and uncertainty regarding the true ICER, MSD have applied to NHS for an extension in the patient access scheme, increasing the discount to [redacted]%. This has reduced the price of letermovir for each formulation to the following: - 240mg oral letermovir o List price: £132.97 o Discounted price: £[redacted] - 480mg oral letermovir o List price: £[redacted] o Discounted price: £[redacted] - 240mg IV infusion letermovir	Comment noted. The committee took the updated patient access scheme into consideration when making its recommendation. See FAD sections 3.17, 3.18 and 3,19.

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
			o List price: £[redacted] o Discounted price: £[redacted] - 480mg IV infusion letermovir o List price: £[redacted] o Discounted price: £[redacted]	
23	Company	MSD (January 2019 response)	***Treatment duration*** As noted in the ACD, in the ERG's base-case "*the mean duration of treatment was assumed to be 83 days. This was based on the duration of therapy in the full analysis set population (72.1 days) plus an additional 10.9 days from the delayed start of prophylaxis".* As a point of clarification, the mean duration of treatment applied from PN001 of 72.1 days for the FAS population includes patients who delayed initiating prophylaxis, and to include an additional 10.9 days would risk an element of double counting. As such, it would be inappropriate to use 83 days as the treatment duration. Additionally, the model does not take into account the delay in starting letermovir prophylaxis as patients enter the model at the time they initiate either letermovir or placebo (i.e. at randomisation). As such, increasing the duration by 10.9 days would not be reflective of what is expected in current practice, based on the clinical trial data. MSD acknowledges that the clinical experts stated "*the duration treatment is likely to be longer than 69.4 days*" and are therefore including an extended treatment duration for letermovir of 72.1 days to reflect the FAS population from PN001. When changing the duration of therapy to 72.1 days, and including the updated PAS of [redacted]%, the ICER is reduced from the ERG base-case to £22,338.	Comment noted. Please see the NICE response to comments 4 and 23.
24	Company	MSD (January 2019 response)	***The use of the 24 week data endpoints versus the 48 week endpoints*** The Committee have deemed that the base-case for the cost effectiveness modelling provided was "*not appropriate for decision-making because of concerns about…the use of 24-week data over 48-week data*", which was supported by the ERG who questioned the relevance of 24-week data "*when 48-week data were available for most outcomes"*. MSD disagrees with this approach and considers the 24-week data to be more appropriate than the 48-week data for the base-case position.	Comment noted. Please see the NICE response to comment 21.

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
			Below, MSD UK questions the reliability and appropriateness of applying the 48-week data to the base-case as considered by the ERG and Committee. The summary of our position is as follows: • The indication of interest in the submission and the primary endpoint of the PN001, cs-CMV reactivation, was collected up until the week 24 timepoint, and was not collected during the safety follow-up period of the study (weeks 24-48). The ACD states "*letermovir statistically significantly reduced the rate of clinically significantly CMV reactivation at week 24 compared with placebo*" providing support that the Committee accepts the evidence that letermovir meets the primary endpoint of PN001. • Without observed data it would be difficult to predict the rate of cs-CMV infection to the extended time point of week 48. The rate of change of cs-CMV infection would be expected to decline between week 24 and week 48 timepoints as the immune system strengthens; however, without observed data this would be difficult to infer. • Letermovir prophylaxis was administered until the week 14 time period, with follow-up until week 24. This is supported by the British Society of Haematology guidelines which state "*Monitoring of CMV load should be undertaken at least weekly for the first 3 months post-HSCT*" [(2)]. • To fully investigate the long-term effect of letermovir a further follow-up phase was agreed between regulatory bodies (EMA and FDA) and MSD, to week 48 to investigate the long-term safety of letermovir. • Using the week 48 data endpoints would not be appropriate to assess the effect of letermovir prophylaxis, as prophylactic treatment would have been stopped for approximately 34 weeks. For the reasons above, MSD does not agree that the analyses on week 48 data endpoints should be the basis of the Committee's decision. When applying the use of the 24-week data end points to inform the analyses, and including the updated PAS of [redacted]%, the ERG base case ICER is reduced to £20,733 (days of	

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
			letermovir therapy remains as ERG base-case).	
25	Company	MSD (January 2019 response)	***Updated base-case*** The company provided additional analyses including an updated base-case in their updated response to the ACD. These analyses are not reproduced here, please see the company's "ACD response updated" document for further detail.	Comment noted. The committee considered the company's updated base-case analysis in making its recommendation. See FAD section 3.17.

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25th July 2018

Letermovir for treating cytomegalovirus reactivation and disease in CMV-seropositive recipients of a allogeneic haematopoietic stem cell transplant [ID1153] – Response to Appraisal Consultation Document (ACD)

Dear Kate,

Having read the ACD, MSD UK was disappointed with the provisional negative recommendation, given our confidence that letermovir is a cost-effective option for treating CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant (HSCT).

Based on the content of the ACD, the key drivers underpinning the draft negative recommendation are uncertainty/scepticism around the following defining points, which result in a disparity between our manufacturer's base-case and the ERG's base-case:

- Mortality data
- Adverse event profile similar to pre-emptive therapy
- Utility values and collection of utility endpoints
- Treatment duration
- The use of the 24 week data endpoints versus the 48 week endpoints
- Additional analyses provided (new base-case)

Our full response is provided below and firstly summarises some key points in the ACD which we believe support the approach taken by MSD in our submission, and highlight the value and clinical relevance of letermovir as a valid and worthy prophylactic option for the patient population covered by this appraisal. Our response then addresses in turn, each of the above mentioned key drivers underpinning the draft negative recommendation.

MSD UK has answered the Committee's concerns to the best of our ability concerning each of the key drivers identified above. In MSD UK's opinion, the primary issues influencing the variability in the ICER for letermovir are the use of week 48 data instead of the week 24 data that represents the primary endpoint of PN001 and the conclusion of the main study period; uncertainty around the magnitude of the mortality benefit seen with letermovir; and the treatment duration of letermovir.

Should you have any questions about the content, please do contact me.

Kind regards,
Chris O'Regan

Executive Director
Head of HTA & OR

Key points mentioned in the ACD that support the approach taken by MSD in the submission of letermovir for prophylaxis of CMV-reactivation and disease in adult CMV-seropositive recipients of an allogeneic HSCT [1]:

- The ACD states that "*clinical trial evidence shows that letermovir is effective in reducing CMV infection. It also reduces the need for pre-emptive therapy".*

- The Committee agree that *"if CMV levels rise, treatment with …pre-emptive therapy is started to prevent disease but this can cause severe side effects".*

- The clinical and patient experts highlighted that "*letermovir reduces the reactivation rates and the need for toxic pre-emptive therapy*". Additionally, the Committee concluded that "*CMV reactivation can have a substantial psychological effect on patients and their families".*

- The Committee stated that PN001 *"was a well conducted trial"* and that "*the generalisability of the PN001 trial results to clinical practice in England made interpreting the results challenging but the committee acknowledged that these factors could both overestimate and underestimate the efficacy of letermovir".*

- The Committee *"concluded that although the model is oversimplified, it was appropriate for decision making*".

- The Committee "*agreed that the company's assumption about intravenous letermovir use (5%) was more appropriate than the ERG's (27%)".*

- The ACD confirms that the Committee and Evidence-Review Group (ERG) *"considered that the company's preferred approach to account for missing data was the most plausible".*

Points of inaccuracy

- The title of the ACD "*Letermovir for preventing cytomegalovirus disease after a stem cell transplant*" is not currently aligned to the submission made to NICE (ID1153). At the time of submission, ID1153 was titled "*Letermovir for the prophylaxis of cytomegalovirus reactivation or disease in people with seropositive-cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant [ID1153]*"; however, MSD has previously proposed that this title should be amended to "*Letermovir for the prophylaxis of cytomegalovirus reactivation* ***and*** *disease in people with seropositive-cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant [ID1153]*", in order to be consistent with the marketing authorisation.

- On Page 8 of the ACD document in line five, the ACD states "*In the trial, a viral load threshold between 150 and 300 copies/ml was used"*. In PN001 the viral load threshold of 150-300 copies/ml was not a stipulation but was merely guidance based on the risk groups characterised in the study as well as consideration of standard practice at the Fred-Hutchinson Cancer Research Centre (FHCRC). It should also be noted that the viral threshold suggested for initiating pre-emptive therapy in low-risk patients may be as high as 1,000 copies/ml according to the assay used by the FHCRC, which corresponds to a level of ~300 copies/ml using the Roche CAP/CTM assay. The Roche CAP/CTM assay was used in PN001.

- On Page 18, for the second bullet point the ACD states "*The committee considered that the company's preferred approach in the efficacy analyses to account for missing data was the most plausible approach (both the company and the ERG's base-case used the 'data as observed' approach). It acknowledged that this would increase the ICER from the ERG's preferred analysis from £27,536 to £30,179 per QALY gained".* MSD would like to clarify that when applying the data as observed (DAO) approach for missing data, the ICER remained at the threshold of £27,536. Only when applying the non-completer equals failure (NC=F) missing data approach did the ICER increase from the ERG's preferred base-case of £27,536 to £30,179. The NC=F missing data approach was neither MSD's nor the ERG's base-case approach, as MSD felt the DAO missing data approach best reflected the likely magnitude of health care resource use.

- MSD has identified a further error in the ERG model. The administration costs of oral pre-emptive therapy had been applied incorrectly to ganciclovir (an IV-administered treatment) instead of valganciclovir (an orally-administered treatment). In the model provided, and base-case results, MSD have therefore amended the oral pre-emptive therapy administration costs to apply to valganciclovir; this marginally reduces.

MSD Response to key drivers underpinning the draft negative recommendation in the ACD:

- **Mortality data**

MSD acknowledges the Committee's comments around the uncertainty associated with the mortality benefit demonstrated in the pivotal PhIII trial for letermovir (PN001). MSD do, however, reiterate that the primary aim of this study was to demonstrate prevention of reactivation of CMV viraemia and disease in patients at high risk of CMV reactivation.

The positive trial for letermovir in this setting and patient population was preceded by a number of PhIII trial failures with other anti-CMV drug candidates. This warranted consideration of alternative endpoints to CMV disease and related mortality. Mortality was therefore an exploratory endpoint for which the study was not designed or powered to demonstrate a benefit. The rationale for this endpoint is highlighted below:

- Currently, with most centres using CMV preventive strategies including pre-emptive therapy, the overall incidence of CMV disease in HSCT patients has declined to around 5% in the first 3 months post-transplant, from 20-30% prior to the routine use of preventive measures. Accordingly, sample sizes required to show efficacy of novel anti-CMV drugs for antiviral prophylaxis using the incidence of CMV disease alone would be high and unrealistic in the transplantation setting. Marty and Boeckh (2011) reported that to reduce CMV disease at day 100 from 2.5% to 1.25%, approximately 1900 patients would be needed. Yet, proper and systematic use of rescue anti-CMV pre-emptive therapy on patients in the study who develop CMV infection is likely to eliminate any difference in CMV disease occurrence[2]. This approach has been further endorsed by Snydman (2011) stating that sample sizes necessary to show even a 50% reduction in disease makes studies in stem-cell transplantation extremely difficult from a drug development standpoint and in the present era of effective CMV disease prevention, to allow patients to proceed to a CMV disease endpoint is unethical[3].
- It was also suggested that virologic endpoints such as the CMV viral load, whether or not they are linked to the need for pre-emptive therapy, should be strongly considered in future efficacy trials. Thus, the primary endpoint of PN001 in addition to CMV disease also included the incidence of anti-CMV pre-emptive therapy initiation based on detection of CMV viraemia and the clinical condition of the patient.
- As detection of CMV in plasma or blood is associated with an increased risk of CMV disease, CMV viral DNA as a measure of CMV infection is already used routinely in clinical practice to initiate and monitor pre-emptive therapy. Patients with high viral loads or with cumulative high viral loads are at an increased risk of developing disease than those with lower viral loads.

It must also be considered that letermovir was granted orphan drug status not only on the basis of the low numbers in the population at risk as per EMA and FDA definitions, but also on the basis of the serious unmet need in this patient population due to severe limitations of existing therapies as well as a demonstrable potential for letermovir to delay the use of pre-emptive therapy[4].

PN001 suggests that CMV reactivation is associated with increased levels of mortality with current standard of care (SoC). As displayed in Table 1 below, after adjusting for age and treating clinically-significant CMV reactivation (cs-CMV reactivation) as a time-varying variable, the hazard ratio (HR) (95% CI) of mortality for cs-CMV reactivation versus no cs-CMV reactivation in the placebo group (SoC) through week 24 is [redacted]. This analysis informs that cs-CMV reactivation increases the hazard of mortality through week 24 by [redacted] times for SoC.

Notably, the HR (95% CI) of mortality with respect to cs-CMV reactivation versus no cs-CMV reactivation in the letermovir group is [redacted] with nominal [redacted] iated with increasing hazard of mortality in the letermovir group. The HR was reduced by [redacted] with the intervention of letermovir, indicating that it is an effect-modifier for cs-CMV reactivation effect on mortality[5].

Table 1: All-cause mortality through week 24 post-transplant among patients with or without cs-CMV reactivation through week 24 post-transplant (FAS population) [5]

	Letermovir (N=325)			Placebo (N=170)		
	n/N (%)	HR† (95% CI)	P-value	n/N (%)	HR† (95% CI)	P-value
CS-CMVi (time-varying)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No CS-CMVi (time-varying)	[redacted]			[redacted]		

† HR is adjusted for baseline age.

Note: Death includes all-cause mortality through Week 24 post-transplant. Week 24 post-transplant is defined as 182 days post-transplant (2 weeks post Week 24 visit). Any death <=182 days post-transplant was counted as death, and any death >182 days post-transplant was counted as alive at Week 24 post-transplant. Clinically significant CMV infection is defined through Week 24 post-transplant. Denominator in the first row only includes subjects with Clinically significant CMV infection and does not include subjects who discontinued early and had missing data.

Every subject is counted a single time for each applicable row and column.

n (%) = Number (percent) of patients in each sub-category.

CS-CMVi = Clinically Significant CMV infection

In response to the identified difficulties of CMV disease/mortality and using these as end points in clinical studies, investigators sought to define a suitable surrogate endpoint for CMV disease using viraemia (a principle that has been universally accepted in the HIV therapy area). Green at al (2016) demonstrated that even when adjusted for the use of pre-emptive therapy, CMV viraemia was indeed a suitable surrogate endpoint for mortality as CMV viraemia after allogeneic haematopoietic stem cell transplantation (HSCT) is associated with overall and non-relapse mortality, independent of pre-emptive therapy to prevent CMV and end-organ disease and other relevant risk factors. A CMV viral load of 250 IU/mL or greater was associated with increased risk of early (day 0–60 post-transplantation) death (adjusted HR 19·8, 95% CI 9·6–41·1)[6].

In addition to the data from Green highlighting that viraemia is a suitable surrogate end point through negative post-transplant outcomes, evidence from numerous other studies suggests that CMV reactivation is associated with increased mortality, independent of CMV disease, which can manifest as a decrease in non-relapse mortality (NRM) and/or increased overall survival (Table 2).

Table 2: CMV and relapse, non-relapse mortality and overall survival outcomes [7]

Table 1
CMV and relapse, NRM, and OS outcomes.

Reference (author, yr)	No. subjects	Primary disease	CMV status	Relapse outcomes	Survival outcomes
Teira, 2016	9469	AML	Reactivation	–	27% relative decrease OS ($P < 0.0001$)
		ALL	Reactivation	–	95% relative increase NRM ($P < 0.0001$)
					46% relative decrease OS ($P < 0.0001$)
		CML	Reactivation	–	49% relative decrease OS ($P = 0.0005$)
		MDS	Reactivation	–	61% relative increase NRM ($P = 0.0002$)
					31% relative decrease OS ($P = 0.003$)
		AML	Seropositive	24% increase ($P = 0.007$) at 6mos	–
Inagaki, 2016	143	Ped. AML	Reactivation	14.3% absolute decrease ($P = 0.041$)	22.6% absolute increase NRM ($P < 0.01$)
		Ped. ALL			
Takenaka, 2015	3539	AML	Reactivation	23% relative decrease ($P = 0.04$)	60% relative increase NRM ($P < 0.01$)
				7.2% absolute decrease ($P < 0.01$)	37% relative decrease OS ($P < 0.01$)
					11.1% absolute decrease OS ($P < 0.01$)
		ALL	Reactivation	Decreased (NS)	74% relative increase NRM ($P = 0.02$)
					8.2% absolute decrease OS($P < 0.01$)
		CML	Reactivation	Increased (NS)	Increased NRM (NS)
					8.2% absolute decrease OS ($P < 0.01$)
		MDS	Reactivation	6.9% absolute decrease ($P < 0.05$)	Increased NRM (NS)
					Decreased OS (NS)
		Combined	Reactivation	18% relative decrease ($P = 0.01$)	66% relative increase NRM ($P < 0.01$)
				5.8% absolute decrease ($P < 0.01$)	30% relative decrease OS ($P < 0.01$)
					8.8% absolute decrease OS ($P < 0.01$)
		Combined	Seropositive	65% relative increase ($P < 0.01$)	34% relative decrease NRM ($P = 0.02$)
Manjappa, 2014	264	AML	Reactivation	7.6% absolute decrease ($P = 0.03$)	Increased NRM (NS)
				35.8% relative decrease ($P = 0.0242$)	Increased OS (NS)
		MAC	Reactivation	11.4% absolute decrease ($P = 0.01$)	Increased NRM (NS)
				47.5% relative decrease ($P = 0.0061$)	Decreased OS (NS)
		RIC	Reactivation	NS	NS
Green, 2013	2342	AML	Reactivation	44% relative decrease in 100d CIR ($P = 0.02$)	46% relative increase NRM ($P = 0.02$)
		ALL	Reactivation	Decreased (NS)	Increased NRM (NS)
					Increased OS (NS)
		CML	Reactivation	Decreased (NS)	68% relative increase NRM ($P = 0.01$)
					51% relative decrease OS ($P = 0.02$)
		MDS	Reactivation	Decreased (NS)	Increased NRM (NS)
					Increased OS (NS)
		Lymphoma	Reactivation	Decreased (NS)	Increased NRM (NS)
					Increased OS (NS)
		Combined	Reactivation	32% relative decrease ($P < 0.001$)	31% relative increase NRM ($P = 0.02$)
					Decreased OS (NS)
		Combined	Seropositive	31% relative decrease ($P = 0.004$)	–
Elmaagacli, 2011	266	AML	Seropositive	18% absolute decrease ($P < 0.0001$)	24% increase OS ($P < 0.005$)
				160% relative decrease ($P < 0.0001$)	
			Reactivation	33% absolute decrease ($P < 0.0001$)	22% absolute increase OS ($P < 0.002$)
				460% relative decrease ($P < 0.0001$)	
Behrendt, 2009	140	Ped. AML, ALL, MDS	Seropositive	315% decrease ($P = 0.003$)	–

Abbreviations: ALL = acute lymphoblastic leukemia AML = acute myelogenous leukemia, CIR = cumulative incidence of relapse, CML = chronic myelogenous leukemia, MA = myeloablative, MDS = myelodysplastic syndrome, mos = months, NRM = non-relapse mortality, NS = not significant, Ped = pediatric, RIC = reduced intensity conditioning, OS = overall survival, yr = year.

Although pre-emptive management strategies have reduced the incidence of CMV disease, this solution remains unsatisfactory, both because CMV disease still occurs in some patients, and because currently-utilised pre-emptive therapies may contribute directly to morbidity in HSCT recipients.

In addition to the effects of CMV disease and side effects of anti-CMV therapy, CMV infection continues to influence a broad range of transplant outcomes, particularly the incidence of NRM, with which CMV has a clear relationship[7] .

Given the limitations described above and the fact that letermovir met its pre-defined primary endpoint, this coupled with the complex and not fully understood effects of CMV in this setting, lends further credence to a fully plausible benefit of letermovir in reducing mortality due to prevention of CMV reactivation.

- **Adverse event profile similar to pre-emptive therapy**

As noted in the ACD "*the ERG commented that the adverse events results were difficult to interpret because of the underlying conditions and treatments as well as toxicity associated with various pre-emptive therapy regimens".*

In PN001, patients were randomised to letermovir or placebo at week 0. Once a threshold of CMV viral DNA is reached, pre-emptive therapy is administered irrespective of the treatment allocation in the trial. MSD would like to clarify that adverse events in PN001 were collected relative to the allocated study therapy, i.e. letermovir or placebo, and not when patients had met the primary endpoint and were receiving pre-emptive therapy. Therefore, the safety profile of letermovir is similar to placebo (no letermovir).

- **Utility values and collection of utility endpoints**

The ACD states that the "*Committee agreed that there could plausibly be a health-related quality-of-life benefit associated with preventing CMV reactivation"*. Despite the Committee acknowledging that the letermovir is effective in reducing CMV reactivation and the need for pre-emptive therapy, the ACD goes on to state that *"the health-related quality-of-life results of PN001 are therefore difficult to interpret"*.

The ACD states that "*at randomisation, the mean values for EQ-5D-3L and FACT-BMT scores represent a mixture of those who have had CMV reactivation and started pre-emptive therapy and those who have not. The direct effect of letermovir on health-related quality of life was therefore confounded".* MSD would like to provide clarification around this point. During the trial the health-related quality of life (HRQoL) assessments were measured at baseline (i.e. week 0), week 14, week 24 and week 48. HRQoL was also measured at the study discontinuation visit, i.e. when a patient met the primary endpoint of cs-CMV infection. The HRQoL assessment was made prior to a patient initiating pre-emptive therapy, and therefore the expected disutility associated with the (as noted in the ACD) "*severe side effects"* of pre-emptive therapy, was not reflected.

Please also note that HRQoL was a pre-defined exploratory endpoint and was not powered to detect statistically significant differences in QoL scores between the treatment groups.

- **Treatment duration**

As noted in the ACD, in the ERG's base-case "*the mean duration of treatment was assumed to be 83 days. This was based on the duration of therapy in the full analysis set population (72.1 days) plus an additional 10.9 days from the delayed start of prophylaxis".*

As a point of clarification, the mean duration of treatment applied from PN001 of 72.1 days for the FAS population includes patients who delayed initiating prophylaxis, and to include an additional 10.9 days would risk an element of double counting. As such, it would be inappropriate to use 83 days as the treatment duration.

Additionally, the model does not take into account the delay in starting letermovir prophylaxis as patients enter the model at the time they initiate either letermovir or placebo (i.e. at randomisation). As such, increasing the duration by 10.9 days would not be reflective of what is expected in current practice, based on the clinical trial data.

MSD acknowledges that the clinical experts stated "*the duration treatment is likely to be longer than 69.4 days*" and are therefore including an extended treatment duration for letermovir of 72.1 days to reflect the FAS population from PN001.

- **<u>The use of the 24 week data endpoints versus the 48 week endpoints</u>**

The Committee have deemed that the base-case for the cost effectiveness modelling provided was "*not appropriate for decision-making because of concerns about…the use of 24-week data over 48-week data*", which was supported by the ERG who questioned the relevance of 24-week data "*when 48-week data were available for most outcomes"*. MSD disagrees with this approach and considers the 24-week data to be more appropriate than the 48-week data for the base-case position.

Below, MSD UK questions the reliability and appropriateness of applying the 48-week data to the base-case as considered by the ERG and Committee. The summary of our position is as follows:

- The indication of interest in the submission and the primary endpoint of the PN001, cs-CMV reactivation, was collected up until the week 24 timepoint, and was not collected during the safety follow-up period of the study (weeks 24-48). The ACD states "*letermovir statistically significantly reduced the rate of clinically significantly CMV reactivation at week 24 compared with placebo*" providing support that the Committee accepts the evidence that letermovir meets the primary endpoint of PN001.
- Without observed data it would be difficult to predict the rate of cs-CMV infection to the extended time point of week 48. The rate of change of cs-CMV infection would be expected to decline between week 24 and week 48 timepoints as the immune system strengthens; however without observed data this would be difficult to infer.
- Letermovir prophylaxis was administered until the week 14 time period, with follow-up until week 24. This is supported by the British Society of Haematology guidelines which state "*Monitoring of CMV load should be undertaken at least weekly for the first 3 months post-HSCT*" [8].
- To fully investigate the long-term effect of letermovir a further follow-up phase was agreed between regulatory bodies (EMA and FDA) and MSD, to week 48 to investigate the long-term safety of letermovir.
- Using the week 48 data endpoints would not be appropriate to assess the effect of letermovir prophylaxis, as prophylactic treatment would have been stopped for approximately 34 weeks.

For the reasons above, MSD does not agree that the analyses on week 48 data endpoints should be the basis of the Committee's decision.

- **Additional analyses (updated base-case)**

Based on the accepted preferred Committee assumptions, MSD has updated the base-case in order to allow the Committee to make an informed decision. Further clarity surrounding the original justification for parameters, and why these amended assumptions were not included in the original base-case has been presented below.

The ACD identifies that the ERG had a preferred assumption whereby the "*disutility associated with graft-versus-host-disease (GvHD) should have been included in the base-case analysis".* It should be noted that this change in utility should only apply to chronic-GvHD (occurring after the first 100 days post-HSCT), as the disutility associated with acute-GvHD (occurring during the first 100 days post-HSCT) will have been captured in the mean change from baseline utility calculation. As an amendment to the ERG model, MSD has applied an element of discounting (3.5%) to the disutility for GvHD and disease relapse beyond the first year.

The Committee and ERG considered that the "*HMRN was a more relevant source [than Wingard et al (2011)]*", however the limitations surrounding the data set should be acknowledged. The Haematological Malignancy Research Network (HMRN) [9] did not have long-term mortality data to the granularity of underlying indication, and it was felt that underlying disease was an important component of the data information that would have been missed with implications on the long-term modelling. It is felt that both the original approach and the approach using HMRN data to model long-term mortality are valid; however both approaches have their limitations. Despite the limitations acknowledged, the HMRN data has been applied to meet the request of the Committee.

The ERG heard from its clinical experts that "*only 5 to 15% of patients would have foscarnet as part of their pre-emptive therapy*". However the clinical experts attending the meeting stated that due to variation between centres and the type of transplant received "*the use of foscarnet is closer to 15 to 25%*", with the Committee concluding "*that foscarnet use in the model should be between 15 and 25%*". A study by Tham et al (2018) investigating the burden of CMV reactivation in a UK haematology centre, reported 23.5% of the patient population received foscarnet as a first-line pre-emptive therapy[10]. Based on the discussion of the Committee's clinicians and supported by the study by Tham et al (2018) [10], the suggested the use of foscarnet at 20% most accurately reflects the variability of use between trusts.

Using the majority of the Committee's preferred assumptions updated base-case results have been presented below (

Table 3) and are inclusive of the PAS discount ([redacted]).

Table 3: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	£38,665	7.35	6.02	-	-	-	-
Letermovir	£46,054	7.83	6.41	£7,400	0.48	0.40	£18,516

ICER=incremental cost-effectiveness ratio; LYG=Life-year gained; QALY=quality-adjusted life year; SoC=standard of care

In order to display the magnitude that the change in base-case had upon the mortality figures included in the model, please find below (
Table 4) the two-way sensitivity analysis when the mortality of both arms (letermovir and SoC) are increased/reduced by 0.5% increments.

Letermovir All-Cause Mortality (24-weeks)

%	7.5%	8.0%	8.5%	9.0%	9.5%	10.0%	10.5%	11.0%	11.5%	12.0%	12.5%	
93	£30,596	£35,582	£42,938	£54,882	£77,645	£138,108	£780,966	-£198,805	-£85,305	-£53,098	-£37,876	-£
87	£26,993	£30,596	£35,582	£42,939	£54,882	£77,647	£138,112	£781,123	-£198,795	-£85,303	-£53,097	-£
74	£24,268	£26,993	£30,596	£35,582	£42,939	£54,883	£77,648	£138,117	£781,280	-£198,784	-£85,301	-£
87	£22,135	£24,268	£26,993	£30,596	£35,583	£42,940	£54,884	£77,650	£138,122	£781,437	-£198,774	-£
23	£20,420	£22,135	£24,268	£26,993	£30,596	£35,583	£42,940	£54,885	£77,651	£138,127	£781,594	-£
79	£19,011	£20,420	£22,136	£24,269	£26,994	£30,597	£35,583	£42,941	£54,885	£77,652	£138,132	£7
53	£17,833	£19,011	£20,420	£22,136	£24,269	£26,994	£30,597	£35,584	£42,941	£54,886	£77,654	£1
43	£16,833	£17,833	£19,011	£20,421	£22,136	£24,269	£26,994	£30,597	£35,584	£42,941	£54,887	£
47	£15,974	£16,834	£17,833	£19,012	£20,421	£22,136	£24,269	£26,994	£30,597	£35,584	£42,942	£
55	£15,228	£15,974	£16,834	£17,833	£19,012	£20,421	£22,136	£24,269	£26,994	£30,597	£35,584	£
04	£14,574	£15,228	£15,975	£16,834	£17,833	£19,012	£20,421	£22,136	£24,269	£26,994	£30,598	£
33	£13,996	£14,574	£15,228	£15,975	£16,834	£17,834	£19,012	£20,421	£22,136	£24,269	£26,995	£
33	£13,482	£13,996	£14,574	£15,229	£15,975	£16,834	£17,834	£19,012	£20,421	£22,136	£24,269	£
41	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£16,834	£17,834	£19,012	£20,421	£22,136	£
07	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£16,834	£17,834	£19,012	£20,421	£
31	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£16,834	£17,834	£19,012	£
51	£11,887	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£16,834	£17,834	£
48	£11,575	£11,887	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£16,834	£
40	£11,288	£11,575	£11,887	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£
38	£11,023	£11,288	£11,575	£11,887	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£
40	£10,779	£11,023	£11,288	£11,575	£11,887	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£
48	£10,553	£10,779	£11,024	£11,288	£11,575	£11,887	£12,230	£12,606	£13,021	£13,482	£13,997	£

Table 4: Two-way sensitivity analysis results

No Letermovir All-Cause Mortality (24-weeks)	Letermovir All-Cause Mortality (24-weeks)													
	7.0%	7.5%	8.0%	8.5%	9.0%	9.5%	10.0%	10.5%	11.0%	11.5%	12.0%	12.5%	13.0%	13.5%
10.5%	£26,993	£30,596	£35,582	£42,938	£54,882	£77,645	£138,108	£780,966	-£198,805	-£85,305	-£53,098	-£37,876	-£29,007	-£23,200
11.0%	£11,887	£26,993	£30,596	£35,582	£42,939	£54,882	£77,647	£138,112	£781,123	-£198,795	-£85,303	-£53,097	-£37,876	-£29,007
11.5%	£11,574	£24,268	£26,993	£30,596	£35,582	£42,939	£54,883	£77,648	£138,117	£781,280	-£198,784	-£85,301	-£53,097	-£37,876
12.0%	£11,287	£22,135	£24,268	£26,993	£30,596	£35,583	£42,940	£54,884	£77,650	£138,122	£781,437	-£198,774	-£85,299	-£53,096
12.5%	£11,023	£20,420	£22,135	£24,268	£26,993	£30,596	£35,583	£42,940	£54,885	£77,651	£138,127	£781,594	-£198,763	-£85,297
13.0%	£10,779	£19,011	£20,420	£22,136	£24,269	£26,994	£30,597	£35,583	£42,941	£54,885	£77,652	£138,132	£781,752	-£198,753
13.5%	£10,553	£17,833	£19,011	£20,420	£22,136	£24,269	£26,994	£30,597	£35,584	£42,941	£54,886	£77,654	£138,136	£781,909
14.0%	£10,343	£16,833	£17,833	£19,011	£20,421	£22,136	£24,269	£26,994	£30,597	£35,584	£42,941	£54,887	£77,655	£138,141
14.5%	£10,147	£15,974	£16,834	£17,833	£19,012	£20,421	£22,136	£24,269	£26,994	£30,597	£35,584	£42,942	£54,887	£77,657
15.0%	£9,965	£15,228	£15,974	£16,834	£17,833	£19,012	£20,421	£22,136	£24,269	£26,994	£30,597	£35,584	£42,942	£54,888
15.5%	£9,794	£14,574	£15,228	£15,975	£16,834	£17,833	£19,012	£20,421	£22,136	£24,269	£26,994	£30,598	£35,585	£42,943
16.0%	£9,633	£13,996	£14,574	£15,228	£15,975	£16,834	£17,834	£19,012	£20,421	£22,136	£24,269	£26,995	£30,598	£35,585
16.5%	£9,483	£13,482	£13,996	£14,574	£15,229	£15,975	£16,834	£17,834	£19,012	£20,421	£22,136	£24,269	£26,995	£30,598
17.0%	£9,341	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£16,834	£17,834	£19,012	£20,421	£22,136	£24,270	£26,995
17.5%	£9,207	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£16,834	£17,834	£19,012	£20,421	£22,136	£24,270
18.0%	£9,081	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£16,834	£17,834	£19,012	£20,421	£22,137
18.5%	£8,961	£11,887	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£16,834	£17,834	£19,012	£20,421
19.0%	£8,848	£11,575	£11,887	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£16,834	£17,834	£19,012
19.5%	£8,740	£11,288	£11,575	£11,887	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£16,834	£17,834
20.0%	£8,638	£11,023	£11,288	£11,575	£11,887	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975	£16,834
20.5%	£8,540	£10,779	£11,023	£11,288	£11,575	£11,887	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229	£15,975
21.0%	£8,448	£10,553	£10,779	£11,024	£11,288	£11,575	£11,887	£12,230	£12,606	£13,021	£13,482	£13,997	£14,575	£15,229

The ACD reports that "*a small change to a key assumption could have a large effect on the ICER. In particular, to the mortality rate, where increasing it by 1% (that is, from 3.8% to 4.8%) decreases the ICER from £27,536 to £23,124 per QALY gained, but decreasing the mortality rate by 1% (from 3.8% to 2.8%) pushes the ICER from £27,536 to £34,471 per QALY gained if all the ERG's preferred assumptions are incorporated".* It should be recognised that altering the difference between the two arms by 1%, is causing a change of approximately 20% in the mortality difference. As such, it is inappropriate to call this a "*small change*" and this change in a parameter should not be the basis of the decision-making.

Since the original submission to NICE (6th March 2018), Tham et al. (2018) have presented data at the European Hematology Association (EHA) annual conference on the burden of CMV reactivation for patients at a large UK haematology centre. The data showed that 45% of patients who had an initial reactivation of CMV went on to have second CMV reactivations[10]. These new data have not been included in the modelling, but would substantially increase the costs of CMV reactivation and reduce the ICER. As such, all ICERs portrayed in this analysis are an over-estimation of the true ICER.

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9th November 2018

Letermovir for treating cytomegalovirus reactivation and disease in CMV-seropositive recipients of a allogeneic haematopoietic stem cell transplant [ID1153] – Updated response to Appraisal Consultation Document (ACD)

Dear Kate,

Having read the ACD, MSD UK was disappointed with the provisional negative recommendation, given our confidence that letermovir is a cost-effective option for treating CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant (HSCT).

Based on the content of the ACD, the key economic drivers underpinning the draft negative recommendation are uncertainty around the following defining points, which result in a disparity between our manufacturer's base-case and the ERG's base-case:

- Treatment duration
- The use of the 24 week data endpoints versus the 48 week endpoints

An updated response is provided below and firstly summarises some key points in the ACD which we believe support the approach taken by MSD in our submission, and highlight the value and clinical relevance of letermovir as a valid prophylactic option for the patient population covered by this appraisal. Our response then addresses in turn, the above mentioned key drivers underpinning the draft negative recommendation; closing with an updated base-case analysis.

MSD UK has answered the Committee's concerns to the best of our ability concerning the key drivers identified above. In MSD UK's opinion, the primary issues influencing the variability in the ICER for letermovir are the use of week 48 data instead of the week 24 data that represents the primary endpoint of PN001; and the treatment duration of letermovir.

Should you have any questions about the content, please do contact me.

Kind regards,
Chris O'Regan

Executive Director
Head of HTA & O

Key points mentioned in the ACD that support the approach taken by MSD in the submission of letermovir for prophylaxis of CMV-reactivation and disease in adult CMV-seropositive recipients of an allogeneic HSCT [(1)]:

- The ACD states that "*clinical trial evidence shows that letermovir is effective in reducing CMV infection. It also reduces the need for pre-emptive therapy".*

- The Committee agree that *"if CMV levels rise, treatment with …pre-emptive therapy is started to prevent disease but this can cause severe side effects".*

- The clinical and patient experts highlighted that "*letermovir reduces the reactivation rates and the need for toxic pre-emptive therapy*". Additionally, the Committee concluded that "*CMV reactivation can have a substantial psychological effect on patients and their families".*

MSD Response to key economic drivers underpinning the draft negative recommendation in the ACD:

- **Updated patient access scheme**

As stated in the ACD "*the [cost-effectiveness] estimates are affected by small changes in letermovir's mortality benefit, the magnitude of which is uncertain. Because of this letermovir cannot be recommended*".

MSD acknowledges the Committee's comments around the uncertainty associated with the mortality benefit demonstrated in the pivotal PhIII trial for letermovir (PN001). MSD do, however, reiterate that the primary aim of this study was to demonstrate prevention of reactivation of CMV viraemia and disease in patients at high risk of CMV reactivation.

Based on the draft negative recommendation in the ACD and uncertainty regarding the true ICER, MSD have applied to NHS for an extension in the patient access scheme, increasing the discount to [redacted]%.

This has reduced the price of letermovir for each formulation to the following:

- 240mg oral letermovir
  - List price: £[redacted]
  - Discounted price: £[redacted]
- 480mg oral letermovir
  - List price: £[redacted]
  - Discounted price: £[redacted]
- 240mg IV infusion letermovir
  - List price: £[redacted]
  - Discounted price: £[redacted]
- 480mg IV infusion letermovir
  - List price: £[redacted]
  - Discounted price: £[redacted]

- **Treatment duration**

As noted in the ACD, in the ERG's base-case "*the mean duration of treatment was assumed to be 83 days. This was based on the duration of therapy in the full analysis set population (72.1 days) plus an additional 10.9 days from the delayed start of prophylaxis".*

As a point of clarification, the mean duration of treatment applied from PN001 of 72.1 days for the FAS population includes patients who delayed initiating prophylaxis, and to include an additional 10.9 days would risk an element of double counting. As such, it would be inappropriate to use 83 days as the treatment duration.

Additionally, the model does not take into account the delay in starting letermovir prophylaxis as patients enter the model at the time they initiate either letermovir or placebo (i.e. at randomisation). As such, increasing the duration by 10.9 days would not be reflective of what is expected in current practice, based on the clinical trial data.

MSD acknowledges that the clinical experts stated "*the duration treatment is likely to be longer than 69.4 days*" and are therefore including an extended treatment duration for letermovir of 72.1 days to reflect the FAS population from PN001.

When changing the duration of therapy to 72.1 days, and including the updated PAS of [redacted]%, the ICER is reduced from the ERG base-case to £22,338.

- **<u>The use of the 24 week data endpoints versus the 48 week endpoints</u>**

The Committee have deemed that the base-case for the cost effectiveness modelling provided was "*not appropriate for decision-making because of concerns about…the use of 24-week data over 48-week data*", which was supported by the ERG who questioned the relevance of 24-week data "*when 48-week data were available for most outcomes"*. MSD disagrees with this approach and considers the 24-week data to be more appropriate than the 48-week data for the base-case position.

Below, MSD UK questions the reliability and appropriateness of applying the 48-week data to the base-case as considered by the ERG and Committee. The summary of our position is as follows:

- The indication of interest in the submission and the primary endpoint of the PN001, cs-CMV reactivation, was collected up until the week 24 timepoint, and was not collected during the safety follow-up period of the study (weeks 24-48). The ACD states "*letermovir statistically significantly reduced the rate of clinically significantly CMV reactivation at week 24 compared with placebo*" providing support that the Committee accepts the evidence that letermovir meets the primary endpoint of PN001.
- Without observed data it would be difficult to predict the rate of cs-CMV infection to the extended time point of week 48. The rate of change of cs-CMV infection would be expected to decline between week 24 and week 48 timepoints as the immune system strengthens; however without observed data this would be difficult to infer.
- Letermovir prophylaxis was administered until the week 14 time period, with follow-up until week 24. This is supported by the British Society of Haematology guidelines which state "*Monitoring of CMV load should be undertaken at least weekly for the first 3 months post-HSCT*" [(2)].
- To fully investigate the long-term effect of letermovir a further follow-up phase was agreed between regulatory bodies (EMA and FDA) and MSD, to week 48 to investigate the long-term safety of letermovir.
- Using the week 48 data endpoints would not be appropriate to assess the effect of letermovir prophylaxis, as prophylactic treatment would have been stopped for approximately 34 weeks.

For the reasons above, MSD does not agree that the analyses on week 48 data endpoints should be the basis of the Committee's decision.

When applying the use of the 24-week data end points to inform the analyses, and including the updated PAS of [redacted]%, the ERG basecase ICER is reduced to £20,733 (days of letermovir therapy remains as ERG base-case).

- **<u>Updated base-case</u>**

Based on the accepted preferred Committee assumptions, and including the two scenarios described above, MSD has updated the base-case in order to allow the Committee to make an informed decision. Further clarity surrounding the original justification for parameters, and why these amended assumptions were not included in the original base-case has been presented below.

The ACD identifies that the ERG had a preferred assumption whereby the "*disutility associated with graft-versus-host-disease (GvHD) should have been included in the base-case analysis".* It should be noted that this change in utility should only apply to chronic-GvHD (occurring after the first 100 days post-HSCT), as the disutility associated with acute-GvHD (occurring during the first 100 days post-HSCT) will have been captured in the mean change from baseline utility calculation. As an amendment to the ERG model, MSD has applied an element of discounting (3.5%) to the disutility for GvHD and disease relapse beyond the first year.

The Committee and ERG considered that the "*HMRN was a more relevant source [than Wingard et al (2011)]*", however the limitations surrounding the data set should be acknowledged. The Haematological Malignancy Research Network (HMRN) [(3)] did not have long-term mortality data to the granularity of underlying indication, and it was felt that underlying disease was an important component of the data information that would have been missed with implications on the long-term modelling. It is felt that both the original approach and the approach using HMRN data to model long-term mortality are valid; however both approaches have their limitations. Despite the limitations acknowledged, the HMRN data has been applied to meet the request of the Committee.

The ERG heard from its clinical experts that "*only 5 to 15% of patients would have foscarnet as part of their pre-emptive therapy*". However the clinical experts attending the meeting stated that due to variation between centres and the type of transplant received "*the use of foscarnet is closer to 15 to 25%*", with the Committee concluding "*that foscarnet use in the model should be between 15 and 25%*". A study by Tham et al (2018) investigating the burden of CMV reactivation in a UK haematology centre, reported 23.5% of the patient population received foscarnet as a first-line pre-emptive therapy[(4)]. Based on the discussion of the Committee's clinicians and supported by the study by Tham et al (2018) [(4)], the suggested the use of foscarnet at 20% most accurately reflects the variability of use between trusts.

Using the majority of the Committee's preferred assumptions, and including the two scenarios described previously, an updated base-case results have been presented below (

Table 1) and are inclusive of the PAS discount ([redacted]%).

Table 1: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	£38,665	7.35	6.02	-	-	-	-
Letermovir	£45,655	7.83	6.41	£7,000	0.48	0.40	£17,713

ICER=incremental cost-effectiveness ratio; LYG=Life-year gained; QALY=quality-adjusted life year; SoC=standard of care

In order to display the magnitude that the change in base-case had upon the mortality figures included in the model, please find below (Table 2) the two-way sensitivity analysis when the mortality of both arms (letermovir and SoC) are increased/reduced by 0.5% increments.

Table 2: Two-way sensitivity analysis results

No Letermovir All-Cause Mortality (24-weeks)	Letermovir All-Cause Mortality (24-weeks)													
	7.0%	7.5%	8.0%	8.5%	9.0%	9.5%	10.0%	10.5%	11.0%	11.5%	12.0%	12.5%	13.0%	13.5%
10.5%	£15,813	£17,856	£20,641	£24,661	£30,973	£42,316	£68,693	£198,723	-£200,849	-£64,459	-£37,574	-£26,091	-£19,721	-£15,672
11.0%	£6,951	£15,814	£17,857	£20,643	£24,664	£30,977	£42,323	£68,712	£198,888	-£200,676	-£64,441	-£37,567	-£26,088	-£19,720
11.5%	£6,762	£14,252	£15,815	£17,859	£20,644	£24,666	£30,980	£42,330	£68,732	£199,053	-£200,504	-£64,423	-£37,561	-£26,084
12.0%	£6,589	£13,018	£14,252	£15,816	£17,860	£20,646	£24,668	£30,984	£42,337	£68,751	£199,218	-£200,332	-£64,405	-£37,555
12.5%	£6,429	£12,019	£13,018	£14,253	£15,817	£17,861	£20,647	£24,671	£30,988	£42,344	£68,770	£199,384	-£200,161	-£64,387
13.0%	£6,282	£11,193	£12,019	£13,019	£14,254	£15,817	£17,862	£20,649	£24,673	£30,992	£42,352	£68,789	£199,550	-£199,990
13.5%	£6,145	£10,499	£11,193	£12,019	£13,019	£14,254	£15,818	£17,863	£20,651	£24,675	£30,995	£42,359	£68,809	£199,716
14.0%	£6,018	£9,909	£10,500	£11,194	£12,020	£13,020	£14,255	£15,819	£17,864	£20,652	£24,678	£30,999	£42,366	£68,828
14.5%	£5,899	£9,399	£9,909	£10,500	£11,194	£12,020	£13,021	£14,256	£15,820	£17,865	£20,654	£24,680	£31,003	£42,373
15.0%	£5,788	£8,955	£9,399	£9,909	£10,500	£11,195	£12,021	£13,021	£14,256	£15,821	£17,867	£20,655	£24,682	£31,007
15.5%	£5,684	£8,565	£8,955	£9,400	£9,909	£10,501	£11,195	£12,021	£13,022	£14,257	£15,822	£17,868	£20,657	£24,684
16.0%	£5,587	£8,220	£8,565	£8,956	£9,400	£9,910	£10,501	£11,195	£12,022	£13,022	£14,258	£15,823	£17,869	£20,659
16.5%	£5,495	£7,912	£8,220	£8,566	£8,956	£9,400	£9,910	£10,502	£11,196	£12,022	£13,023	£14,259	£15,824	£17,870
17.0%	£5,409	£7,635	£7,912	£8,220	£8,566	£8,956	£9,400	£9,910	£10,502	£11,196	£12,023	£13,023	£14,259	£15,825
17.5%	£5,327	£7,385	£7,635	£7,912	£8,220	£8,566	£8,956	£9,401	£9,911	£10,502	£11,197	£12,023	£13,024	£14,260
18.0%	£5,250	£7,159	£7,386	£7,635	£7,912	£8,221	£8,566	£8,957	£9,401	£9,911	£10,503	£11,197	£12,024	£13,025
18.5%	£5,177	£6,953	£7,159	£7,386	£7,636	£7,912	£8,221	£8,567	£8,957	£9,401	£9,911	£10,503	£11,198	£12,024
19.0%	£5,108	£6,764	£6,953	£7,159	£7,386	£7,636	£7,912	£8,221	£8,567	£8,957	£9,401	£9,912	£10,503	£11,198
19.5%	£5,043	£6,591	£6,764	£6,953	£7,159	£7,386	£7,636	£7,913	£8,221	£8,567	£8,957	£9,402	£9,912	£10,504
20.0%	£4,980	£6,431	£6,591	£6,764	£6,953	£7,160	£7,386	£7,636	£7,913	£8,221	£8,567	£8,958	£9,402	£9,912
20.5%	£4,921	£6,283	£6,431	£6,591	£6,764	£6,953	£7,160	£7,386	£7,636	£7,913	£8,222	£8,567	£8,958	£9,402
21.0%	£4,864	£6,146	£6,283	£6,431	£6,591	£6,764	£6,953	£7,160	£7,386	£7,636	£7,913	£8,222	£8,568	£8,958

The ACD reports that "*a small change to a key assumption could have a large effect on the ICER. In particular, to the mortality rate, where increasing it by 1% (that is, from 3.8% to 4.8%) decreases the ICER from £27,536 to £23,124 per QALY gained, but decreasing the mortality rate by 1% (from 3.8% to 2.8%) pushes the ICER from £27,536 to £34,471 per QALY gained if all the ERG's preferred assumptions are incorporated".* It should be recognised that altering the difference between the two arms by 1%, is causing a change of approximately 20% in the mortality difference. As such, it is inappropriate to call this a "*small change*" and this change in a parameter should not be the basis of the decision-making.

Since the original submission to NICE (6th March 2018), Tham et al. (2018) have presented data at the European Hematology Association (EHA) annual conference on the burden of CMV reactivation for patients at a large UK haematology centre. The data showed that 45% of patients who had an initial reactivation of CMV went on to have second CMV reactivations[4]. These new data have not been included in the modelling, but would substantially increase the costs of CMV reactivation and reduce the ICER. As such, all ICERs portrayed in this analysis are an over-estimation of the true ICER.

References

1. (NICE) NIfHaCE. Appraisal consultation document: Letermovir for preventing cytomegalovirus desease after a stem cell transplant. 2018.
2. Emery V, Zuckerman M, Jackson G, Aitken C, Osman H, Pagliuca A, et al. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. Br J Haematol. 2013;162(1):25-39.
3. Network HMR. [Available from: https://www.hmrn.org/.
4. Tham C MS, Lozano S, Avenoso D, Sevillano B, Fernando F, Farah N, Paliompeis C, Milojkovic D, Palanicawandar R, Olavarria E, editor Analysis of the Burden of Cytomegalovirus Reactivation in Patients Undergoing Hematopoietic Stem Cell Transplantation. European Hematology Associatoin; 2018; Stockholm, Sweden: HemaSphere.

NICE National Institute for Health and Care Excellence

Letermovir prophylaxis for cytomegalovirus disease after allogeneic stem cell transplant [ID1153]

Consultation on the appraisal consultation document – deadline for comments **5pm on 25 July 2018.** Please submit these through 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

NICE National Institute for Health and Care Excellence

Letermovir prophylaxis for cytomegalovirus disease after allogeneic stem cell transplant [ID1153]

Consultation on the appraisal consultation document – deadline for comments **5pm on 25 July 2018.** Please submit these through 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 too much emphasis is being placed on mortality in this submission (and the consequent decision made by the committee); mortality was only an exploratory endpoint in the company's trial. Cytomegalovirus (CMV) reactivation itself is only linked to mortality if it is able to progress to CMV disease. However, this has become largely uncommon thanks to pre-emptive therapies. Therefore, letermovir is unlikely to reduce mortality, and consequently distort the true QALY.
2	We are concerned that the significant benefit in patient quality of life is not adequately taken into account. The ACD acknowledges that trial PN001 did not prove that there was a health-related quality of life compared to placebo. However, this could not be demonstrated by the trial, as the quality of life diminishments described by patients are not a result of the CMV reactivation, but of the pre-emptive therapies which are used to stop progression to CMV disease. Although clinically effective, patients have told us that the side effects of pre-emptive therapy significantly lower their quality of life (see Anthony Nolan original submission). Although the psychological effect is taken into account, the physical side effects are not mentioned. As well as causing severe physical side effects, pre-emptive therapies such as valganciclovir are cited on the UK's electronic Medicines Compendium as causing neutropenia. For patients after transplant, neutropenia increases the chance of potentially fatal infections. Prophylaxis (letermovir) would reduce the need for pre-emptive therapy and lower this risk. Indeed, section 3.2 of the ACD reads that the committee concludes that "an effective treatment that specifically acts to prevent CMV reactivation would benefit people who are seropositive for CMV who have had an allogeneic HSCT", whilst the ACD also accepts that "letermovir is effective in reducing CMV infection", "reduces the need for pre-emptive therapy", and "has a better safety profile than pre-emptive therapy". Given that this has been recognised, we believe that patients should have access to letermovir in order to prevent the reduced quality of life associated with pre-emptive therapy. Stem cell transplant is one of the most difficult pathways for a patient, and anything which can be done to reduce the burden would be greatly beneficial to patients.
3	
4	

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,

Letermovir prophylaxis for cytomegalovirus disease after allogeneic stem cell transplant [ID1153]

Consultation on the appraisal consultation document – deadline for comments **5pm on 25 July 2018.** Please submit these through 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.

NICE National Institute for Health and Care Excellence

Letermovir prophylaxis for cytomegalovirus disease after allogeneic stem cell transplant [ID1153]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of Physicians (RCP)
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:	Dr Andrew Goddard, RCP registrar
Comment number	**Comments**

NICE National Institute for Health and Care Excellence

Letermovir prophylaxis for cytomegalovirus disease after allogeneic stem cell transplant [ID1153]

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	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	The RCP is grateful for the opportunity to comment on this ACD. We have liaised with the Intercollegiate Committee on Haematology and would like to make the following comments • We are concerned that too much emphasis is being placed on mortality in this submission (and the consequent decision made by the committee); mortality was only an exploratory endpoint in the company's trial. Cytomegalovirus (CMV) reactivation itself is only linked to mortality if it is able to progress to CMV disease. However, this has become largely uncommon thanks to pre-emptive therapies. Therefore, letermovir is unlikely to reduce mortality, and consequently distort the true QALY. • We are concerned that the significant benefit in patient quality of life is not adequately taken into account. • The ACD acknowledges that trial PN001 did not prove that there was a health-related quality of life compared to placebo. However, this could not be demonstrated by the trial, as the quality of life diminishments described by patients are not a result of the CMV reactivation, but of the pre-emptive therapies which are used to stop progression to CMV disease. • As well as causing severe physical side effects, pre-emptive therapies such as valganciclovir are cited on the UK's electronic Medicines Compendium as causing neutropenia. For patients after transplant, neutropenia increases the chance of potentially fatal infections. Prophylaxis (letermovir) would reduce the need for pre-emptive therapy and lower this risk. • Indeed, section 3.2 of the ACD reads that the committee concludes that "an effective treatment that specifically acts to prevent CMV reactivation would benefit people who are seropositive for CMV who have had an allogeneic HSCT", whilst the ACD also accepts that "letermovir is effective in reducing CMV infection", "reduces the need for pre-emptive therapy", and "has a better safety profile than pre-emptive therapy". • Given that this has been recognised, we believe that patients should have access to letermovir in order to prevent the reduced quality of life associated with pre-emptive therapy. Stem cell transplant is one of the most difficult pathways for a patient, and anything which can be done to reduce the burden would be greatly beneficial to patients.

Insert extra rows as needed

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Letermovir prophylaxis for cytomegalovirus disease after allogeneic stem cell transplant [ID1153]

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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.

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I read with interest the appraisal consultation document. I was glad to see that a number of the expert recommendations had been incorporated following the meeting at NICE in Manchester. However, I was disappointed by a number of inaccurate statements and with the final outcome, and would raise a number of points, specifically regarding conclusions that were made that I consider being incorrect.

Generalizability:

The committee agreed that it was a well-conducted trial, but were concerned that the results were not generalizable to UK populations. As an expert in the field I believe this to be wrong. It is stated that the maximum treatment duration was 100 days but that this was 'inappropriate in clinical practice' because some people 'may need longer prophylaxis'. Firstly, it is unclear how they reach this conclusion. The trial was well designed and demonstrated the impact of 100 days prophylaxis, with appropriate collection of data through a washout period. Some patients did experience CMV events during this later phase. However, it is not clear that they would 'need longer prophylaxis'. This is conjecture. Patients may or may not benefit from longer prophylaxis, but there is no data that speaks to this. Furthermore, limitation of duration of therapy in commissioning would prevent this use, which is off license in any case. Whether or not this is the case, I cannot see why this is relevant to UK use as opposed to other countries. The high risk of CMV reactivation with T cell depletion is an early event. Late events associated with graft versus host disease and steroid use. These would be less likely in the UK patient population because of T cell depletion, so this argument is flawed, especially if it is used to speak to lack of generalizability.

Much of what follows in terms of argument for lack of generalizability does not suggest a lesser therapeutic impact in the UK population, but rather a larger one. It is therefore disappointing that the argument has been used in this inverted way.

Regarding threshold levels of viraemia for intervention – as noted on the day, the clinical difference between a level of 150-300 copies, and 400-700 copies is negligible. Less than 3% of patients in our practice who have detectable DNA would clear this spontaneously. The trial absolutely does not 'overestimate CMV infection rate' – this is defined by detection of circulating DNS, not by a threshold.

The committee suggests these uncertainties could overestimate or underestimate efficacy - but should be taken into account. All the expert comment suggests if anything an underestimation of efficacy, and this is what should be taken into account rather than a more general stated issue re lack of generalizability and level of uncertainty.

Mortality data from HMRN:

The report states that clinical experts agreed that mortality in year 2 would be 'much higher' than in year 3, more in line with 19% vs company reported 3%. I do not recall the experts being specifically asked re absolute numbers. The ERG highlight that the data in Wingard is old, and contains >40% paediatric data. This is therefore not relevant to current NHS adult transplantation practice. The way we perform transplants has evolved significantly over the past decade, and I do not think the Wingard data is relevant.

Duration of therapy:
This is particularly difficult, as I suspect it has a significant impact on cost utility, and anything beyond the trial data is guess work. If prophylaxis is started at day 0, then the patients who would reactivate within the first 11 days will be included. In the trial a number were excluded because they were deemed screen failures if they became PCR positive prior to planned initiation of drug. Early reactivators may be at higher risk of failing prophylactic therapy – in which case treatment duration would be curtailed. A simplistic approach of adding 72.1 to 10.9 = 83 likely overestimates real world mean duration. I would suggest this is reduced to somewhere between 72 and 83.

Finally, even if these issues remain unaltered, it appears that the uncertainty re the true ICER cost puts it in a range of £20000-£30200. I would assume that the methods guide referring to decision where the most plausible ICER was above £20000 but uncertain is largely to deal with larger variances where uncertainty puts the possible true ICER significantly higher than the £30000 threshold. Using this method guide as an argument against commissioning a drug where the uncertainty barely stretches above £30000 at all seems particularly inappropriate to me, and will result in many patients failing to receive a truly transformative medicine which is already available in the USA,, Germany, and Scotland.

10th April 2019

Letermovir for treating cytomegalovirus reactivation and disease in CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant [ID1153] – Appraisal Consultation Document response addendum

MSD are providing the updated base case analyses and two-way deterministic sensitivity analyses, having adjusted the population to reflect the currently available formulations of letermovir in England.

The population pertaining to the analyses has been adjusted to 100% treated with oral letermovir, and 0% treated with IV letermovir, altering cell G:32 in the "Cost" sheet.

The small change in the population initiating on the IV formulation of letermovir, reduces the weighted-average daily cost of letermovir from £114.52 to £112.55. This is reflected in the base case results in Table 1 below, reducing the ICER from £17,713 in the ACD response (November 2018) to £17,352.

Table 1: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	£38,665	7.35	5.95	-	-	-	-
Letermovir	£45,512	7.83	6.35	£6,858	0.48	0.40	£17,352

To fully replicate the analysis provided in the MSD ACD response, please find below (Table 2) the two-way sensitivity analysis when the mortality of both arms (letermovir and SoC) are increased/reduced by 0.5% increments.

Table 2: Two-way deterministic sensitivity analysis

No Letermovir All-Cause Mortality (24-weeks)	Letermovir All-Cause Mortality (24-weeks)													
	7.0%	7.5%	8.0%	8.5%	9.0%	9.5%	10.0%	10.5%	11.0%	11.5%	12.0%	12.5%	13.0%	13.5%
10.5%	£25,084	£28,369	£32,916	£39,623	£50,508	£71,244	£126,255	£705,190	-£181,524	-£77,499	-£48,044	-£34,132	-£26,029	-£20,725
11.0%	**£11,304**	£25,084	£28,369	£32,916	£39,623	£50,508	£71,245	£126,259	£705,332	-£181,515	-£77,497	-£48,043	-£34,132	-£26,029
11.5%	**£11,019**	£22,599	£25,084	£28,370	£32,916	£39,623	£50,509	£71,247	£126,263	£705,474	-£181,505	-£77,496	-£48,043	-£34,132
12.0%	**£10,757**	£20,654	£22,599	£25,084	£28,370	£32,917	£39,624	£50,510	£71,248	£126,268	£705,616	-£181,495	-£77,494	-£48,042
12.5%	**£10,516**	**£19,089**	£20,654	£22,599	£25,084	£28,370	£32,917	£39,624	£50,510	£71,249	£126,272	£705,758	-£181,486	-£77,492
13.0%	**£10,294**	**£17,804**	**£19,089**	£20,654	£22,599	£25,085	£28,370	£32,917	£39,625	£50,511	£71,251	£126,277	£705,900	-£181,476
13.5%	**£10,087**	**£16,729**	**£17,804**	**£19,089**	£20,654	£22,599	£25,085	£28,370	£32,918	£39,625	£50,512	£71,252	£126,281	£706,042
14.0%	**£9,896**	**£15,817**	**£16,729**	**£17,804**	**£19,089**	£20,654	£22,599	£25,085	£28,371	£32,918	£39,625	£50,512	£71,253	£126,285
14.5%	**£9,717**	**£15,034**	**£15,817**	**£16,729**	**£17,804**	**£19,090**	£20,654	£22,600	£25,085	£28,371	£32,918	£39,626	£50,513	£71,255
15.0%	**£9,551**	**£14,353**	**£15,034**	**£15,817**	**£16,729**	**£17,804**	**£19,090**	£20,654	£22,600	£25,085	£28,371	£32,918	£39,626	£50,514
15.5%	**£9,395**	**£13,756**	**£14,353**	**£15,034**	**£15,817**	**£16,729**	**£17,804**	**£19,090**	£20,654	£22,600	£25,085	£28,371	£32,919	£39,627
16.0%	**£9,248**	**£13,229**	**£13,756**	**£14,353**	**£15,034**	**£15,817**	**£16,730**	**£17,804**	**£19,090**	£20,654	£22,600	£25,085	£28,371	£32,919
16.5%	**£9,111**	**£12,760**	**£13,229**	**£13,756**	**£14,353**	**£15,034**	**£15,817**	**£16,730**	**£17,804**	**£19,090**	£20,654	£22,600	£25,086	£28,372
17.0%	**£8,981**	**£12,339**	**£12,760**	**£13,229**	**£13,756**	**£14,353**	**£15,034**	**£15,818**	**£16,730**	**£17,804**	**£19,090**	£20,654	£22,600	£25,086
17.5%	**£8,859**	**£11,960**	**£12,339**	**£12,760**	**£13,229**	**£13,756**	**£14,353**	**£15,034**	**£15,818**	**£16,730**	**£17,805**	**£19,090**	£20,655	£22,600
18.0%	**£8,744**	**£11,617**	**£11,960**	**£12,339**	**£12,760**	**£13,229**	**£13,756**	**£14,353**	**£15,034**	**£15,818**	**£16,730**	**£17,805**	**£19,090**	£20,655
18.5%	**£8,635**	**£11,305**	**£11,617**	**£11,960**	**£12,339**	**£12,760**	**£13,229**	**£13,757**	**£14,353**	**£15,034**	**£15,818**	**£16,730**	**£17,805**	**£19,090**
19.0%	**£8,531**	**£11,019**	**£11,305**	**£11,617**	**£11,960**	**£12,339**	**£12,760**	**£13,229**	**£13,757**	**£14,353**	**£15,034**	**£15,818**	**£16,730**	**£17,805**
19.5%	**£8,433**	**£10,758**	**£11,019**	**£11,305**	**£11,617**	**£11,960**	**£12,339**	**£12,760**	**£13,229**	**£13,757**	**£14,353**	**£15,034**	**£15,818**	**£16,730**
20.0%	**£8,340**	**£10,517**	**£10,758**	**£11,019**	**£11,305**	**£11,617**	**£11,960**	**£12,339**	**£12,760**	**£13,229**	**£13,757**	**£14,353**	**£15,034**	**£15,818**
20.5%	**£8,251**	**£10,294**	**£10,517**	**£10,758**	**£11,019**	**£11,305**	**£11,617**	**£11,960**	**£12,339**	**£12,760**	**£13,229**	**£13,757**	**£14,353**	**£15,034**
21.0%	**£8,166**	**£10,088**	**£10,294**	**£10,517**	**£10,758**	**£11,019**	**£11,305**	**£11,617**	**£11,960**	**£12,339**	**£12,760**	**£13,229**	**£13,757**	**£14,353**

Single Technology Appraisal (STA)

Letermovir for the prophylaxis of cytomegalovirus reactivation or disease in people with seropositive-cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant [ID1153]

ERG commentary on the Company's response to the ACD

Produced by **CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD**

Date **29th April 2019**

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

1 Overview

The evidence review group (ERG) was requested by NICE to provide a critique on the discussion and updated base-case submitted by the company in response to the appraisal consultation document (ACD).

Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. However, the ERG has checked the implementation of the proposed changes and ensured replicability of the results presented by the company.

The company provide a number of arguments in favour of alternative assumptions around the use of 24 week endpoints, and a shorter treatment duration for letermovir than is preferred by the ERG and Committee. The company then presents results from an amended version of the ERG's base-case model which incorporates their preferred assumptions, a number of the Committee's preferred assumptions, and an updated patient access scheme (PAS) discount. The ERG accepts the Committee's preferred assumptions which were incorporated into the company's model, thus the following critique focuses primarily upon the two other scenarios included by the company in their updated analysis.

The ERG identified two errors in the labelling of the ERG's preferred assumptions in the executable model. This led the company use ERG exploratory scenario-values for some utility inputs, rather than the settings described in the ERG Report. The following sections therefore also include results the company likely intended to produce in their ACD response, rather than those which may have unintentionally included these alternative assumptions. For consistency, the ERG's base-case results also include a correction to the calculation of unit costs for letermovir, and the company's preferred method of discounting cGVHD disutility.

The following table provides a summary of the key differences in assumptions and inputs between the main iterations of the economic model.

Table 1 Differences in key assumptions between model iterations

Parameter	CS base-case	ERG base-case	Committee's preferred assumptions	Company updated base-case	ERG updated base-case
Trial endpoints	24-week	48-week	48-week	24-week	48-week
Treatment duration	69.4 days	83 days	83 days	72.1 days	83 days
Foscarnet use	25%	15%	15-25%	20%	20%
IV letermovir use	5%	27%	5%	5%	5%
Ciclosporin A use	95%	95%	90%	90%	90%

ICER	£10,904	£27,536	£23,124 to >30,000	£16,982	£24,269

2 ERG commentary on the company's ACD response

2.1 Updated patient access scheme

The company acknowledged the sensitivity of the ICER to small changes in the putative mortality benefit associated with letermovir, and the role of this uncertainty in the Committee's negative preliminary recommendation. In light of this, an increase of a [redacted] in the PAS discount for letermovir has been applied for, bringing the total discount to [redacted] off the list price. This reduces the price of each formulation to the following:

- 240mg oral letermovir
  - List price: £132.97
  - Discounted price: [redacted]
- 480mg oral letermovir
  - List price: [redacted]
  - Discounted price: [redacted]
- 240mg IV infusion letermovir
  - List price: [redacted]
  - Discounted price: [redacted]
- 480mg IV infusion letermovir
  - List price: [redacted]
  - Discounted price: [redacted]

This reduces the ERG's alternative base-case ICER from £25,766 to £24,269 per QALY gained. All of the ERG scenarios presented below incorporate this increased discount. The corrected company base-case decreases from £17,950 to £16,982 with the inclusion of the updated PAS.

2.2 Treatment duration

The company argue that the ERG's preferred estimate of letermovir treatment duration (83 days) was too high, however, the discussion presented in their response to the ACD does not appear to address the ERG's reasoning behind the inclusion of 10.9 additional days of treatment in the ERG alternative base-case.

Clinical advice to the ERG suggested that the delay between HSCT and initiation of prophylaxis seen in the PN001 trial was due to clinical concern around potential effects upon graft response, which was assuaged following positive safety outcomes from this trial. This delay is unlikely to exist in clinical practice as the safety of letermovir following allografts has been now demonstrated, and clinicians will seek to gain the maximum possible benefit from prophylaxis. Patients would therefore be expected to initiate letermovir much sooner, and as reasons for discontinuation were not related to the

study drug, patients would stop treatment at the same point. Furthermore, the ERG notes that patients with particular clinical need would plausibly receive prophylaxis for over 100 days, as is permitted under the product license.

The ERG considers the 83 day treatment duration favoured by the Committee to represent a more realistic estimate than the average derived from the PN001 FAS population. The ERG considers it most plausible that clinicians will aim to maximise treatment benefit by providing prophylaxis as early and for as long as possible, and thus 83 days may represent a conservative estimate of treatment duration.

Table 2 explores the effect of a variety of assumptions around treatment duration upon the ICER when applied to the updated ERG base-case. The exploratory analyses from the ERG report assume the 45% of trial patients who were still receiving letermovir at 100 days would continue for a further 2 weeks and 6 weeks respectively. This reflects how UK clinicians could use letermovir given the lack of stopping rules defined in the EMA license to limit treatment to 100 days.

Table 2 Effect of different treatment durations upon the updated ERG base-case ICER

Source	Treatment duration (days)	ICER
Company Submission base-case (PN001 ASaT)	69.4	£19,414
Company ACD Response (PN001 FAS)	72.1	£20,378
ERG base-case (PN001 FAS + 10.9 day delay)	83	£24,269
ERG Report exploratory analysis (max. duration 100 days +2 weeks)	89.3	£26,518
ERG Report exploratory analysis (max. duration 100 days +6 weeks)	101.9	£31,016

The ERG's base-case ICER using a 72.1 day treatment duration is £20,378, which increases to £24,269 using the Committee's preferred 83 day treatment duration. The company's base-case ICER increases from £16,982 to £19,877 when the additional 10.9 days of treatment are included.

2.3 Use of 24 week trial endpoints over 48 week endpoints

The company questioned the ERG and Committee's preference for the use of 48-week trial data over 24-week data, and presented for the following reasons for use of the 24-week data in the Committee's base-case:

- The primary endpoint of the PN001 trial was CMV reactivation, which was only collected up until the week 24 timepoint.
- Prediction of the rate of cs-CMV infection would be difficult between weeks 24 and 48 due to a lack of data on rate of change.
- Letermovir prophylaxis was administered until week 14, with monitoring of CMV undertaken in practice for three months.

- A follow-up phase was agreed between the EMA, FDA, and MSD to investigate the long-term safety of letermovir up to week 48.
- Prophylaxis would have been stopped for 34 weeks by week 48.

While the ERG accepts that the CMV reactivation was the primary trial outcome and that additional follow was the result of additional follow up agreed with the EMA and FDA, the company's economic model sought to value the costs and benefits of treatment with letermovir over a lifetime time horizon, and is driven primarily by improvements in mortality not CMV reactivation events. As it is clear that mortality events occurred between the 24- and 48-week timepoints in the PN001 trial, the ERG consider the most appropriate approach to be one that makes maximum use of the available data, rather than assuming that no further events occurred beyond 24-weeks as is implicit in the company's analysis. Such an assumption clearly lacks face validity, as the model assumes an additional 1.9% of patients remain alive and continue to accrue QALYs beyond 48-weeks despite the very same patients having demonstrably died in the trial. This essentially arbitrary increase in mortality benefit has a substantial deflationary effect upon the ICER.

The company express concerns around the inference of rates of CMV reactivation rates at 48 weeks based on those at 24 weeks, and therefore the 24 week data is most appropriate for modelling. However, as the rates of CMV infection between 24 and 48 weeks would undergo a significant reduction, it is unlikely that differences on the scale observed would have any substantial impact upon the model results. Furthermore, given that the primary benefit of avoiding CMV reactivation is the prevention of CMV related mortality, the use of 48 week data for mortality means that the most important consequences are therefore already being captured by the model.

Implementing the 24-week endpoints into the ERG preferred base-case including the updated PAS produces an ICER of £19,877 versus £24,269 per QALY gained using 48-week endpoints. This analysis uses the point-estimates for all-cause mortality which imply a 5.7% reduction in mortality at 24 weeks and 3.8% difference at 48 weeks between letermovir and no letermovir.

2.4 Company's updated base-case

The company present an updated base-case analysis in the ACD response, which is based primarily upon the ERG's alternative base-case, but includes the company's preferred inputs described in the two scenarios above, along with several further changes and justification for the their preferred assumptions. These changes include:

- Reduction in treatment duration and associated resource use from 83 days to 72.1 days.
- Use of 24-week PN001 endpoints (5.7% mortality benefit) over 48-week endpoints (3.8% mortality benefit)

- Amended discounting for chronic-GvHD disutility
- Proportion of patients receiving foscarnet pre-emptive therapy increased to 20%.
- Patient Access Scheme Discount increased from [redacted]
- Concomitant ciclosporin use reduced from 95% to 90%
- IV letermovir used in 5% of patients (reduced from 27% in ERG model)

The ERG accepts the Committee's preferences regarding the discounting of cGvHD disutilities, the proportion of patients receiving foscarnet as PET, the rates of concomitant CsA, and the proportion of patients receiving letermovir intravenously.

The company's updated base-case analysis produces an ICER of £17,713 per QALY gained. Amending this to account for the company's misinterpretation of the ERG base-case reduces this marginally to £16,982 per QALY gained.

The company presented the results of a two-way sensitivity analysis which explored the effects of different levels of all-cause mortality at 24-weeks. This table shows that in order to achieve an ICER under £20,000 per QALY gained in the company's updated base-case, letermovir must reduce all-cause mortality at 24 weeks by 3%. In a scenario where there is no significant difference in mortality between the two treatment groups, the ICER of letermovir prophylaxis versus no letermovir is between £198,723 and £199,716 per QALY gained. As the PN001 trial did not demonstrate any mortality benefit, the ERG considers this a plausible scenario. While the company states that referring to a change of 1% in mortality benefit as 'small' in relation to the sensitivity of the ICER is inappropriate, it should be noted that this difference is well within the 95% confidence intervals in the PN001 trial (anywhere between a 15.3% reduction to a 7.7% increase in mortality associated with letermovir prophylaxis). It is critical to explore this uncertainty (see Table 4) as the sensitivity of the ICER to a 1% change in mortality benefit is illustrative of sensitivity of model results to this input as consequence significant decision uncertainty. In this regard is important while is entirely plausible that a avoidance of CMV relationship will reduce mortality, no case has been made by the company for a causal relationship between CMV reactivation and mortality.

The company go on to state that *"all ICERs portrayed in this analysis are an over-estimation of the true ICER",* as observational data presented in a poster by Tham *et al.* which suggests the rate of multiple CMV reactivations post-HSCT is higher than the PN001 trial showed. Firstly, if reactivation events are common beyond the 24 week trial period, the possibility that this would be the case in patients who previously received letermovir prophylaxis cannot be excluded. Secondly, given that no causal relationship between the prevention of CMV reactivation and mortality has been demonstrated, coupled with the relative insensitivity of the ICER to CMV infection, a modest increase the incidence of CMV reactivation is unlikely to significantly affect the results.

2.5 Updated ERG-base case

The ERG's updated base-case includes the Committee's preferred inputs for prevalence of foscarnet and ciclosporin use, and the proportion of patients requiring intravenous letermovir. In contrast with the revised company base-case, this analysis uses 48-week endpoints where available, and assumes patients receive letermovir prophylaxis for an average of 83 days. Table 3 below presents the results of the ERG's updated base-case analysis, and includes the updated PAS price for letermovir.

Table 3 Results of updated ERG-base case

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
SoC	29,646	5.36	-	-	-
Letermovir	37,090	5.66	7,444	0.307	£24,269

The deterministic ICER produced by the ERG's updated base-case is £24,269 per QALY gained. A two-way deterministic sensitivity analysis equivalent to that produced by the company in their response to the ACD is presented in Table 4 below for the ERG's base-case. This examines the impact of uncertainty surrounding the putative mortality benefit associated with letermovir prophylaxis, including much of the 95% CIs associated with both point estimates for 48-week mortality. If we are to assume there to be no mortality benefit associated with letermovir prophylaxis, the ICER of prophylaxis versus no prophylaxis ranges between £137,891 and £139,231 per QALY gained. According to this analysis, in order to achieve an ICER of under £20,000 per QALY, letermovir must reduce mortality by 5% reduction at 48-weeks.

Table 4 Two-way sensitivity analysis results

No Letermovir All-Cause Mortality (48-weeks)	Letermovir All-Cause Mortality (48-weeks)														
	20.0%	20.5%	21.0%	21.5%	22.0%	22.5%	23.0%	23.5%	24.0%*	24.5%	25.0%	25.5%	26.0%	26.5%	27.0%
22.0%	£38,194	£46,128	£58,728	£81,824	£137,891	£473,605	-£311,568	-£114,670	-£69,289	-£49,127	-£37,733	-£30,408	-£25,304	-£21,543	-£18,657
22.5%	£32,746	£38,203	£46,142	£58,752	£81,870	£138,024	£475,201	-£310,868	-£114,573	-£69,253	-£49,108	-£37,721	-£30,401	-£25,299	-£21,539
23.0%	£28,768	£32,753	£38,213	£46,157	£58,775	£81,916	£138,157	£476,809	-£310,172	-£114,477	-£69,217	-£49,090	-£37,710	-£30,394	-£25,294
23.5%	£25,737	£28,773	£32,759	£38,223	£46,171	£58,798	£81,962	£138,290	£478,428	-£309,479	-£114,380	-£69,181	-£49,072	-£37,699	-£30,386
24.0%	£23,350	£25,741	£28,779	£32,766	£38,232	£46,185	£58,822	£82,009	£138,424	£480,057	-£308,789	-£114,284	-£69,146	-£49,053	-£37,688
24.5%	£21,422	£23,353	£25,745	£28,784	£32,773	£38,242	£46,199	£58,845	£82,055	£138,558	£481,698	-£308,102	-£114,188	-£69,110	-£49,035
25.0%	**£19,831**	£21,424	£23,357	£25,749	£28,789	£32,780	£38,251	£46,213	£58,868	£82,101	£138,692	£483,350	-£307,419	-£114,093	-£69,074
25.5%	**£18,497**	**£19,834**	£21,427	£23,360	£25,753	£28,794	£32,787	£38,261	£46,227	£58,892	£82,147	£138,826	£485,013	-£306,738	-£113,997
26.0%	**£17,362**	**£18,499**	**£19,836**	£21,430	£23,363	£25,758	£28,800	£32,794	£38,270	£46,242	£58,915	£82,193	£138,961	£486,688	-£306,060
26.5%	**£16,385**	**£17,364**	**£18,501**	**£19,838**	£21,433	£23,367	£25,762	£28,805	£32,801	£38,280	£46,256	£58,939	£82,240	£139,095	£488,374
27.0%	**£15,535**	**£16,387**	**£17,366**	**£18,503**	**£19,841**	£21,435	£23,370	£25,766	£28,810	£32,808	£38,289	£46,270	£58,962	£82,286	£139,231
27.5%*	**£14,788**	**£15,536**	**£16,388**	**£17,368**	**£18,505**	**£19,843**	£21,438	£23,373	£25,770	£28,815	£32,815	£38,299	£46,284	£58,985	£82,333
28.0%	**£14,127**	**£14,789**	**£15,537**	**£16,390**	**£17,369**	**£18,507**	**£19,845**	£21,441	£23,377	£25,774	£28,821	£32,822	£38,309	£46,298	£59,009
28.5%	**£13,537**	**£14,128**	**£14,790**	**£15,539**	**£16,391**	**£17,371**	**£18,510**	**£19,848**	£21,444	£23,380	£25,778	£28,826	£32,829	£38,318	£46,313
29.0%	**£13,009**	**£13,538**	**£14,129**	**£14,791**	**£15,540**	**£16,393**	**£17,373**	**£18,512**	**£19,850**	£21,447	£23,383	£25,782	£28,831	£32,836	£38,328
29.5%	**£12,532**	**£13,010**	**£13,539**	**£14,130**	**£14,793**	**£15,541**	**£16,394**	**£17,375**	**£18,514**	**£19,852**	£21,449	£23,387	£25,786	£28,836	£32,842
30.0%	**£12,100**	**£12,533**	**£13,011**	**£13,540**	**£14,131**	**£14,794**	**£15,543**	**£16,396**	**£17,376**	**£18,516**	**£19,855**	£21,452	£23,390	£25,791	£28,842
30.5%	**£11,706**	**£12,101**	**£12,534**	**£13,012**	**£13,541**	**£14,132**	**£14,795**	**£15,544**	**£16,397**	**£17,378**	**£18,518**	**£19,857**	£21,455	£23,393	£25,795
31.0%	**£11,346**	**£11,707**	**£12,101**	**£12,535**	**£13,012**	**£13,542**	**£14,133**	**£14,796**	**£15,545**	**£16,399**	**£17,380**	**£18,520**	**£19,860**	£21,458	£23,397
31.5%	**£11,016**	**£11,347**	**£11,708**	**£12,102**	**£12,535**	**£13,013**	**£13,543**	**£14,134**	**£14,797**	**£15,547**	**£16,400**	**£17,382**	**£18,522**	**£19,862**	£21,461
32.0%	**£10,711**	**£11,016**	**£11,348**	**£11,708**	**£12,103**	**£12,536**	**£13,014**	**£13,544**	**£14,135**	**£14,799**	**£15,548**	**£16,402**	**£17,383**	**£18,524**	**£19,864**
32.5%	**£10,430**	**£10,712**	**£11,017**	**£11,348**	**£11,709**	**£12,104**	**£12,537**	**£13,015**	**£13,545**	**£14,136**	**£14,800**	**£15,550**	**£16,403**	**£17,385**	**£18,526**

*Point estimates for 48-week mortality were 23.8% for letermovir and 27.6% for no letermovir

Single Technology Appraisal (STA)

Letermovir for the prophylaxis of cytomegalovirus reactivation or disease in people with seropositive-cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant [ID1153]

ERG commentary on the Company's response to the ACD - Addendum

Produced by **CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD**

Date **11th April 2019**

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined

1 Overview

This addendum reports the results of the analyses provided in the ERG's review of the company's ACD response including an adjustment to the treatment costs for letermovir. This single change to the model was requested by NICE because the IV formulation of letermovir has not been launched in the UK. In the following analyses, the proportion of patients receiving IV letermovir is reduced from 5% as in the company and ERG updated base-cases to 0%, i.e. 100% of patients receive oral letermovir.

Note that the company analyses presented by the ERG use the corrected model assumptions, as described in the ERG's comments on the company's ACD response.

Table 1 Differences in key assumptions between model iterations

Parameter	Committee's preferred assumptions	Company updated base-case	ERG updated base-case	Company's updated base-case (addendum)	ERG updated base-case (addendum)
Trial endpoints	48-week	24-week	48-week	24-week	48-week
Treatment duration	83 days	72.1 days	83 days	72.1 days	83 days
Foscarnet use	15-25%	20%	20%	20%	20%
IV letermovir use	5%	5%	5%	**0%**	**0%**
Ciclosporin A use	90%	90%	90%	90%	90%
ICER	£23,124 to >30,000	£16,982	£24,269	£16,636	£23,822

2 ERG commentary on the company's ACD response

2.1 Updated patient access scheme

This analysis includes the increase of [redacted] in the PAS discount for letermovir, bringing the total discount to [redacted] off the list price. This reduces the price of each formulation to the following:

- 240mg oral letermovir
  - List price: £132.97
  - Discounted price: [redacted]
- 480mg oral letermovir
  - List price: [redacted]
  - Discounted price: [redacted]

Including only patients receiving the oral formulation of letermovir, this reduces the ERG's alternative base-case ICER from £25,324 to £23,822 per QALY gained.

2.2 Treatment duration

Table 2 is equivalent to Table 2 presented in the ERG comments on the company's ACD response, but 100% of patients now receive oral letermovir.

These analyses explore the effect of a variety of assumptions around treatment duration upon the ICER when applied to the updated ERG base-case. This reflects how UK clinicians could use letermovir given the lack of stopping rules defined in the EMA license to limit treatment to 100 days.

Table 2 Effect of different treatment durations upon the updated ERG base-case ICER

Source	Treatment duration (days)	ICER
Company Submission base-case (PN001 ASaT)	69.4	£18,945
Company ACD Response (PN001 FAS)	72.1	£19,913
ERG base-case (PN001 FAS + 10.9 day delay)	83	£23,822
ERG Report exploratory analysis (max. duration 100 days +2 weeks)	89.3	£26,081
ERG Report exploratory analysis (max. duration 100 days +6 weeks)	101.9	£30,600

The ERG's base-case ICER using a 72.1 day treatment duration is £19,913, which increases to £23,822 using the Committee's preferred 83 day treatment duration. The company's base-case ICER increases from £16,636 to £19,544 when the additional 10.9 days of treatment are included.

2.3 Use of 24 week trial endpoints over 48 week endpoints

Table 3 presents the results equivalent to those in Section 2.3 of the ERG's comments on the company's ACD response, but assumes 100% of patients receive the oral letermovir formulation.

Implementing the 24-week endpoints into the ERG preferred base-case including the updated PAS produces an ICER of £19,544 versus £23,822 per QALY gained using 48-week endpoints. This analysis uses the point-estimates for all-cause mortality which imply a 5.7% reduction in mortality at 24 weeks and 3.8% difference at 48 weeks between letermovir and no letermovir.

Table 3 Use of 24-week trial endpoints in ERG alternative base-case

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
ERG's alternative base-case using 48-week endpoints					
SoC	£29,646	5.36	-	-	-
Letermovir	£36,953	5.66	£ 7,307	0.3067	£23,822
ERG's alternative base-case using 24-week endpoints					
SoC	38,655	6.02	-	-	-
Letermovir	£46,711	6.44	£8,057	0.4122	£19,544

2.4 Company's updated base-case

The company present an updated base-case analysis in the ACD response, which is based primarily upon the ERG's alternative base-case, but includes the company's preferred inputs described in the two scenarios above, along with several further changes and justification for the their preferred assumptions. These changes include:

- Reduction in treatment duration and associated resource use from 83 days to 72.1 days.
- Use of 24-week PN001 endpoints (5.7% mortality benefit) over 48-week endpoints (3.8% mortality benefit)
- Amended discounting for chronic-GvHD disutility
- Proportion of patients receiving foscarnet pre-emptive therapy increased to 20%.
- Patient Access Scheme Discount increased from [redacted]
- Concomitant ciclosporin use reduced from 95% to 90%
- IV letermovir used in 0% of patients

Table 4 presents the results of the company's updated base-case from the ACD addendum, and a corrected version accounting for the company's use of incorrect model settings.

Table 4 Company's amended base-case post-ACD

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
Company-presented ACD response addendum base-case					
SoC	£38,665	5.95	-	-	-
Letermovir	£45,512	6.35	£6,858	0.40	£17,352
Corrected company ACD response addendum base-case					
SoC	£38,655	6.02	-	-	-
Letermovir	£45,512	6.44	£6,858	0.41	£16,636

The company presented the results of a two-way sensitivity analysis which explored the effects of different levels of all-cause mortality at 24-weeks. However, due to the reduced number of incremental QALYs gained when the incorrect model assumptions are used by the company, the resulting ICERs in a no-mortality benefit scenario are vastly inflated. Table 5 presents the company's two-way deterministic sensitivity analyses using the correct model assumptions. This table shows that in order to achieve an ICER under £20,000 per QALY gained in the company's updated base-case, letermovir must reduce all-cause mortality at 24 weeks by 4.5%.

In a scenario where there is no significant difference in mortality between the two treatment groups, the ICER of letermovir prophylaxis versus no letermovir is between £256,422 and £257,703 per QALY gained.

Table 5 Corrected company two-way DSA

No Letermovir All-Cause Mortality (24-weeks)	Letermovir All-Cause Mortality (24-weeks)													
	7.0%	7.5%	8.0%	8.5%	9.0%	9.5%	10.0%	10.5%	11.0%	11.5%	12.0%	12.5%	13.0%	13.5%
10.5%	£23,605	£26,494	£30,419	£36,063	£44,867	£60,521	£96,108	£256,422	-£330,037	-£95,901	-£54,521	-£37,274	-£27,814	-£21,839
11.0%	**£21,392**	£23,607	£26,496	£30,422	£36,066	£44,873	£60,532	£96,137	£256,635	-£329,674	-£95,869	-£54,510	-£37,269	-£27,811
11.5%	**£19,641**	£21,393	£23,608	£26,497	£30,424	£36,070	£44,879	£60,543	£96,166	£256,848	-£329,312	-£95,838	-£54,500	-£37,264
12.0%	**£18,221**	**£19,642**	£21,394	£23,609	£26,499	£30,427	£36,074	£44,885	£60,554	£96,195	£257,061	-£328,950	-£95,806	-£54,489
12.5%	**£17,047**	**£18,222**	**£19,643**	£21,395	£23,611	£26,501	£30,430	£36,077	£44,891	£60,566	£96,224	£257,275	-£328,590	-£95,774
13.0%	**£16,059**	**£17,047**	**£18,223**	**£19,644**	£21,396	£23,612	£26,503	£30,432	£36,081	£44,897	£60,577	£96,253	£257,489	-£328,230
13.5%	**£15,217**	**£16,060**	**£17,048**	**£18,223**	**£19,645**	£21,398	£23,614	£26,505	£30,435	£36,085	£44,902	£60,588	£96,282	£257,703
14.0%	**£14,490**	**£15,217**	**£16,060**	**£17,049**	**£18,224**	**£19,646**	£21,399	£23,615	£26,507	£30,437	£36,089	£44,908	£60,599	£96,311
14.5%	**£13,857**	**£14,491**	**£15,218**	**£16,061**	**£17,049**	**£18,225**	**£19,647**	£21,400	£23,617	£26,509	£30,440	£36,092	£44,914	£60,610
15.0%	**£13,300**	**£13,857**	**£14,491**	**£15,218**	**£16,061**	**£17,050**	**£18,226**	**£19,648**	£21,401	£23,618	£26,511	£30,442	£36,096	£44,920
15.5%	**£12,807**	**£13,301**	**£13,858**	**£14,492**	**£15,219**	**£16,062**	**£17,051**	**£18,227**	**£19,649**	£21,402	£23,620	£26,513	£30,445	£36,100
16.0%	**£12,367**	**£12,807**	**£13,301**	**£13,858**	**£14,492**	**£15,219**	**£16,063**	**£17,051**	**£18,228**	**£19,650**	£21,404	£23,621	£26,515	£30,448
16.5%	**£11,971**	**£12,367**	**£12,807**	**£13,301**	**£13,859**	**£14,493**	**£15,220**	**£16,063**	**£17,052**	**£18,228**	**£19,651**	£21,405	£23,623	£26,516
17.0%	**£11,614**	**£11,971**	**£12,367**	**£12,808**	**£13,302**	**£13,859**	**£14,493**	**£15,221**	**£16,064**	**£17,053**	**£18,229**	**£19,651**	£21,406	£23,624
17.5%	**£11,290**	**£11,614**	**£11,972**	**£12,367**	**£12,808**	**£13,302**	**£13,859**	**£14,494**	**£15,221**	**£16,064**	**£17,054**	**£18,230**	**£19,652**	£21,407
18.0%	**£10,995**	**£11,290**	**£11,615**	**£11,972**	**£12,368**	**£12,808**	**£13,302**	**£13,860**	**£14,494**	**£15,222**	**£16,065**	**£17,054**	**£18,231**	**£19,653**
18.5%	**£10,725**	**£10,995**	**£11,291**	**£11,615**	**£11,972**	**£12,368**	**£12,809**	**£13,303**	**£13,860**	**£14,494**	**£15,222**	**£16,066**	**£17,055**	**£18,232**
19.0%	**£10,477**	**£10,725**	**£10,996**	**£11,291**	**£11,615**	**£11,972**	**£12,368**	**£12,809**	**£13,303**	**£13,861**	**£14,495**	**£15,223**	**£16,066**	**£17,056**
19.5%	**£10,248**	**£10,477**	**£10,725**	**£10,996**	**£11,291**	**£11,615**	**£11,973**	**£12,369**	**£12,809**	**£13,304**	**£13,861**	**£14,495**	**£15,223**	**£16,067**
20.0%	**£10,037**	**£10,248**	**£10,477**	**£10,726**	**£10,996**	**£11,291**	**£11,616**	**£11,973**	**£12,369**	**£12,810**	**£13,304**	**£13,862**	**£14,496**	**£15,224**
20.5%	**£9,840**	**£10,037**	**£10,249**	**£10,477**	**£10,726**	**£10,996**	**£11,292**	**£11,616**	**£11,973**	**£12,369**	**£12,810**	**£13,304**	**£13,862**	**£14,496**
21.0%	**£9,658**	**£9,841**	**£10,037**	**£10,249**	**£10,478**	**£10,726**	**£10,996**	**£11,292**	**£11,616**	**£11,974**	**£12,369**	**£12,810**	**£13,305**	**£13,862**

2.5 Updated ERG-base case

Table 6 below presents the results of the ERG's updated base-case analysis, with 100% of patients receiving the oral formulation of letermovir. These results are equivalent to those presented in Table 3 of the ERG's comments on the company's ACD response.

Table 6 Results of updated ERG-base case (100% oral letermovir)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
SoC	£29,646	5.36	-	-	-
Letermovir	£36,953	5.66	£7,307	0.3067	£23,822

A two-way deterministic sensitivity analysis equivalent to that produced by the company in their response to the ACD is presented in Table 7 for the ERG's base-case. This examines the impact of uncertainty surrounding the putative mortality benefit associated with letermovir prophylaxis, including much of the 95% CIs associated with both point estimates for 48-week mortality.

If we are to assume there to be no mortality benefit associated with letermovir prophylaxis, the ICER of prophylaxis versus no prophylaxis ranges between £135,025 and £136,336 per QALY gained. According to this analysis, in order to achieve an ICER of under £20,000 per QALY, letermovir must reduce mortality by 5% at 48-weeks.

Table 7 ERG updated base-case Two-way sensitivity analysis results

No Letermovir All-Cause Mortality (48-weeks)	Letermovir All-Cause Mortality (48-weeks)														
	20.0%	20.5%	21.0%	21.5%	22.0%	22.5%	23.0%	23.5%	24.0%*	24.5%	25.0%	25.5%	26.0%	26.5%	27.0%
22.0%	£37,450	£45,216	£57,548	£80,152	£135,025	£463,590	-£304,864	-£112,158	-£67,744	-£48,011	-£36,859	-£29,691	-£24,696	-£21,015	-£18,190
22.5%	£32,118	£37,460	£45,230	£57,571	£80,197	£135,155	£465,153	-£304,180	-£112,064	-£67,709	-£47,993	-£36,849	-£29,684	-£24,691	-£21,011
23.0%	£28,225	£32,125	£37,469	£45,244	£57,593	£80,242	£135,285	£466,727	-£303,499	-£111,970	-£67,674	-£47,975	-£36,838	-£29,677	-£24,685
23.5%	£25,259	£28,231	£32,132	£37,479	£45,257	£57,616	£80,287	£135,416	£468,311	-£302,820	-£111,875	-£67,639	-£47,957	-£36,827	-£29,670
24.0%	£22,922	£25,263	£28,236	£32,138	£37,488	£45,271	£57,639	£80,332	£135,547	£469,906	-£302,145	-£111,781	-£67,604	-£47,939	-£36,816
24.5%	£21,035	£22,926	£25,267	£28,241	£32,145	£37,497	£45,285	£57,662	£80,377	£135,678	£471,512	-£301,473	-£111,688	-£67,569	-£47,921
25.0%	**£19,479**	£21,038	£22,929	£25,271	£28,246	£32,152	£37,507	£45,299	£57,685	£80,423	£135,809	£473,129	-£300,804	-£111,594	-£67,534
25.5%	**£18,173**	**£19,481**	£21,041	£22,932	£25,275	£28,251	£32,159	£37,516	£45,313	£57,708	£80,468	£135,940	£474,758	-£300,138	-£111,501
26.0%	**£17,063**	**£18,175**	**£19,483**	£21,043	£22,936	£25,279	£28,256	£32,166	£37,525	£45,327	£57,731	£80,513	£136,072	£476,397	-£299,475
26.5%	**£16,106**	**£17,064**	**£18,177**	**£19,486**	£21,046	£22,939	£25,283	£28,261	£32,172	£37,535	£45,341	£57,754	£80,559	£136,204	£478,048
27.0%	**£15,274**	**£16,107**	**£17,066**	**£18,179**	**£19,488**	£21,049	£22,942	£25,287	£28,267	£32,179	£37,544	£45,355	£57,777	£80,604	£136,336
27.5%*	**£14,543**	**£15,275**	**£16,109**	**£17,068**	**£18,181**	**£19,490**	£21,052	£22,946	£25,291	£28,272	£32,186	£37,554	£45,369	£57,800	£80,650
28.0%	**£13,896**	**£14,544**	**£15,276**	**£16,111**	**£17,069**	**£18,183**	**£19,493**	£21,054	£22,949	£25,295	£28,277	£32,193	£37,563	£45,383	£57,823
28.5%	**£13,319**	**£13,897**	**£14,545**	**£15,278**	**£16,112**	**£17,071**	**£18,185**	**£19,495**	£21,057	£22,952	£25,299	£28,282	£32,200	£37,572	£45,397
29.0%	**£12,802**	**£13,320**	**£13,898**	**£14,546**	**£15,279**	**£16,114**	**£17,073**	**£18,187**	**£19,497**	£21,060	£22,955	£25,303	£28,287	£32,206	£37,582
29.5%	**£12,335**	**£12,803**	**£13,321**	**£13,899**	**£14,547**	**£15,280**	**£16,115**	**£17,075**	**£18,189**	**£19,500**	£21,063	£22,959	£25,307	£28,292	£32,213
30.0%	**£11,912**	**£12,336**	**£12,803**	**£13,322**	**£13,900**	**£14,549**	**£15,282**	**£16,117**	**£17,076**	**£18,191**	**£19,502**	£21,065	£22,962	£25,311	£28,298
30.5%	**£11,527**	**£11,913**	**£12,337**	**£12,804**	**£13,323**	**£13,901**	**£14,550**	**£15,283**	**£16,118**	**£17,078**	**£18,193**	**£19,504**	£21,068	£22,965	£25,315
31.0%	**£11,175**	**£11,528**	**£11,914**	**£12,338**	**£12,805**	**£13,324**	**£13,902**	**£14,551**	**£15,284**	**£16,120**	**£17,080**	**£18,195**	**£19,507**	£21,071	£22,969
31.5%	**£10,851**	**£11,175**	**£11,528**	**£11,914**	**£12,338**	**£12,806**	**£13,325**	**£13,903**	**£14,552**	**£15,286**	**£16,121**	**£17,081**	**£18,197**	**£19,509**	£21,074
32.0%	**£10,553**	**£10,852**	**£11,176**	**£11,529**	**£11,915**	**£12,339**	**£12,807**	**£13,326**	**£13,904**	**£14,553**	**£15,287**	**£16,123**	**£17,083**	**£18,199**	**£19,511**
32.5%	**£10,278**	**£10,554**	**£10,852**	**£11,176**	**£11,530**	**£11,916**	**£12,340**	**£12,808**	**£13,327**	**£13,905**	**£14,555**	**£15,288**	**£16,124**	**£17,085**	**£18,201**

*Point estimates for 48-week mortality were 23.8% for letermovir and 27.6% for no letermovir