NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The final scope and list of stakeholders is available to view on the NICE website.

Contents:

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

Pre-meeting briefing

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

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

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- with input from the Lead Team (Dr Malcolm Oswald, Dr Bernard Khoo, Dr Paula Parvulescu)

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Key clinical issues

- Are the PN001 trial results generalisable to NHS clinical practice?
  - What proportion would be expected to have treatment beyond 100 days? (Mean duration in trial 69.4 days)
  - Is a delay in initiating prophylaxis post HSCT likely to occur in NHS practice? (Mean delay in trial of [redacted])
  - What proportion of patients would receive CsA in NHS practice? (51.7% in trial)
  - What proportion of patients would receive alemtuzumab in NHS practice? (4% in trial)
- Should the Full Analysis Set (FAS; company base case) or the All Subjects as Treated (ASaT) be used to evaluate efficacy?
- The FAS population in the trial excluded people with detectable CMV on day 1. In clinical practice, would people with detectable CMV DNA have letermovir prophylaxis?
- Patients who had missing data or prematurely discontinued from study, their treatments were considered as 'Failures' - Is this an appropriate way of handling missing data?

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Key cost-effectiveness issues

- In the company model, there are no health states to capture differences in QALYs in the two treatment groups and no link between the rate of CMV events and mortality. Is the company's modelling approach appropriate?
- Is the clinical data used to populate the model appropriate?
  - 24 week data used instead of 48 week data
  - No imputation of missing data
- All-cause mortality differences are the primary drivers of QALY benefits and even increasing it by 1% pushes the ICER over £30,000 per QALY. The company assumed that mortality rate in year 2 was equal to year 3. Is this plausible?
- Are the company's assumptions plausible?
  - 95% of patients to receive concomitant cyclosporin A (51% in the trial)
  - 95% of patients to receive IV letermovir (27% in the trial)
  - 25% of patients to receive foscarnet (ERG suggest 15%)
  - No administration costs for oral therapy

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Disease background

- Cytomegalovirus (CMV) is a common viral pathogen of the *Herpesviridae* family
- Approx. 50% to 60% of adults in the UK are infected with CMV
- Higher incidence with increasing age
- In healthy people, CMV is usually dormant and asymptomatic
- For people undergoing haematopoietic stem cell transplant (HSCT) the virus can become active again (80% of cases) because of a weakened immune system, causing serious complications and increased mortality
- CMV infection post-HSCT is further increased with use of T-cell depleting agents and/or prolonged immunosuppression for graft versus host disease (GvHD)

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Letermovir (Prevymis)

Marketing authorisation (MA): - Full MA: Jan 2018	Prevymis is indicated for the prophylaxis of CMV reactivation and disease in adult CMV-seropositive [R+] recipients of an allogeneic HSCT*
Mechanism of action	Inhibits viral replication by targeting the pUL56 subunit of the CMV viral terminase complex
Administration & dosage	Oral tablets or intravenously (IV), 480 mg once daily, decreased to 240 mg once daily if co-administered with cyclosporin A (CsA)
Duration of treatment	Up to 100 days post-transplant
Cost (list price)	[redacted]/cycle (69.4 days* x 240mg tablets) [redacted]/cycle (69.4 days* x 480mg tablets) [redacted]/cycle (69.4 days* x 240mg IV) [redacted]/cycle (69.4 days* x 480mg IV) A confidential patient access scheme has been proposed ** 69.4 days was the mean duration of letermovir exposure (both formulations) recorded in PN001.*

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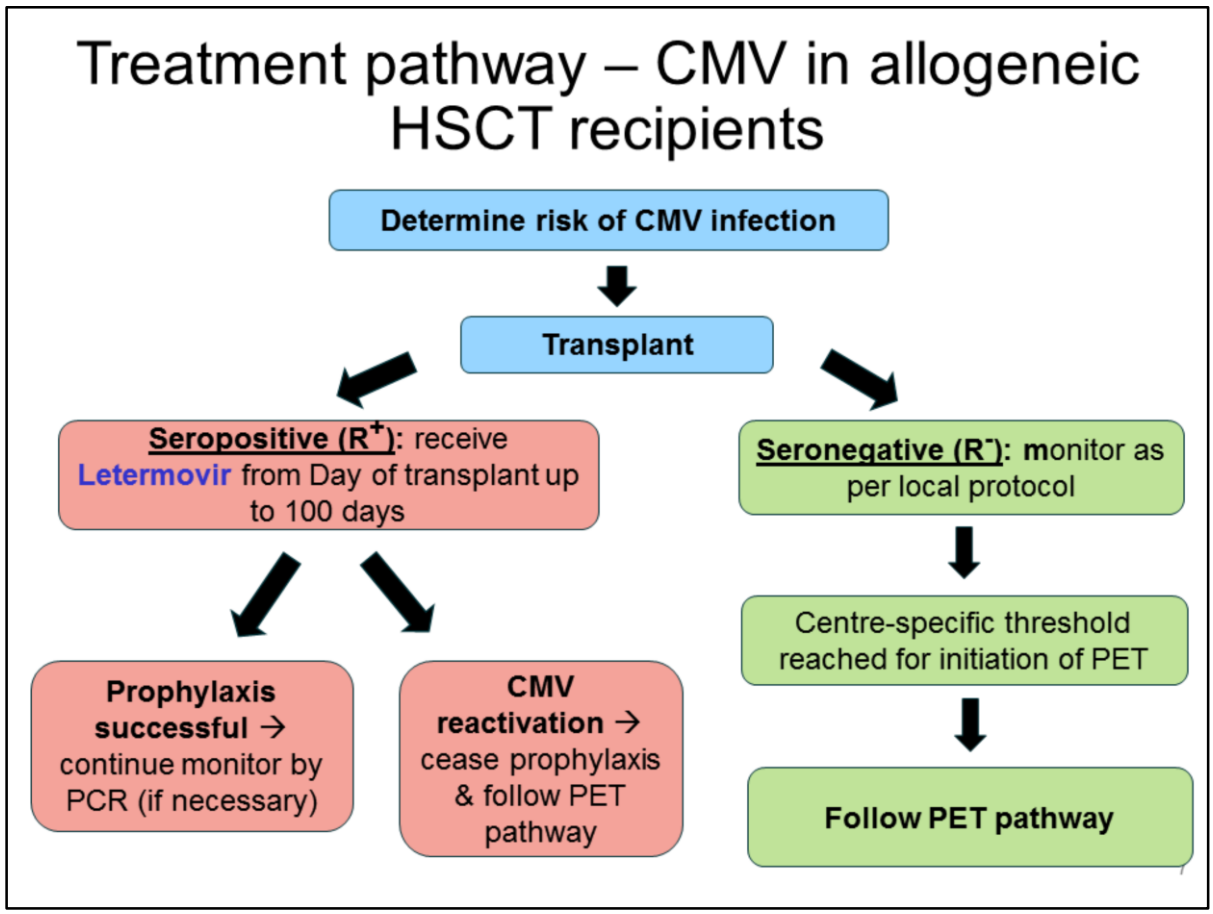
- At the time of the launch, the company is only making the 240mg strength available in the UK

*The summary of product characteristics states that letermovir may be started on the day of transplant and no later than 28 days post-transplant. letermovir may be started before or after engraftment. Prophylaxis with letermovir should continue through 100 days post-transplant.

It also states that the safety and efficacy of letermovir use for more than 100 days has not been studied in clinical trials but that prolonged letermovir prophylaxis beyond 100 days post-transplant may be of benefit in some patients at high risk for late CMV reactivation (see section 5.1). Use of letermovir prophylaxis for greater than 100 days requires a careful assessment of the benefit-risk balance



- R^+= Recipient-positive = high CVM reactivation risk
- R^- = Recipient-negative = low CMV reactivation risk
- PET = Pre-emptive therapy

- The licence for letermovir states that prophylaxis should be started after HSCT, between the day of transplant and no later than 28 days post-transplant and should continue through 100 days post-transplant, thereby minimising the use of PET and its associated sequelae and costs
- Letermovir can be started before or after engraftment occurs.
- The ERG notes some regional difference within England with regards to the monitoring and management of CMV infection in clinical practice

Patient experts comments
Anthony Nolan

- No authorised treatments available for CMV prophylaxis directly following HSCT
- Current treatments have serious side effects that causes severe problems. Patients stated: *"A kinder treatment is definitely needed; after going through chemo and total body irradiation the treatment for CMV was by far the worst part"*
- CMV reactivation affects quality of life and causes patients to return to hospital without the protections against infection associated with a transplant unit
- *"8 of 13 (62%) patients surveyed said that CMV reactivation had a 'negative' or 'very negative' effect on their mental health and well-being"*
- Patients would welcome the fact that letermovir has the option to be taken orally, allowing them to manage their condition at home in conjunction with a blood test schedule at their blood clinic
- Patients and their families would benefit significantly from a treatment which could prevent CMV reactivation

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Clinical expert comments

Anthony Nolan & Royal College of Pathologists/ British Society for Haematology

- Letermovir is a novel therapy that has shown to significantly reduce CMV reactivation/infection following allogeneic HSCT without high risk of adverse events, in particular myelotoxicity, graft failure and renal toxicity
- Letermovir should reduce the need for exposure to PET, which is associated with significant toxicity, morbidity, reduced quality of life and increased treatment costs
- Letermovir could improve mortality without relapse/recurrence
- Use of the technology: *"Oral medication. No current standard in this indication. So very easy to introduce, and no practical issues regarding increased testing or monitoring. It may even be possible to curtail surveillance monitoring"*
- Rules: start between day 0 and 28 of transplant and stopping either at day 100, or on failure and emergence of viral DNAemia (switch to PET)

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NHS England comments

- Current prophylaxis with antivirals drugs are ineffective and associated with significant toxicity and morbidity
- Therefore, the current standard approach in Europe is to reduce CMV-related morbidity and mortality post-HSCT transplant by early initiation of PET against CMV
- Letermovir has demonstrated superior efficacy over placebo in PN001 trial in prevention of clinically significant CMV infection and its safety profile (unlike current options) is comparable to placebo
- It would therefore become the 1st line option for prophylaxis if approved given the issues with current treatment options and it would potentially reduce the need for PET

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Decision problem:
Deviations from final scope

	Final scope	Company submission and rationale for deviations
Population	Adults with sero-positive cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant	
Intervention	Letermovir	
Comparators	• Aciclovir • Valaciclovir • No preventative treatment	Company included a placebo group and did not consider aciclovir and valaciclovir because for this indication and population: - no relevant/robust UK evidence supporting their use - lack of observed efficacy with aciclovir and both aciclovir and valaciclovir associated with neurotoxicity

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- Population: There is some lack of clarity regarding whether patients with detectable CMV DNA but a low viral load would be initiated on letermovir in clinical practice.

- Outcomes (final scope vs. company submission):
  - CMV infection rate are replaced with clinically-significant CMV infection
  - Initiation of PET referred to the initiation with ganciclovir, valganciclovir, foscarnet and/or cidofovir
  - 'Time to all-cause mortality' and 'overall survival' are replaced with 'all-cause mortality' (incidence rates at set time points were compared)

- Subgroups:
  - Analyses were presented for high-risk subgroup but the base case covers all patients eligible for letermovir.
  - The company also included additional analyses based on risk categories for CMV reactivation, patient characteristics, and conditioning and concomitant immunosuppressive regimen as per study protocol.

	Final scope	Company submission and rationale for deviations
Outcomes	• CMV infection rate • Reduction of hospital in-patient days • Time to onset of clinically significant CMV infection • Time to initiation of pre-emptive therapy for CMV viraemia • Time to all-cause mortality • Overall survival • Adverse effects of treatment • Health-related quality of life	Outcomes reflect but do not exactly match those listed in the final scope: • Clinically-significant CMV infection • Time to onset of clinically-significant CMV infection • CMV disease • Initiation of pre-emptive therapy for documented CMV viraemia • Time to initiation of pre-emptive therapy for documented CMV viraemia • All-cause mortality • Opportunistic infections • Acute and/or chronic GvHD • Re-hospitalisations • Adverse events • Health-related quality of life
Subgroups	People at high risk of CMV reactivation (if evidence allows)	As per scope plus additional subgroup analyses as per study protocol

⊙ ***Is the decision problem addressed appropriately?***

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Clinical effectiveness

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PN001 Trial

Study type	Phase III, International, multicentre, randomised, double-blind, placebo-controlled trial
Population	Adult CMV-seropositive recipients of an allogeneic HSCT (n= 570)
Intervention	Oral or IV letermovir 480 mg once-daily (OD, n=376), adjusted to 240 mg OD if co-administered with CsA)
Comparator	Placebo (mimicking pre-emptive therapy; the current standard of care)
Outcomes **(outcomes in bold are incorporated in the model)**	• **Clinically-significant CMV infection** • Time to onset of clinically-significant CMV infection • **Initiation of pre-emptive therapy for documented CMV viraemia** • Time to initiation of pre-emptive therapy for documented CMV viraemia • **All-cause mortality** • **Reduction of hospital in-patient days** • **Adverse events** • **Health-related quality of life**
Time points	• Efficacy data: week 14 (end of therapy) and 24 post-transplant • Safety data: week 14, 24 and 48 post-transplant

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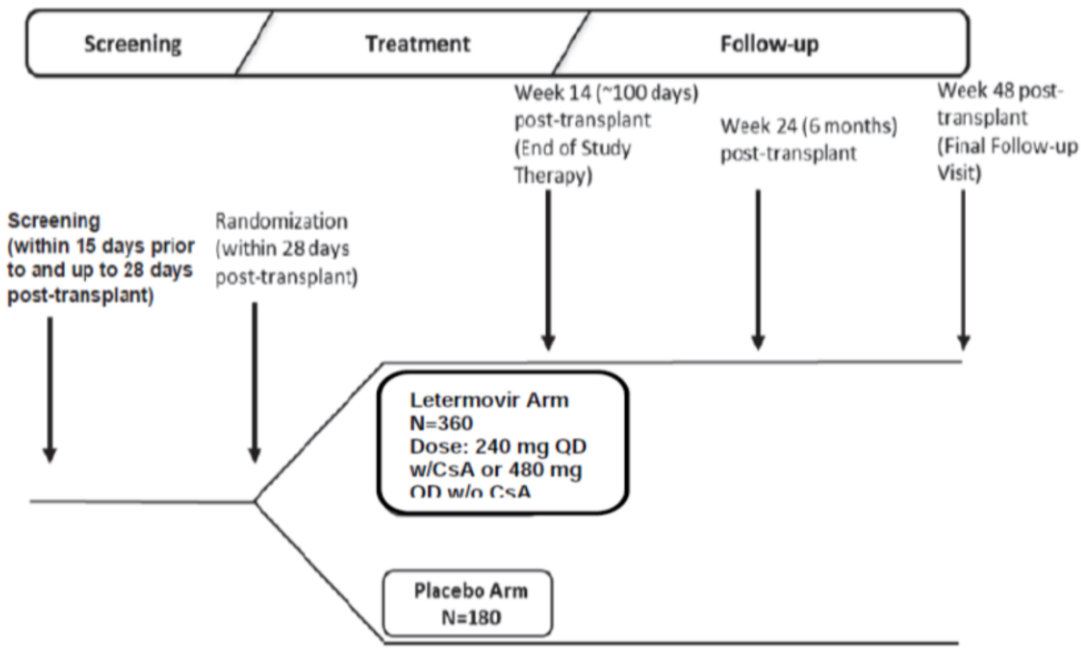
- Population: Adult patients with documented CMV **but no detectable CMV DNA at baseline**, within 28 days of a first HSCT, randomised to receive letermovir or placebo (2:1 ratio).
- CMV infection by week 24 is the primary efficacy endpoint
- Clinically-significant CMV infection post transplant defined as the occurrence of either:
    1. Initiation of anti-CMV pre-emptive therapy (PET) based on documented CMV viraemia (as measured by the central or local laboratory test results) and the clinical condition of the patient. Initiation of PET in this study referred to treatment with ganciclovir, valganciclovir, foscarnet and/or cidofovir

OR

    2. Onset of CMV end-organ disease

- Only 12 patients from 2 UK centres were enrolled in the study.

PN001 study design



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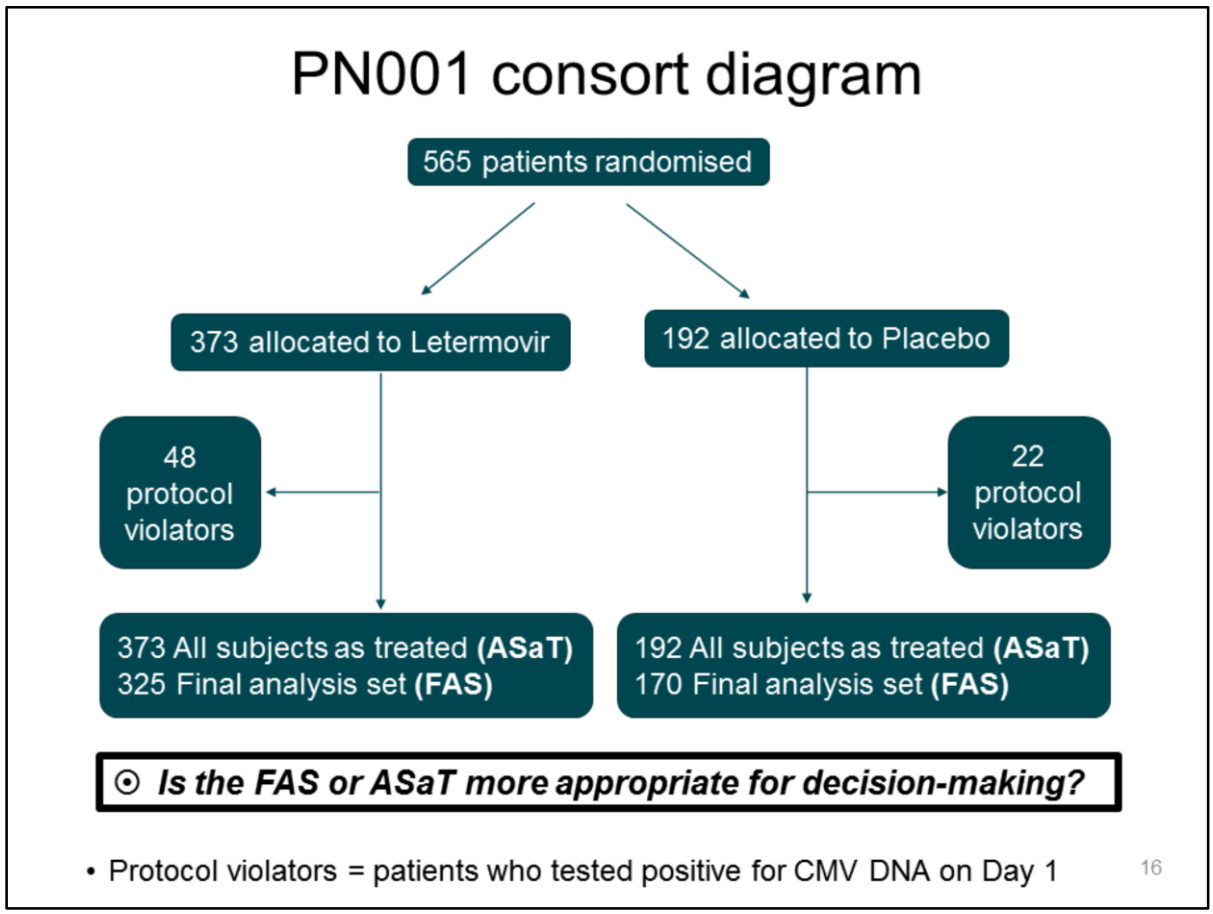

- All subjects as treated (ASaT) = All randomised and treated
- Final analysis set (FAS) = Served as the primary population for the analysis of the primary outcome in PN001. The FAS consisted of all randomised patients who received at least one dose of study medication and had no detectable CMV viral DNA as measured by the central laboratory (n=70; 48 letermovir and 22 placebo) on day 1 (when study medication was initiated)

PN001 (ASaT) – baseline characteristics

	Letermovir (n=325) n (%)	Placebo (n=170) n (%)
Age (yr), median (range)	53.0 (18.0 - 75.0)	54.0 (19.0 - 78.0)
Male	211 (56.6)	116 (60.4)
Weight (kg), median (range)	76.2 (35.1 - 141.5)	74.4 (40.9 - 113.1)
Region, n (%):		
- Asia Pacific	37 (9.9)	16 (8.3)
- Latin America	7 (1.9)	2 (1.0)
- Europe	185 (49.6)	97 (50.5)
- **UK**	**6 (3.2)**	**6 (6.2)**
- North America	144 (38.6)	77 (40.1)
- High risk of CMV reactivation	121 (32.4)	54 (28.1)
- Low risk of CMV reactivation	252 (67.6)	138 (71.9)
- Cyclosporin A use	193 (51.7)	100 (52.1)
- Tacrolimus use	160 (42.9)	79 (41.1)
Antithymocyte globulin (ATG) use	140 (37.5)	58 (30.2)
Alemtuzumab use	12 (3.2)	11 (5.7)

⊙ **Does the trial reflect people with CMV reactivation post R+ allogeneic HSCT in clinical practice?**

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Source: Company submission table 9, page 42-44 (ASaT population; all randomised and treated).

The primary efficacy analysis was performed on the FAS (Full Analysis Set) population and the ASaT (All Subjects as Treated) population was used for safety analyses. The baseline characteristics between the FAS and ASaT population were broadly similar.

Overall (n=565):

- Majority of patients were male (58%), white (82%), and with a mean age of 51 years old.
- 31% of patients were at high risk of reactivation at baseline and 52% were receiving concomitant CsA.
- Most common primary reasons for transplant were acute myeloid leukaemia (38%), myelodysplastic syndrome (17%), and lymphoma (13%).
- Majority of patients had received transplants using peripheral blood stem cells (73%).
- Baseline aciclovir use for prior HSV prophylaxis was similar across letermovir group (83%) and placebo (79%) (overall: 82%).
- Only a small proportion of patients were receiving ATG or alemtuzumab at baseline for T-cell depletion; both these drugs are commonly used in the UK for this subpopulation
- The doses and sequences of pre-emptive therapy were not reported in the study,

which may have varied across countries

- Randomisation was stratified by study centre and high or low risk for CMV reactivation**:**
    - High risk: Patients meeting one or more of the following criteria at the time of randomisation:
        - Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or –DR
        - Haploidentical donor
        - Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and –DRB1
        - Use of umbilical cord blood as stem cell source
        - Use of *ex vivo* T-cell-depleted grafts (including *ex vivo* use of alemtuzumab)
        - Grade 2 or greater graft-versus host disease, requiring the use of systemic corticosteroids (defined as the use of ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid)
    - Low risk: All patients not meeting the definition of high risk

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Efficacy results:
Clinically significant CMV infection by week 24

	FAS, %		ASaT, %	
Parameter	**Letermovir (n=325)**	**Placebo (n=170)**	**Letermovir (n=373)**	**Placebo (n=192)**
Primary endpoint				
% failed prophylaxis by wk24 (clinically significant CMV infection[a]) **(Non-completer=Failure)**[b]	37.5	60.6	[redacted]	[redacted]
Difference* (95% CI)	-23.5 (-32.5, -14.6); p<0.0001		[redacted]	
CMV infection[a] **(data as observed)**	[redacted]	[redacted]	[redacted]	[redacted]
Diff.* (95% CI)	[redacted]		-	
Initiation of PET[c]	16.0	40.0	[redacted]	[redacted]
CMV end-organ disease	1.5	1.8	[redacted]	[redacted]

[a] Clinically significant; [b] Non-completer-failure refer to those who discontinued from the study early and assumed that prophylaxis has failed; [c] Based on documented CMV viraemia; * Stratum-adjusted treatment difference (95% CI) (letermovir-placebo). One sided p value

Source: company submission table 11 and clarification response tables 7 & 9

- Primary efficacy endpoint was the proportion of failed prophylaxis by week 24, i.e. clinically significant CMV infection by week 24, as assessed by the % of patients with CMV end-organ disease or initiation of pre-emptive therapy (PET) based on documented viraemia and the patient's clinical condition.
- All cases of CMV disease are confirmed by an independent and blinded Clinical Adjudication Committee (CAC)
- Primary analysis was of the FAS population, which included all randomised patients who received at least one dose of study medication and had no detectable CMV viral DNA (measured by the central laboratory) on day 1 (when study medication was initiated). It used an assumption that patients who discontinued from study before week 24 or had missing data points in the week 24 visit window equalled a CMV infection event. This 'non-completer = failure' (NC=F) approach was the primary method used for missing data - the ERG considered this a conservative approach.
- Company also presented results for the population that was **excluded from the FAS** because they had detectable CMV DNA on day 1 of the study: % with CMV infection by wk 24 [NC=F]: letermovir **64.6%** vs placebo **90.9%** (difference 26.1 (95% CI, -45.9 to -6.3), p<0.0048). Initiation of PET: **43.8% vs 77.3%**

- A secondary missing data approach was the ‘data-as-observed’ (DAO) approach, where any patient with a missing value for a particular endpoint was excluded from the analysis – the ERG considered this is an optimistic approach, which ignores any attrition bias.
    - The ERG notes that clinical inputs used in the economic model were based on DAO analyses only.

- The company also presented 2 additional sensitivity analyses to the methods for imputation in the analysis of the FAS dataset - ‘missing-at-random’ and ‘missing-not-at-random.

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Efficacy results (FAS):

Initiation of PET for documented viraemia by week 24

Parameter	Letermovir (n=325), n(%)	Placebo (n=170), n(%)	Difference (95% CI) , one-sided p-value
Initiation of PET based on Central laboratory			
FAS population			
Initiation of PET (**NC=F**)	119 (36.6)	101 (59.4)	-23.3 (-32.3, -14.3), p<0.0001
Initiation of PET (no imputation)	52 (16.0)*	68 (40.0)*	-30.6 (-40.2, -21.0), p<0.0001
Discontinued before Week 24	57 (17.5)	28 (16.5)	
Missing outcome	10 (3.1)	5 (2.9)	
ASaT population			
Initiation of PET (NC=F)	[redacted]	[redacted]	[redacted]
Initiation of PET (no imputation)	[redacted]	[redacted]	
Discontinued before Week 24	[redacted]	[redacted]	
Missing outcome	[redacted]	[redacted]	

* Percentage based on intention-to-treat

Source: Table 10 in ERG report

- Initiation of anti-CMV PET based on documented CMV viraemia (detectable presence of CMV DNA, as measured by the central laboratory)
    - a decision to initiate PET could also be made on an individual basis based on a positive local laboratory test. As long as the result was later confirmed by the standardised central laboratory test, the lower threshold was acceptable
- Results reflect those of the primary endpoint.
- ASaT results were similar to FAS results but the number of events was higher in the ASaT population, reflecting that patients excluded from the FAS population were at higher risk of developing a clinically significant infection requiring initiation of PET

Efficacy results: CMV disease by week 14 and 24 (FAS)

Parameter	Letermovir (n=285) n (%)	Placebo (n=145) n (%)	Difference (95% CI)*
CMV Disease by Week 14 (no imputation)	1 (0.4)	2 (1.4)	-1.0 (-3.5, 1.5) p=0.2258
CMV Disease by Week 24 (no imputation)	5 (2.0)	3 (2.4)	-0.4 (-4.0%, 3.2%), p=0.4056
* Nominal one-sided p-value			

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Source: Company clarification response table 13

- The overall incidence of CMV end-organ disease was low through both the Week 14 and Week 24 post-transplant time points. Therefore, only DAO analyses were used so as not to classify patients who discontinued before Week 24 post-transplant or had missing data as failures, which could lead to potentially misleading estimates of CMV end-organ disease rates.

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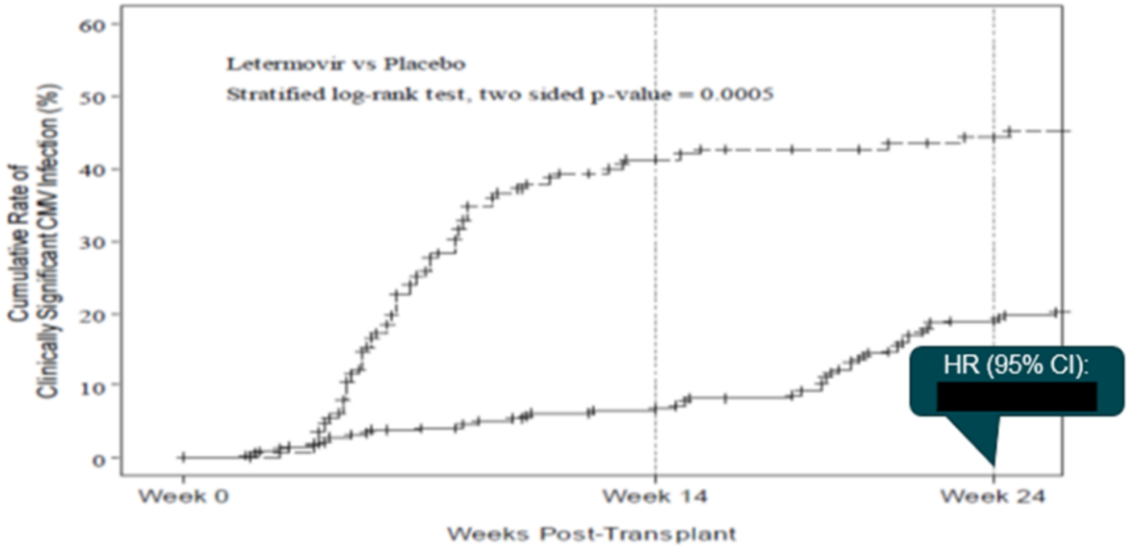
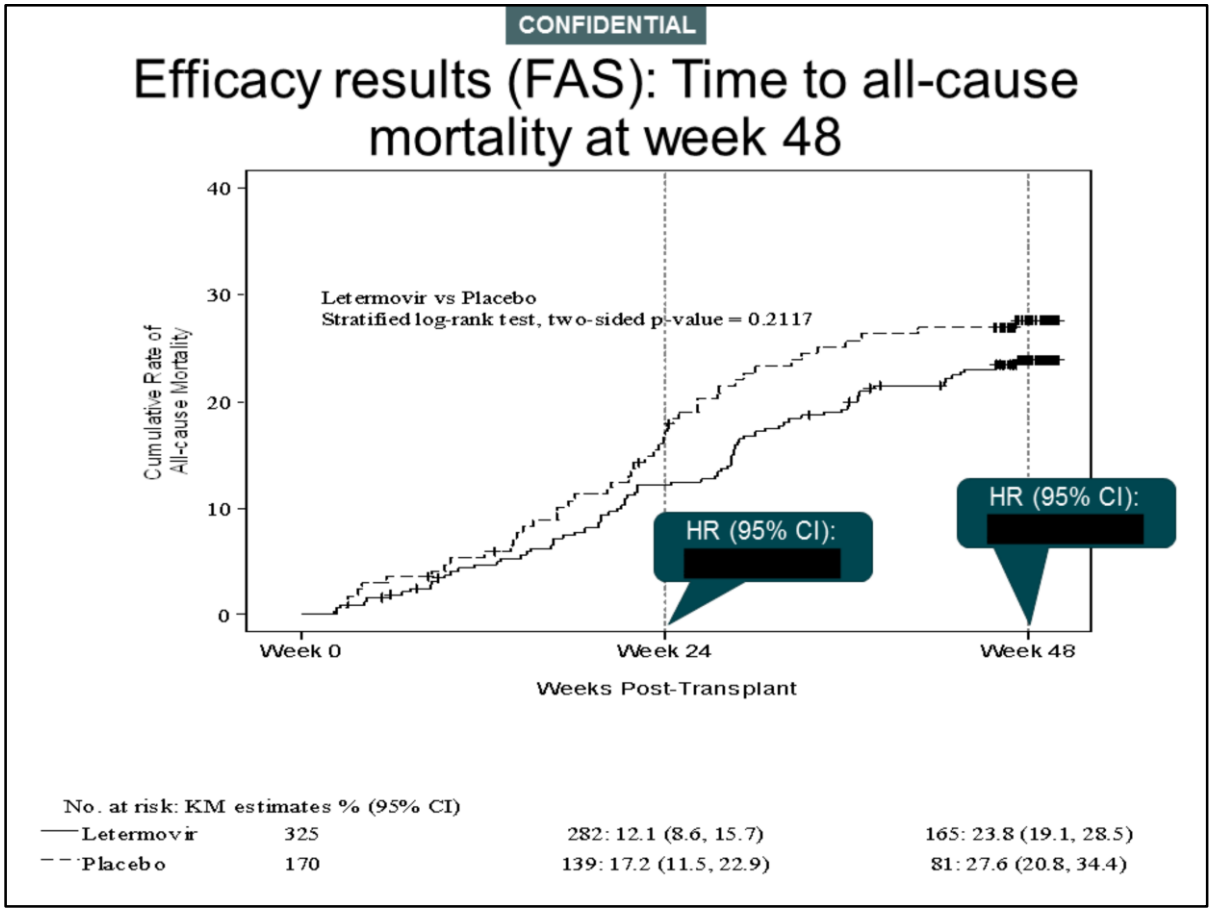
Efficacy results (FAS): Time to onset of clinically-significant CMV infection by week 24



[redacted]

- There is a large separation between the curves from Day 0 to week 14 while patients were on study drug. Following week 14 (end of therapy), there was a small rebound effect in letermovir group.
- Factors associated with CMV infection after cessation of letermovir included high baseline risk for CMV reactivation, GvHD and corticosteroid use.
- The results are after controlling for stratification of high and low risk of CMV end-organ disease at baseline (p-value <0.0005).



- All-cause mortality was lower in the letermovir group than in the placebo group at week 24 (p-value=0.0401) but in week 48 the difference was not statistically significant (p-value=0.2117).

- When stratified by prior CMV infection in an ad hoc analysis there was a lower mortality rate through week 48 in the letermovir group (15.8%) vs. placebo group (31%) among patients with clinically-significant CMV infection through week 24; and in patients without clinically significant CMV infection through week 24, the mortality rates between letermovir (52/268 [19.4%]) and placebo (18/99 [18.2%]) were similar.

- The ERG suggests that the results indicate that letermovir may have some impact on additional CMV-related mortality, despite not completely preventing CMV reactivation.

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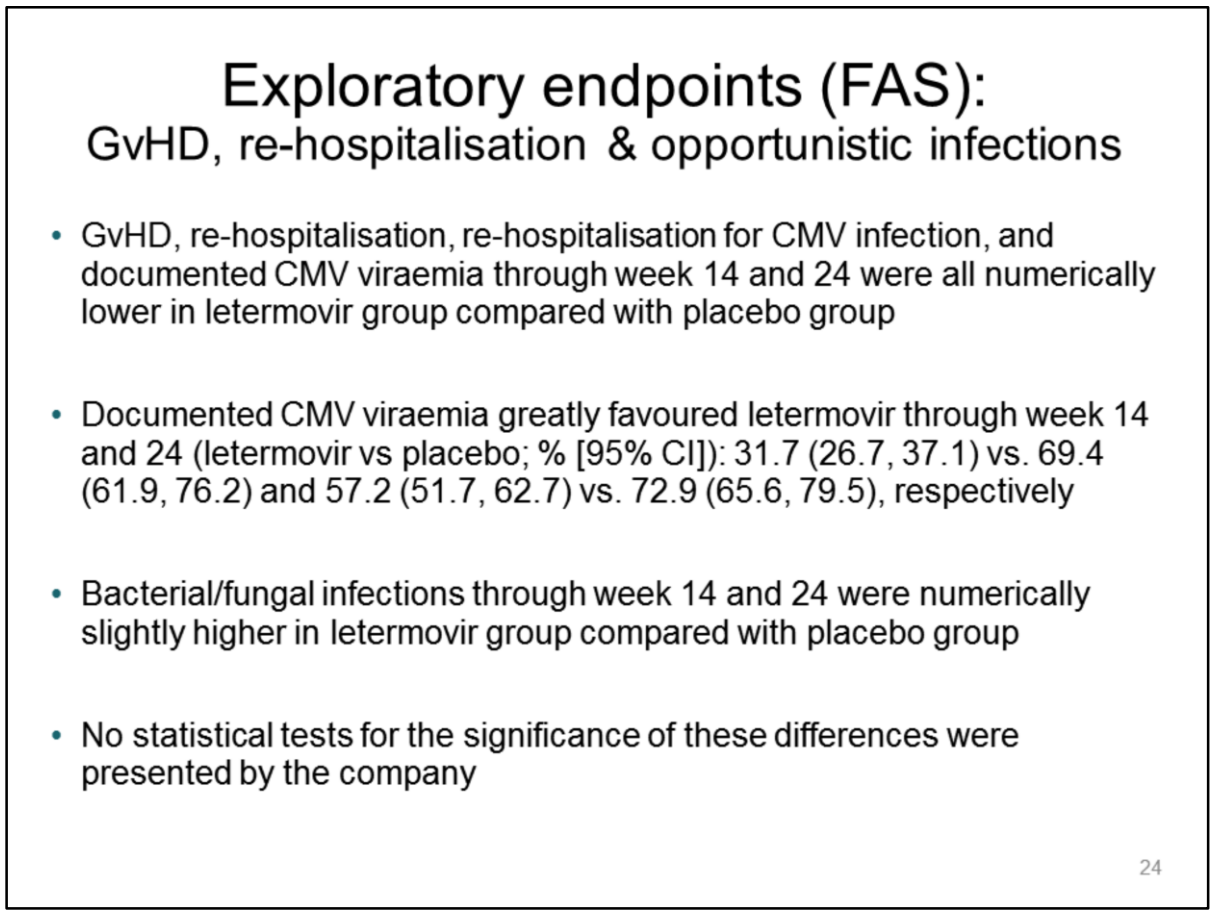
HrQoL results (FAS):
EQ-5D Index and FACT-BMT total score

	Letermovir vs Placebo	
	Mean difference (95% CI)	p-value
EQ-5D UK Index		
Baseline	[redacted]	[redacted]
Week 14 post-transplant	[redacted]	[redacted]
Week 24 post-transplant	[redacted]	[redacted]
Week 48 post-transplant	[redacted]	[redacted]
FACT-BMT total score		
Baseline	[redacted]	[redacted]
Week 14 post-transplant	[redacted]	[redacted]
Week 24 post-transplant	[redacted]	[redacted]
Week 48 post-transplant	[redacted]	[redacted]

Source: ERG report table 15, page 60 (the ERG adapted tables 34 and 44 of the EQ5D and FACT-BMT analysis report provided by the company)

- EQ-5D (version 3L) & FACT-BMT (version 4)
- The ERG notes that:
  - three of the four assessment points (baseline, week 24 and 48 post-transplant) are when the patient is not taking letermovir
  - The mean values of EQ-5D and FACT-BMT scores do not represent any single condition, instead a mixture of those who have had CMV reactivation and will have initiated PET and those who have not → difference in HrQoL scores will therefore only reflect the difference between these two health states rather than any direct impact of letermovir on HrQoL



Source: Company submission table 15 and clarification response table 17

Subgroup analyses

- Subgroup analyses were based on risk categories for CMV reactivation, patient characteristics, and conditioning and concomitant immunosuppressive regimen

Results showed that:

- Letermovir reduces incidence of clinically significant CMV infection in all subgroup analyses
- Its effect size was numerically higher than that of the whole trial population in: high risk patients, donor mismatch subgroups, haploidentical donors, female subgroups, and with use of non-myeloablative conditioning regimen
- It was numerically lower in non-European patients, and use of tacrolimus as immunosuppressant
- No tests for interaction were conducted to evaluate the statistical significance of these subgroup differences

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Although analyses have been presented for the high-risk subgroup (which demonstrated no difference in efficacy compared with the low-risk population), the base-case analysis covers all patients eligible to receive letermovir.

No tests for interaction were conducted to evaluate the statistical significance of these subgroup differences.

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Overall safety profile (ASaT)

	Letermovir (n=373)	Placebo (n=192)	Letermovir (n=373)	Placebo (n=192)	Letermovir (n=373)	Placebo (n=192)
	By week 14, n (%)		By week 24, n (%)		By week 48, n (%)	
With ≥1 AEs	365 (97.9)	192 (100)	366 (98.1)	192 (100)	[redacted]	[redacted]
With drug-related† AEs	63 (16.9)	23 (12.0)	63 (16.9)	23 (12.0)	[redacted]	[redacted]
With non-serious AEs	-	-	364 (97.6)	190 (99.0)	-	-
With SAEs	165 (44.2)	90 (46.9)	193 (51.7)	109 (56.8)	[redacted]	[redacted]
With serious drug-related AEs	3 (0.8)	3 (1.6)	3 (0.8)	3 (1.6)	[redacted]	[redacted]
Who died	38 (10.2)	17 (8.9)	61 (16.4)	38 (19.8)	[redacted]	[redacted]
Discontinued due to an AE	72 (19.3)	98 (51.0)	72 (19.2)	98 (51.0)	[redacted]	[redacted]
Discontinued due to a drug-related AE	18 (4.8)	7 (3.6)	18 (4.8)	7 (3.6)	[redacted]	[redacted]
Discontinued due to a SAE	35 (9.4)	27 (14.1)	35 (9.4)	27 (14.1)	[redacted]	[redacted]
Discontinued due to a serious drug-related AE	3 (0.8)	3 (1.6)	3 (0.8)	3 (1.6)	[redacted]	[redacted]

† Determined by the investigator to be related to the drug

ERG critique of the company's clinical effectiveness evidence

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ERG critique: Design limitations

- Treatment period was fixed at maximum 100 days (14 weeks) – Plausible that some patients (high risk of reactivation) may require longer treatments in clinical practice
- Follow-up period for primary end-point was limited to 24 weeks and mortality was only an exploratory analysis
- Clinically-significant CMV infection is defined differently in trial than in UK practice → potentially overestimating the CMV infection rate and underestimating the potential efficacy of letermovir
- Requirement for no detectable CMV DNA at baseline – appropriate?

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ERG critique: Generalisability issues

- Numerous differences between PN001 trial and UK practice:
  - Only 12 patients from UK enrolled in the trial
  - Average age: ~51 years in trial vs. ~45 years in NHS practice and include more matched unrelated patients than in the trial
  - Prevalence of CsA use, which significantly increases the bioavailability of letermovir: 51.7% in trial (ASaT population) vs. 90% in NHS practice
  - Prevalence of alemtuzumab use: 4% in trial vs. ~85% in some UK centres → trial likely to underestimate CMV reactivation rates and overestimate incidence of GvHD
  - Level of CMV-DNA at which PET was initiated in the trial was considerably lower than seen in NHS practice → likely that trial population initiated PET sooner and more frequently, potentially underestimating the expected duration of letermovir prophylaxis in practice
  - A delay (median 9 days, ASaT population; [redacted], FAS population) in between HSCT and start of prophylaxis in trial – likely in NHS practice?

Is the trial generalisable to clinical practice in the NHS?

Cost effectiveness

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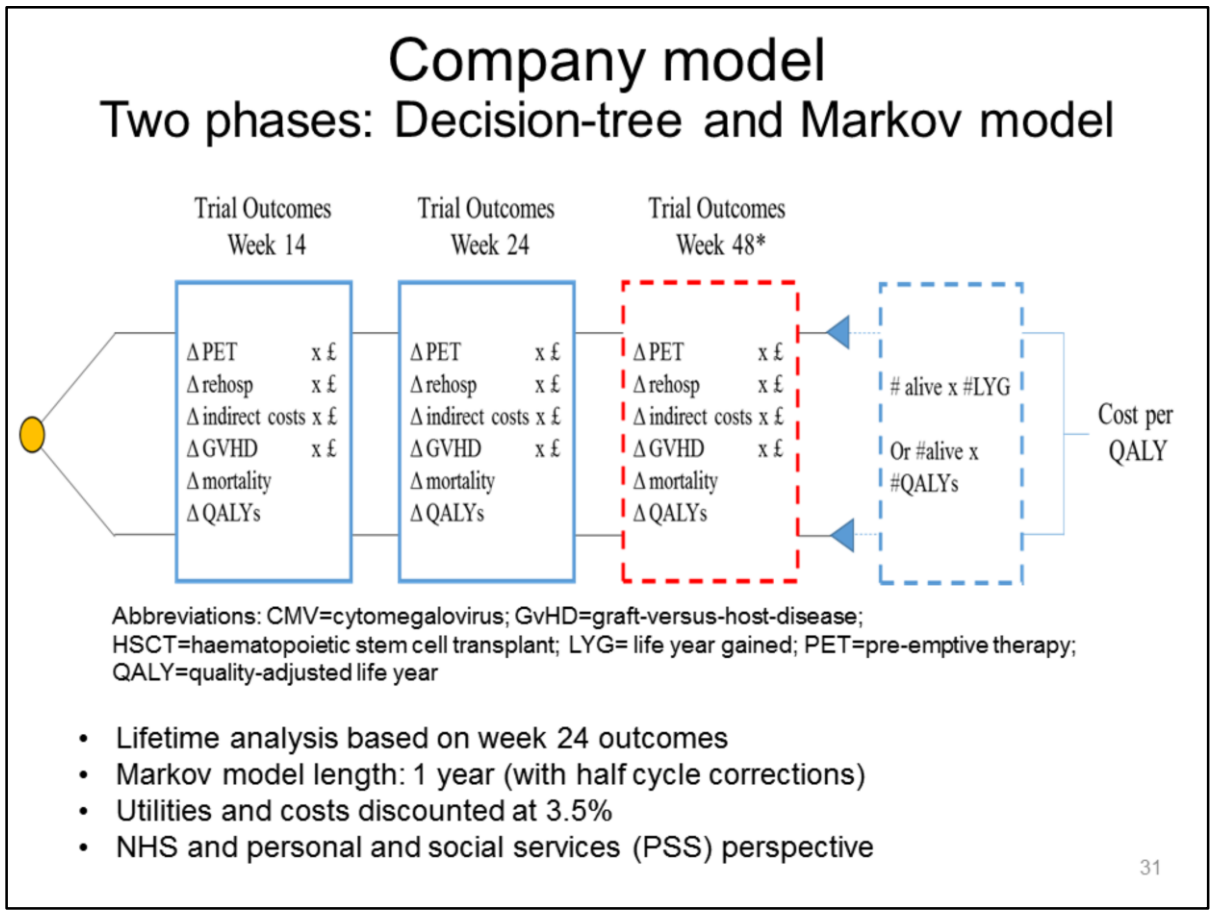

- A de novo model was used to estimate the cost-effectiveness of letermovir prophylaxis vs. standard care (no prophylaxis).
- The model structure consists of a decision tree phase covering the first 24 weeks post-transplant (48 weeks in scenario analysis) and Markov model phase covering the remaining time horizon of the model.
- In the decision tree phase, differences in the rate pre-emptive therapy CMV disease, re-hospitalisations, opportunistic infection, GvHD, AEs and mortality were accounted for using cumulative probabilities from the PN001 trial (based on DAO) with events permitted to occur at week 14, 24 and 48 (week 48 is for scenario analysis only)
- Patients then move into a simple two-state Markov model (alive or dead) to account for the mortality benefits associated with letermovir.

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Modelling clinical outcomes: Decision-tree phase

- Cumulative probabilities of 6 different clinical events from PN001 (week 24 DAO outcomes; FAS population) were included in the model

Clinical outcome	24 weeks		48 weeks	
	Letermovir	Placebo	Letermovir	Placebo
Initiation of PET	[redacted]	[redacted]	[redacted]	[redacted]
CMV disease	[redacted]	[redacted]	[redacted]	[redacted]
CMV-related re-hospitalisation	[redacted]	[redacted]	[redacted]	[redacted]
PET-related AEs	[redacted]	[redacted]	[redacted]	[redacted]
GvHD	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]

- No treatment-related AEs included – Only patients who initiate PET were assumed to experience AEs, these include neutropaenia (5.3%), thrombocytopaenia (7.8%) and leukopaenia (3.9%)
- Week 24 outcomes were extrapolated (assuming no further events) to the end of year 1 where patients enter the Markov model phase

Modelling clinical outcomes: Markov model phase

- This phase determine the life-expectancy and rate of QALY accrual in patients who are alive at the end of the decision-tree phase
- Mortality rate assumed to be the same in both treatment groups and was based on general population mortality data from ONS, with a standardised mortality rate (SMR) from Wingard et al. (2011) applied to account for the impact of the underlying condition
- Excess risk of mortality data in Wingard et al (2011) was calculated from 2 years to 15 years post-transplant, after which the excess risk of mortality was assumed to remain constant

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

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- ONS = Office for National Statistics
- HMRN = Haematological Malignancy Research Network
- The SMR applied was generated using a weighted average of 5 SMR for acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS), severe aplastic anaemia (SAA), and Lymphoma reported in Wingard *et al.* (2011).
- The weights applied are determined based on the proportion of patients in the ASaT population of the PN001 trial with each underlying condition.
- Wingard study did not report SMRs for all primary conditions, a number of assumptions were therefore made in the model to estimate the SMR in these:
    - For chronic myeloid leukaemia (CML), chronic lymphocytic leukaemia (CLL) and others (not ALL, AML, MDS, SAA, CLL, CML, myelofibrosis or PCM) the SMR applied was assumed equal to that of myelodysplastic syndrome (MDS)
    - For myelofibrosis and plasma cell myeloma (PCM) the SMR applied was assumed equal to SAA.

Assumptions used in the CE model (base case)

Duration of therapy was 69.4 days (ASaT population)
95% concomitant CsA use
95% of patients initiate with oral letermovir
Average duration of PET was 21 days
Two PCR tests per week applied to both arms of the model
Prescribing pattern of PETs: 37.5% ganciclovir, 37.5% valganciclovir and 25% foscarnet
CMV disease equal to the total cost of PET
RR of mortality at two years from Wingard et al (2011) is equal to the RR at 1 year
RR of mortality for CML, CLL and other assumed equal to SAA
RR of mortality for myelofibrosis and PCM assumed equal to MDS
Opportunistic infections treated in the outpatient setting
Methylprednisolone IV administration for GvHD takes place in the outpatient setting

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CsA = cyclosporin A
PCR = polymerase chain reaction
PET = pre-emptive therapy
RR = relative risk
CML = chronic myeloid leukaemia
CLL = chronic lymphocytic leukaemia
SAA = severe aplastic anaemia
PCM = plasma cell myeloma
MDS = myelodysplastic syndrome

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Utility values are derived from EQ-5D scores from PN001

Time point utility values		
Time point	**Letermovir**	**Placebo**
Change at Week 14	[redacted]	[redacted]
Change at week 24	[redacted]	[redacted]
Change at week 48	[redacted]	[redacted]
Post-trial utility	0.82	0.82

General UK population utility values	
Age	**Utility value EQ-5D (95% CI)**
60 to ≤ 65	0.8072 (0.793,0.821)
65 to ≤ 70	0.8041 (0.790, 0.817)
70 to ≤ 75	0.7790 (0.766,0.791)
75 to ≤ 80	0.7533 (0.739,0.767)
80 to ≤ 85	0.6985 (0.677,0.719)
> 85	0.65497 (0.624,0.675)

- Utility expected for survivors 1 year post-transplant was either 0.82 from an acute myeloid leukemia population who underwent a HSCT (Leunis et al., 2014 based on EQ-5D-5L) or the age-specific general population utility (Ara et al., 2011), whichever was lowest
- No disutilities were applied within the model – assumed to be captured in EQ-5D utility

Company base case model results (with PAS)

Deterministic base case ICER

	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Placebo	£28,805	7.91	6.73	£5,014	0.52	0.46	**£10,904**
Letermovir	£33,891	8.43	7.19				

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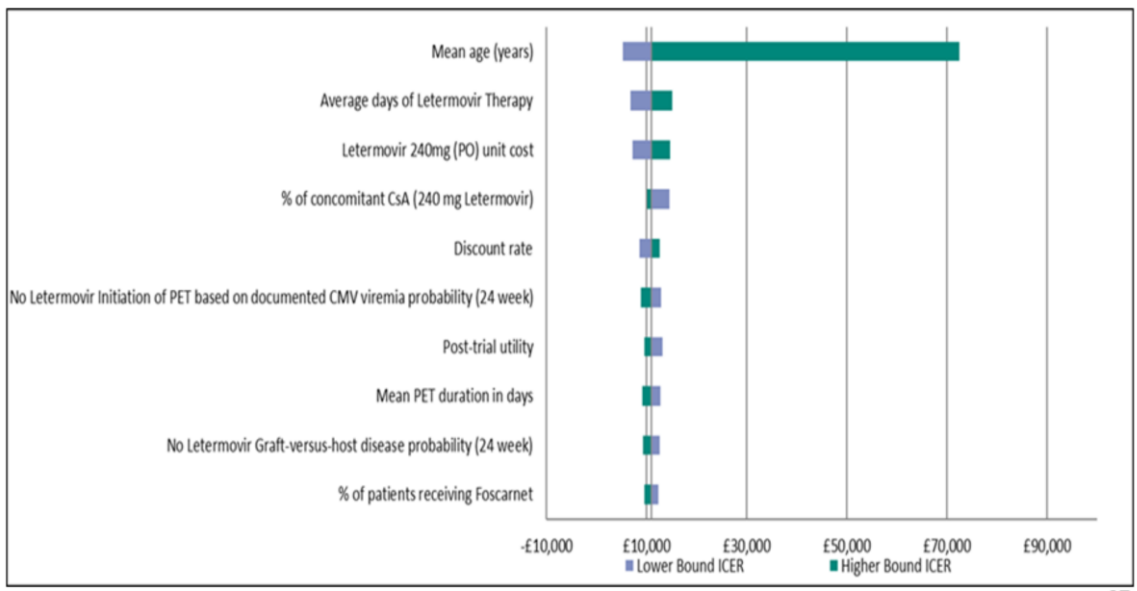
Deterministic sensitivity analyses

- A one-way sensitivity analysis results show that the base-case ICER is most sensitive to the age parameter



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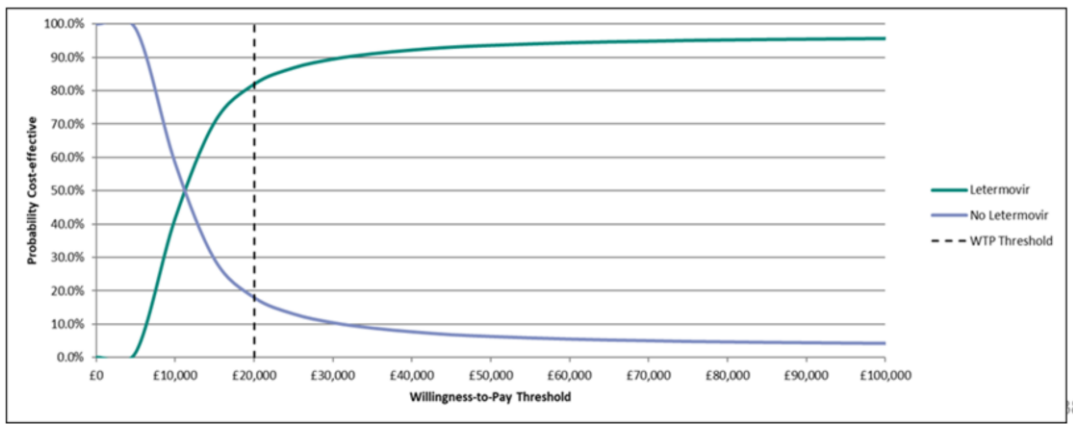
Probabilistic sensitivity analyses (with PAS)

Outcome	Letermovir	Standard of care
Total cost		
Mean	£33,826	£28,790
Standard deviation	£945	£847
QALYs		
Mean	7.19	6.72
Standard deviation	0.17	0.24
ICER for letermovir vs placebo	**£10,913**	



Company scenario analyses (with PAS) (1)

Model input	Parameter	ICER	Changes from base-case ICER (%)
Base case		**£10,904**	
Average days of letermovir therapy	81	**£13,679**	£2,775 (25%)
Average days of letermovir therapy	100	**£18,226**	£7,322 (67%)
% of patients receiving letermovir Therapy (PO)	73%	**£12,432**	£1,528 (14%)
Percentage of patients receiving oral letermovir therapy (PO)	100%	**£10,556**	-£348 (3%)
Average days of letermovir IV therapy	28	**£11,285**	£381 (3%)
Percentage of patients receiving 240mg Letermovir	51.9%	**£17,471**	£6,567 (60%)
Average days of pre-emptive therapy	59	**Letermovir dominant**	n/a
Beyond trial mortality in year 1 and 2 based on probability of mortality between 24-week and 48-week	11.5%	**£13,629***	£2,725 (25%)
cGvHD disutility	0.090	**£10,871**	-£33 (0%)

ICER=incremental cost-effectiveness ratio; IV=intravenous; NC=F=non-completer=failure; PO=oral; SoC=standard of care; *Model run based on week 48 data

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Source: Adapted from table 34 in the ERG report

Company scenario analyses (with PAS) (2)

Model input	Parameter	ICER	Changes from base-case ICER (%)
Base case		**£10,904**	
Medicine dose and duration			
Percentage of concomitant CsA (240 mg letermovir)	51.9%	**£14,962**	£4,058 (37%)
Percentage of IV letermovir	27%		
Average days of pre-emptive therapy	59		
NC=F (non-completer= failure) approach for missing data			
Letermovir initiation of pre-emptive therapy	16.0%	**£12,204**	£1,300 (12%)
Letermovir CMV disease	1.5%		
SoC initiation of pre-emptive therapy	40.0%		
SoC CMV disease	1.7%		

ICER=incremental cost-effectiveness ratio; IV=intravenous; NC=F=non-completer=failure; PO=oral; SoC=standard of care; *Model run based on week 48 data

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Source: adapted from table 34 in the ERG report

Company scenario analyses (with PAS) (3)

Scenarios/Model input	ICER (Lifetime based on 24-week)	Changes from base-case ICER (%)
Base-case	**£10,904**	
Long-term disutility following SCT		
Long term utility decrement (0.0144 per year) applied to the general population utilities	£10,959	£55 (1%)
Long-term costs following SCT		
Follow-up cost year 1 and 2 post SCT =£12,378 and £3,565, respectively	£12,322	£1,418 (13%)
***Relapse after SCT**		
Scenario – 6 month survival	£11,041	£137 (1.26%)
Scenario - 1 year survival	£11,156	£252 (2.31%)
Scenario - 2 year survival	£11,387	£483 (4.43%)
****Second-line treatment costs for GvHD and disutility for GvHD**		
Additional costs for acute GvHD and chronic GvHD included	£10,793	-£111 (-1.02%)
Additional disutility for acute GvHD and chronic GvHD included	£10,977	£73 (0.67%)
Both additional costs and disutility included	£10,866	-£38 (-0.35%)

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Additional scenario analyses requested by the ERG at the clarification stage.
Sources: tables 39-42 in the ERG report

Long-term disutility following SCT:

- Long term utility decrement of 0.0144 per year was calculated based on the difference between the utility reported in Leunis et al. 2014 (EQ-5D-5L) and general population mortality source from Ara et al. 2011 (based on EQ-5D-3L)

***Relapse after SCT:**

- The company presented scenarios for incorporating additional costs and disutilities associated with patients relapsing after SCT, assuming survival is 6 months, 1 year or 2 years
- In all scenarios, 10% of patients are assumed to relapse and a relapse is assumed to be associated with a 0.0114 disutility and a per cycle costs of £6,460
- ERG noted a small error in company's model which assumes that all patients incur a disutility associated with relapse rather than just the 10% of patients experiencing relapsed disease – ICERs presented here include this correction.

****Costs and disutilities associated with GvHD:**

- The company assumed 10% of patients developed acute GvHD and 6% of patients

acquired chronic GvHD

- ERG noted an error with the implementation of this scenario in the company's model – all the costs associated with GvHD were included in the trial time period, which is inappropriate because chronic GvHD usually manifest after a year post-SCT. The ERG therefore made the following amendments to the scenario:
    1. The cost of 10% of patients with aGvHD requiring second line treatment is added to the aGvHD costs in the model (an additional cost of £1,810.63);
    2. The cost of 6% of patients with aGvHD requiring second line treatment is added to the cGvHD costs in the model (an additional cost of £325.91).

Company scenario analyses (with PAS) (4): Using alternative time horizons to the base case

Model time horizon		ICER	Changes from base-case ICER (%)
Base case		**£10,904**	
Lifetime based on week 24 data	At 5 years	**£21,723**	£10,819 (99%)
	At 10 years	**£14,274**	£3,370 (31%)
	At 20 years	**£11,132**	£228 (2%)
Lifetime based on week 48 data	At 5 years	**£22,662**	£11,758 (108%)
	At 10 years	**£15,355**	£4,451 (41%)
	At 20 years	**£12,135**	£1,231 (11%)
	Lifetime	£11,897	£993 (9%)

Letermovir is suggested to be cost-effective compared to placebo at a short time horizon of 5 years and the ICER drops significantly for a time horizon of 10 years and more

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Source: adapted from table 35 in the ERG report.

Company scenario analyses (with PAS) (5): FAS/ASaT populations using time-to-event/ DAO analyses

Scenarios/Model input	ICER (Lifetime based on 24-week)	Changes from base-case ICER (%)
Base-case	**£10,904**	-
All clinical inputs using DAO analysis using ASaT population	£11,888	£984 (9%)
All clinical inputs using DAO analysis using FAS population	£11,966	£1,062 (10%)
All clinical inputs using missing-not-at-random analysis method to adjust of missing data and using the ASaT population	£13,329	£2,425 (22%)
All clinical inputs using missing-not-at-random analysis method to adjust of missing data and using the FAS population	£12,602	£1,698 (16%)

Additional scenario analyses requested by the ERG at the clarification stage.
Source: Table 36 from ERG report

- ERG considered the FAS population using DAO analysis as the most appropriate to include in the ERG's preferred base case analysis.

Company scenario analyses (with PAS) (6)
Parametric extrapolation of OS

Scenarios/Model input	ICER (Lifetime based on 24-week)	Changes from base-case ICER (%)
Base-case	**£10,904**	
Extrapolating survival data		
Exponential distribution – AsaT population	**£8,598**	-£2,306 (21%)
Weibull distribution - ASaT population	**£11,453**	£549 (5%)
Lognormal distribution - ASaT population	**£6,379**	-£4,525 (41%)
Loglogistic distribution - ASaT population	**£7,920**	-£2,984 (27%)
Gompertz distribution - ASaT population	**£14,309**	£3,405 (31%)
Exponential distribution - FAS population	**£7,910**	-£2,994 (27%)
Weibull distribution - FAS population	**£10,279**	-£625 (6%)
Lognormal distribution - FAS population	**£5,645**	-£5,259 (48%)
Loglogistic distribution - FAS population	**£7,158**	-£3,746 (34%)
Gompertz distribution - FAS population	**£10,531**	-£373 (3%)

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Additional scenario analyses requested by the ERG at the clarification stage.
Source: Table 37 in the ERG report

Company's approach in this analysis:
- Assumed no survival benefits attributable to letermovir beyond week 24 data from PN001
- The extrapolated curves for the whole post decision tree phase were relied on rather than moving to natural history data at an appropriate point e.g. 2 years post HSCT

Company scenario analyses (with PAS) (7)
Results using 48 week data from PN001 trial

Scenarios/Model input	ICER (Lifetime based on 24-week)	Changes from base-case ICER (%)
Base-case	**£10,904**	
48 week data – DAO_ASaT population	£11,168	£264 (2.42%)
48 week data – DAO_FAS population	£13,069	£2,165 (19.86%)
Revised mortality data - DAO_ASaT population	£10,687	-£217 (-1.99%)
Revised mortality data - DAO_FAS population	£15,071	£4,167 (38.22%)

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Source: Table 38 in the ERG report

Additional scenario analyses requested by the ERG at the clarification stage:

- To include clinical inputs available at week 48 in the PN001 trial
- To include life-time analysis using mortality data at 48-week elicited by the US FDA on those who withdrew from the study

ERG critique of the company's cost-effectiveness evidence

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ERG critique:
Structure of the model

1. **Over simplified modelling approach → company model lacks explicit health states to capture differences in QALYs**
   - No link between the occurrence of CMV events and the accrual of QALYs or the rate of CMV events and mortality, which is the key driver of cost-effectiveness
   - Direct impact of a CMV event and other clinical events e.g. GvHD on QoL are therefore not fully explored in the model.
2. **A major cost category associated with having received a HSCT has been omitted**
   - Ongoing care and management costs
   - Costs associated with a relapse in the underlying condition

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ERG critique: Clinical data inputs

3. **Clinical inputs based on 24 week data instead of 48 week data**
   - Inappropriate and inadequately justified by the company
4. **Data-as-observed approach used to account for missing data**
   - Incomplete follow ups are not adjusted
   - More complete data is available following a request by the FDA with just 3.2% patients lost to follow up vs. 13.5% in the main analysis
5. **Uncertainty in mortality benefits and data used to calculate SMR**
   - All-cause mortality in year 2 assumed equal to that in the year 3 – plausible?
     - HMRN reports 19% vs 3% in the company model
   - Wingard data used to calculate SMR covers 1980 to 2003 and >40% of the data set are from paediatric population – relevant to current practice?
6. **Considerable uncertainty in duration of letermovir prophylaxis**
   - Unlikely to be delays in initiating letermovir in practice and plausible that some patients require >100 days prophylaxis → ERG considers the FAS data (people with no CMV DNA on Day 1; mean 72 treatment days + mean 11 days treatment delay) to be most reflective of current practice

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SMR = standardized mortality ratio
HMRN = Haematological Malignancy Research Network

ERG critique: Disutilities

7. **Company model does not fully capture the long-term utility decrement associated with people having undergone SCT:**
   - The disutility applied in the company analysis (0.0114) is based on a mix of EQ-5D-5L and EQ-5D-3L values
   - The ERG considers this an inconsistent approach and is inconsistent with the value reported in Leunis et al. based on EQ-5D VA scores of 0.046
8. **Disutilities due to GvHD**
   - The ERG considers this should be included in the base-case analysis (only a scenario analysis was provided by the company)

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ERG critique: Costs and resource use assumptions

9. **Proportion of patients assumed to receive IV letermovir**
   - 27% observed in trial more representative of UK practice than the assumption of 95% made in the company base case
10. **Administration costs for oral letermovir therapy**
   - Should be included to reflect the resources required to give patients administration instructions and the dispensing costs for pharmacists' time
11. **CMV disease monitoring costs**
   - ERG's clinical advisor state twice-weekly monitoring would not continue for the entire duration of post-transplant care → costs overestimated in the model?
12. **Pre-emptive therapy costs:**
   - ERG's clinical advisors assume 5-15% would receive foscarnet (aligning with PN001) vs. 25% in company's base case
   - Valganciclovir should be associated with oral administration costs
   - IV administration costs for ganciclovir and foscarnet are calculated by multiplying costs by the number of infusions required → likely to overestimate the costs

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ERG corrections of company analysis

The ERG noted some errors within the company's scenario analyses. These scenario with errors and the errors identified were:

- The long-term disutility calculated for survivors of HSCT;
- The disutility associated with a relapse in the patients' underlying condition; and
- The costs and disutilities associated with acute GvHD and chronic GvHD

Scenario 1 and 3 above are included in the ERG's preferred base-case analysis, with the ERG's corrections incorporated.

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ERG exploratory analyses

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ERG alternative base case: summary of changes

The ERG's base case makes the following amendments to the company's base case model:

1. FAS population used for all clinical parameters;
2. 48 Week trial data used together with post-hoc analysis of all-cause mortality;
3. Mean duration of therapy assumed to be 83 days (FAS population duration of therapy)
4. Inclusion of medium-term care costs for survivors of HSCT and survivor disutility
5. Revisions to assumptions regarding GvHD costs and QALYs;
6. Inclusion of relapse disease based on HMRN rate of relapse (47% vs. 10% in company's scenario analysis);
7. Revisions to administration cost for letermovir and PET;
8. Foscarnet use assumed to be 15%;
9. Mortality data in the Markov phase based on HMRN data and relative risk from Martin et al. (2010)

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- Survivor disutility = based on the difference between the mean utility of patients in PN001 at 48 weeks and general population utilities from Ara et al. 2011

- Martin et al. (2010) trial included fewer paediatric patients and had a longer median follow up

Results of ERG alternative base case deterministic ICER (with PAS) (1)

Letermovir vs placebo	Inc. Cost	Inc. QALY	ICER	Change in ICER
Company's base-case analysis	5,014	0.46	**10,904**	-
#1. FAS population used for all clinical parameters	5,306	0.44	**11,966**	9.74%
#2. 48 Week trial data used together with post-hoc analysis of mortality	4,641	0.34	**13,710**	25.73%
#3. Mean duration of therapy assumed to be 83 days	6,510	0.46	**14,158**	29.84%
#4. Inclusion of medium-term care costs for survivors of HSCT and survivor disutility	5,666	0.45	**12,535**	14.96%
#5. Revisions to assumptions regarding GvHD costs and QALYs	4,963	0.46	**10,866**	-0.35%

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Source: Adapted from table 1 in the ERG report

Results of ERG alternative base case deterministic ICER (with PAS) (2)

Letermovir vs placebo	Inc. Cost	Inc. QALY	ICER	Change in ICER
#6. Inclusion of relapse disease based on HMRN rate of relapse	5,262	0.46	**11,449**	5%
#7. Revisions to administration cost for letermovir and PET	6,588	0.46	**14,328**	31.40%
#8. Foscarnet use assumed to be 15%	5,644	0.46	**12,274**	12.56%
#9. Mortality data in the Markov phase of the model based on date from HMRN and relative risk from Martin et al. 2010	4,899	0.44	**11,242**	3.1%

Letermovir vs placebo	Inc. Cost	Inc. QALY	ICER
ERG preferred base case analysis (scenarios #1 to #9 combined)			
Letermovir vs placebo	8,433	0.31	**27,536**

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Source: Adapted from table 1 in the ERG report

In the company's one-way sensitivity analysis (slide 37), the base-case ICER was shown to be most sensitive to the age parameter. The true ICER could therefore potentially be lower because the mean age of patients in the model is higher than the mean age of patients receiving allograft SCT according to HMRN data (50.8 vs. 45 years)

Scenario analysis on the ERG's preferred base case

Additional scenario analyses considering uncertainties surrounding 3 assumptions/ inputs used in the model:

1. **Duration of therapy**
   - 45% of patients receiving letermovir prophylaxis at 100 days were assumed to continue therapy for a fixed period 2, 4 and 6 weeks post 100 days
2. **Alternative approaches to handling missing data**
   - NC=F
   - MNAR
3. **Mortality at 48 weeks**
   - Alternative values for the mortality benefit associated with letermovir were considered

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Results of ERG scenario analyses (with PAS)

Scenario	ICER (£/QALY)
ERG preferred base-case analysis	**27,536**
Assumed maximum duration of therapy	
100 days + 2 wks	**29,776**
100 days + 4 wks	**31,909**
100 days + 6 wks	**34,255**
Approach for handling missing data	
failure (NC=F)	**30,179**
standard care arm (MNAR)	**30,567**
Mortality difference	
+2.8%	**34,471**
+3.3%	**30,570**
+4.3%	**25,110**
+4.8%	**23,124**

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Source: adapted tables 51-53 in the ERG report

- Mortality difference in the ERG preferred base-case analysis: +3.8%

- Exploratory analyses show that small changes to key assumptions can have considerably large impact on the ICER. In particular, even a small change to the mortality benefit associated with letermovir, results in very significant changes to ICER.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

March 2018

File name	Version	Contains confidential information	Date
ID1153_MSD_Letermovir_cytomegalovirus [ACIC]_redacted	1	Yes	6th March 2018

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

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Contents

Tables and figures

Abbreviations

AE	Adverse event (also adverse experience)
ALL	Acute lymphocytic leukaemia
ALT	Alanine transaminase
AML	Acute myeloid leukaemia
ASaT	All Subjects as Treated (All Randomised and Treated)
ASBMT	American Society for Blood and Marrow Transplantation
ASH	American Society of Hematology
AST	Aspartate transaminase
AUC	Area Under the Curve
BCSH	British Committee for Standards in Haematology
BSBMT	British Society of Blood and Marrow Transplantation
BSH	British Society for Haematology
CAC	Clinical Adjudication Committee
CEAC	Cost-effectiveness Acceptability Curve
CHMP	Committee on Human use of Medicinal Products
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CMV	Cytomegalovirus
CsA	Ciclosporin A
CSR	Clinical study report
DAO	Data as observed
DDF	Drug Development Forum
DBL	Database Lock
DNA	Deoxyribonucleic acid
DSU	Decision Support Unit
EBMT	European Society for Blood and Marrow Transplantation
ECG	Electrocardiogram
ECIL	European Conference on Infections in Leukaemia
eDMC	External Data Monitoring Committee
EMA	European Medicines Agency
eMC	Electronic Medicines Compendium

EQ-5D	EuroQol-5 Dimensions
FACT-BMT	Functional Assessment of Cancer Therapy (FACT-G) and Bone Marrow Transplantation Subscale (BMTS)
FAS	Full Analysis Set
FSH	Follicle-stimulating hormone
FUO	Fever of Unknown Origin
G-CSF	Granulocyte colony stimulating factor
GvHD	Graft-versus-host Disease
HBsAg	Hepatitis B surface antigen
HCV-Ab	Hepatitis C virus antibody
HIVAb	HIV antibody
HLA	Human leukocyte antigen
HRQoL	Health-related quality of life
H(S)CT	Haematopoietic (stem) cell transplant
HSV	Herpes simplex virus
HTA	Health Technology Assessment(s)
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
ICTRP	International Clinical Trials Registry Platform
IgG	Immunoglobulin G
INR	International Normalised Ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IUD	Intrauterine device
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Integrated web response system
K-M	Kaplan-Meier
LH	Luteinising hormone
LLoQ	Lower limit of quantification
MAIC	Matching Adjusted Indirect Comparison
MAR	Missing-at-random
MDR	Multi-drug resistant
MDS	Myelodysplastic syndrome
MID	Minimally Important Difference(s)

MNAR	Missing-not-at-random
MSD	Merck Sharp and Dohme Ltd
MTC	Mixed treatment comparison
NC=F	Non-completer=Failure
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OAT	Organic anion transporter
OATP	Organic anion transporter polypeptide
OD	Once-daily
PbR	Payment by results
P-gp	P-glycoprotein
PAS	Patient Access Scheme
PCM	Plasma cell myeloma
PCR	Polymerase chain reaction
PICOS	Population, Intervention, Comparator(s), Outcome(s), Study Type(s)
PO	Per oral
PP	Per protocol
PRO	Patient-reported Outcome(s)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
PT	Preferred Term
QALY(s)	Quality-Adjusted Life-Year(s)
QID	Quater in die (four times daily)
QoL	Quality of life
RNA	Ribonucleic acid
SAA	Severe aplastic anaemia
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query/ies
SMR	Standardised mortality ratio
SoC	Standard of Care

SOC	System Organ Class
TA	Technology Appraisal
UK	United Kingdom of Great Britain and Northern Ireland
ULN	Upper limit of normal
US(A)	United States (of America)
VAS	Visual analogue scale
VZV	Varicella zoster virus
WHO	World Health Organisation
WTP	Willingness-to-Pay

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. Letermovir (PREVYMIS®) is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT). [1]

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with sero-positive cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant	Adult CMV-seropositive [R+] recipients of an allogeneic haematopoietic stem cell transplant (HSCT).	Not required.
Intervention	Letermovir	Letermovir	Not required.

Comparator(s)	• Aciclovir (does not currently have a marketing authorisation in the UK for this indication) • Valaciclovir (does not currently have a marketing authorisation in the UK for this indication) • No preventative treatment	No prophylaxis against CMV reactivation (i.e. no comparators)	Aciclovir and valaciclovir have not been considered as relevant comparators for the following reasons: - Neither drug currently has a marketing authorisation in the UK for this indication - There is no relevant UK evidence supporting use of either treatment for CMV prophylaxis in this patient population (based on a systematic literature review (SLR)), and the overall evidence base is not considered to be robust by professional bodies[2] - Aciclovir is primarily initiated in this patient population as broad coverage against herpes simplex viruses (HSV). In the letermovir phase III study (PN001) concomitant aciclovir was permitted for this purpose, and was used by 82% of all randomised patients - UK clinician feedback indicates a lack of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			observed efficacy with aciclovir as CMV prophylaxis in clinical practice, and neurotoxicity associated with both aciclovir and valaciclovir[3]
Outcomes	• CMV infection rate • Reduction of hospital in-patient days • Time to onset of clinically-significant CMV infection • Time to initiation of pre-emptive therapy for CMV viraemia • Time to all-cause mortality • Overall survival • Adverse effects of treatment • Health-related quality of life	• Clinically-significant CMV infection • Time to onset of clinically-significant CMV infection • CMV disease • Initiation of pre-emptive therapy for documented CMV viraemia • Time to initiation of pre-emptive therapy for documented CMV viraemia • All-cause mortality • Opportunistic infections • Acute and/or chronic GvHD • Re-hospitalisations • Adverse events • Health-related quality of life	The listed outcomes are addressed in this submission in order to accurately reflect key endpoints/outcomes in PN001 and to allow for accurate modelling of downstream events from an allogeneic HSCT, which can lead to CMV reactivation.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	People at high risk of CMV reactivation (if the evidence allows for consideration of this subgroup)	Subgroup analyses are reported based on risk categories for CMV reactivation, patient characteristics, and conditioning and concomitant immunosuppressive regimen as per study protocol: • CMV reactivation risk stratum (high/low risk) • Stem cell source (peripheral blood, bone marrow) • Donor mismatch (matched related, mismatched related, matched unrelated, mismatched unrelated) • Haploidentical donor (yes, no) • Sex (male, female) • Age (< or ≥median (55 years)) • Race (white vs non-white, Asian vs non-Asian) • Ethnicity (Hispanic or Latino, Not Hispanic or Latino) • Region (Europe vs North America, US vs ex-US) • Weight • Days from transplantation to randomisation (<2 weeks, ≥2 weeks) • Conditioning regimen (myeloablative, reduced intensity, non-myeloablative) • Immunosuppressive regimen (ciclosporin A (CsA), tacrolimus)	Although analyses have been presented for the high-risk subgroup (which demonstrated no difference in efficacy compared with the low-risk population), the base-case analysis covers all patients eligible to receive letermovir.

1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Letermovir (Prevymis®)
Mechanism of action	Letermovir is a first-in-class antiviral that targets the pUL56 subunit of the CMV viral terminase complex, thus affecting the formation of proper unit length genomes from viral DNA concatemers and interfering with virion maturation.
Marketing authorisation/CE mark status	Marketing Authorisation for letermovir was granted by the European Medicines Agency (EMA) via the centralised procedure for a new active substance on 8th January 2018.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Letermovir is indicated for the prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive [R+] recipients of an allogeneic haematopoietic stem cell transplant (HSCT). Consideration should be given to official guidance on the appropriate use of antiviral agents.
Method of administration and dosage	Letermovir is available in film-coated tablets containing 240 mg or 480 mg of letermovir, and as a concentrate for solution for infusion (240 mg and 480 mg). The recommended dosage of letermovir is 480 mg once daily, decreased to 240 mg once daily if co-administered with CsA. Letermovir tablets and concentrate for solution for infusion may be used interchangeably at the discretion of the physician, and no dose adjustment is necessary.
Additional tests or investigations	Not applicable.
List price and average cost of a course of treatment	**List prices** 240 mg tablet (PO)= [redacted] Cost per course (69.4 days*) = [redacted] 480 mg tablet (PO)= [redacted] Cost per course (69.4 days*) = [redacted] 240 mg vial (IV)= [redacted] Cost per course (69.4 days*) = [redacted] 480 mg vial (IV)= [redacted] Cost per course (69.4 days*) = [redacted] ** 69.4 days was the mean duration of letermovir exposure (both formulations) recorded in PN001.*

Patient access scheme (PAS)	MSD are proposing a simple rebate scheme for the indication considered within this submission, equating to a [redacted] discount on the list price of letermovir. The NHS acquisition costs (excl. VAT) at PAS prices for each formulation are as follows: [redacted] per unit cost of letermovir 240 mg (PO) [redacted] per unit cost of letermovir 480 mg (PO) [redacted] per unit cost of letermovir 240 mg (IV) [redacted] per unit cost of letermovir 480 mg (IV)

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

1.3.1 Disease overview

Human cytomegalovirus (CMV) is a common viral pathogen of the wide-ranging *Herpesviridae* family, which also comprises the HSV and varicella zoster viruses (VZV). Estimates on the proportion of adults in the United Kingdom (UK) general population whom have been infected with CMV (i.e. those who are seropositive, or R+) range from 50% to 60% [4, 5].

CMV can be transmitted via saliva, body fluids, cells, and tissues [6]. As with other herpesviruses, CMV remains dormant in the human body for life following primary infection [7], which is generally mild or asymptomatic and occurs early in life. Reactivation of latent CMV infection is usually asymptomatic in healthy immunocompetent individuals; however, in immunocompromised allogeneic HSCT patients it is the most common clinically-significant viral infection as the known correlation of CMV seroprevalence with age, added to the increasing age of transplant patients, poses a high risk of CMV reactivation and severe downstream complications in this population [8, 9]. Other risk factors for CMV infection after allogeneic HSCT include the use of high-dose corticosteroids, T-cell depletion, acute and chronic graft-versus-host disease (GvHD), and the use of mismatched or unrelated donors. [7] Data from the British Society for Bone and Marrow Transplantation (BSBMT) show that 1,152 first-time adult, allogeneic HSCTs were performed in England in 2016. [10] Seroprevalence for this population is approximately 54%, [11] while the incidence of post-transplant CMV reactivation is 80%. [12, 13]

The clinical effects of CMV infection and reactivation, particularly in R+ HSCT recipients, may be divided into direct and indirect effects. Direct effects, namely the spectrum of fatal CMV disease manifestations including pneumonitis, gastroenteritis and encephalitis [7], have been largely prevented by the use of pre-emptive therapy post-transplant, and disease-related mortality in the immediate 100 day post-transplant period is now in the region of 2%[9].

However, CMV remains a leading cause of morbidity and mortality due to its indirect effects in the 100 day post-transplant period, including acute and chronic GvHD and opportunistic bacterial and fungal infections[14].

The aforementioned use of pre-emptive therapy is another contributing factor to post-transplant morbidity and mortality despite its successful implementation against CMV disease. Firstly, target-related toxicities such as myelosuppression with ganciclovir/valganciclovir and nephrotoxicity with foscarnet frequently require lengthy and costly hospitalisation [15], and neutropaenia has been reported in up to 30% patients receiving ganciclovir, [7] which can incur additional management costs arising from use of granulocyte colony-stimulating factor (G-CSF). Myelotoxicity caused by pre-emptive therapy may also compromise engraftment, incurring high post-transplant resource costs. [16]

Secondly, the practice of initiating pre-emptive therapy only upon emergence of a centre-specific CMV viraemia threshold presents an additional concern, as the presence of *any* CMV viraemia in the first 100 days post-HSCT is associated with increased healthcare resource utilisation and mortality. [14, 17] Escalation of pre-emptive therapy may also be required due to partial response, or a subsequent CMV reactivation. [13]

Table 3 below summarises the definitions for CMV infections as established by the CMV Drug Development Forum (DDF):

Table 3: Definitions of CMV Infection [18]

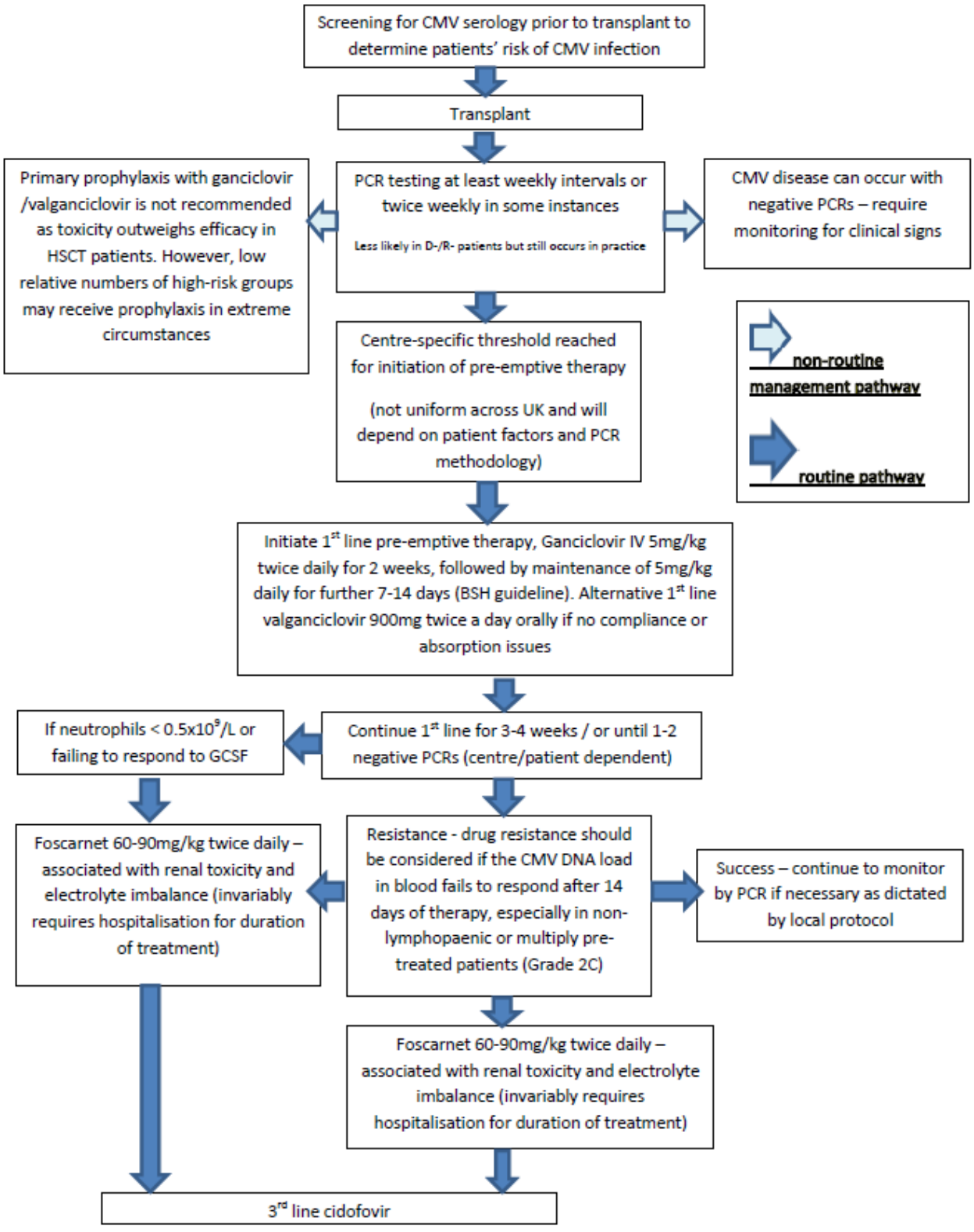
Definitions of CMV Infection	Description
CMV Infection	CMV infection is defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen.
CMV Replication	The term "replication" can be used to indicate evidence of viral multiplication and is sometimes used instead of CMV infection.
Primary CMV Infection	Primary CMV infection is defined as the first detection of CMV infection in an individual who has no evidence of CMV exposure before transplantation. It is recognised that severely immunocompromised individuals such as transplant recipients might not develop CMV-specific antibodies.
Recurrent CMV Infection	"Recurrent infection" is defined as new CMV infection in a patient with previous evidence of CMV infection that has not had virus detected for an interval of at least 4 weeks during active surveillance. Recurrent infection may result from reactivation of latent virus (endogenous) or reinfection (exogenous).
CMV Reinfection	Reinfection is defined as detection of a CMV strain that is distinct from the strain that caused the initial infection.
CMV Reactivation	A recurrent infection is defined as reactivation when the CMV strains that caused the primary infection and recurrent infection are indistinguishable.

B.1.3.2 Clinical pathway of care

There are no licensed treatment options or extant NICE recommendations on antiviral agents for prophylaxis of CMV reactivation in R+ allogeneic HSCT recipients, and there is limited high-quality evidence informing current management choices. As a consequence of this and some recent drug development failures, management of CMV in this population has remained unchanged for many years. The last approval of an anti-CMV agent in this discipline (valganciclovir) occurred in 2001 [9] and another (cidofovir) has recently had its marketing authorisation withdrawn [19]; however, none of the currently-used agents are licensed for the population and indication addressed by this submission.

The current pathway of CMV management in allogeneic HSCT patients, as summarised in Figure 1 below, largely follows the British Society for Haematology (BSH) guidelines[20]. Although aciclovir is recommended as an option for CMV prophylaxis (with the caveat of frequent CMV monitoring in blood), its use in this patient population is primarily due to its activity against HSV (and VZV to a lesser extent). Aciclovir has poor activity against CMV because CMV does not have a unique thymidine kinase, and CMV DNA polymerase is poorly inhibited by aciclovir triphosphate[21]. Aciclovir is also associated with toxicities including gastrointestinal upset, neutropaenia and neurotoxicity [21]. Current UK clinical practice therefore relies on initiating pre-emptive therapy for approximately 21 days [22] with antiviral agents upon emergence of CMV viraemia, in order to prevent CMV disease. The most frequently used agents are first-line intravenous (IV) ganciclovir, with valganciclovir as an oral alternative for patients not experiencing absorption issues (valganciclovir is the only oral pre-emptive agent. Foscarnet is used in patients who are ineligible for or intolerant to ganciclovir/valganciclovir, and cidofovir may be used less frequently either as due to foscarnet toxicity or as a rescue option (despite the withdrawal of its marketing authorisation).

Figure 1: Current CMV management practice in allogeneic HSCT recipients [20]



In addition to the aforementioned BSH guidelines, draft recommendations on CMV prophylaxis have recently been presented at the European Conference on Infections in Leukaemia (ECIL-7, Table 4). This is the first suite of guidance to include letermovir, for which the supporting evidence is ranked as grade AI. Although this evidence grade was originally a provisional ranking as the relevant study had only been presented as a conference abstract, the subsequent publication of the full journal article has resulted in the AI grading being ratified. Additionally, the supporting evidence behind aciclovir is graded CI, reflecting its aforementioned well-characterised poor activity against CMV.

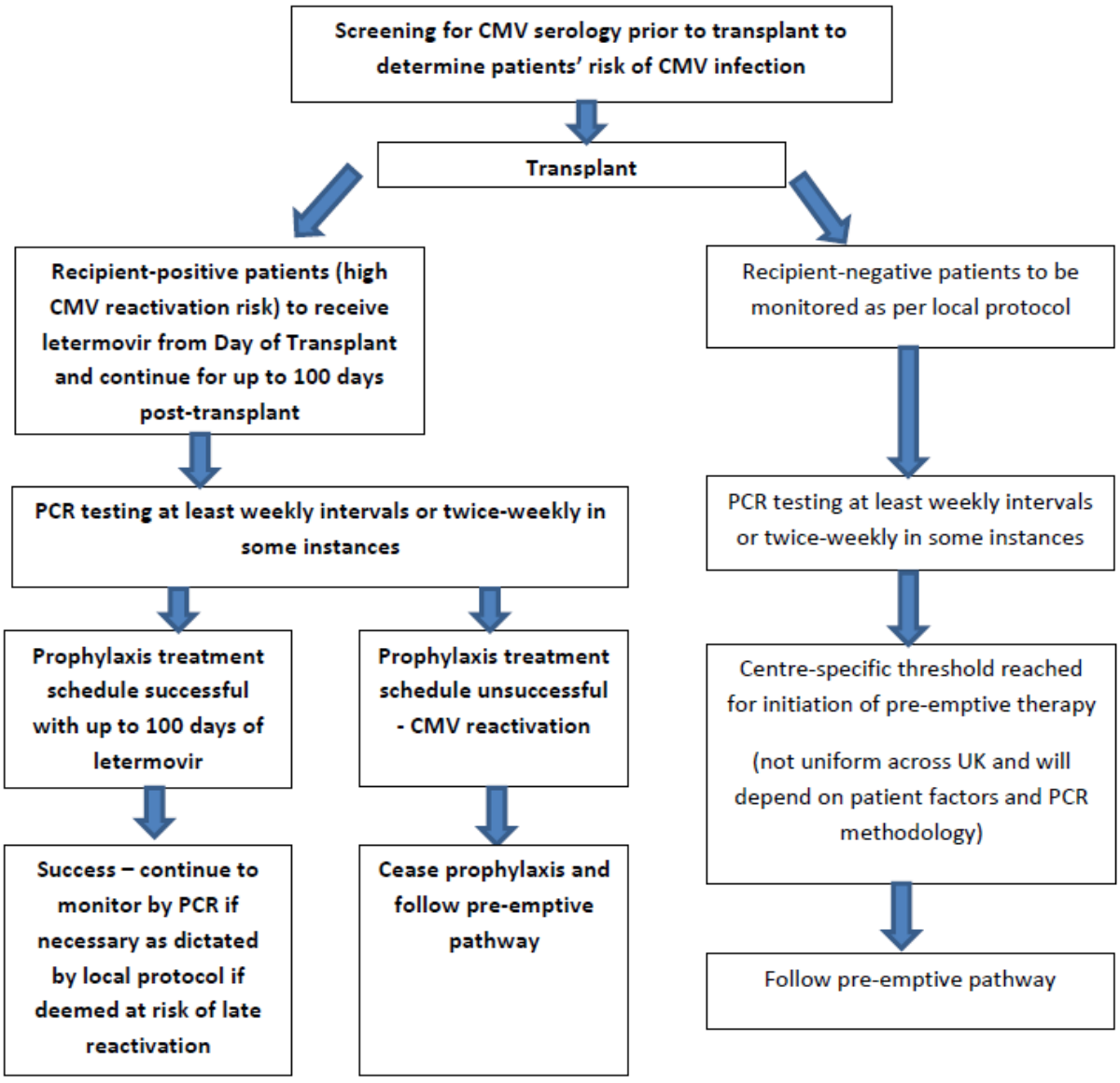
Table 4: Guidelines for management of CMV infection/reactivation in allogeneic HSCT recipients [2, 20]

Organisation	Recommendation(s)
BSH, 2013	*CMV prophylaxis* • Primary prophylaxis with ganciclovir is not generally recommended as toxicity outweighs efficacy in HSCT patients • Primary prophylaxis with aciclovir or valaciclovir can be deployed but only in conjunction with appropriate monitoring of CMV in blood • Valaciclovir or valganciclovir are valid treatment options for secondary prophylaxis with appropriate monitoring of CMV in blood • IV immunoglobulin is not recommended for prophylaxis of CMV infection *Pre-emptive therapy* • Ganciclovir is recommended as first line pre-emptive therapy for CMV in HSCT patients • Oral valganciclovir is a valid alternative when gastrointestinal absorption is normal or only minimally impaired • Foscarnet is recommended as an alternative first-line agent if neutropaenia is present or for ganciclovir treatment failure • Pre-emptive therapy with cidofovir can be considered as third-line in patients unresponsive to, or intolerant of, both a ganciclovir preparation and foscarnet • In patients in whom CMV DNA loads in blood increase by 1 $\log_{10}$ over 2 weeks of pre-emptive therapy with a first line drug, an alternative agent and drug resistance profiling should be considered • Drug resistance should start to be suspected if CMV loads in the blood fail to respond after 14 days of therapy, especially in non-lymphopaenic or multiply pre-treated patients
ECIL, 2017	*CMV prophylaxis in allogeneic HCT; antiviral drugs* • Aciclovir (evidence grade CI) • Valaciclovir (evidence grade BI) • Ganciclovir (evidence grade CI)

	• Valganciclovir (evidence grade CIIh) • Foscarnet (evidence grade DIIu) • Letermovir (provisional evidence grade AI)

The context for the proposed use of letermovir is summarised in Figure 2 below. Within this submission letermovir is positioned for first-line use as prophylaxis against CMV reactivation and disease, to be initiated as early as the day of allogeneic HSCT in R+ patients (i.e. Day 0). This new management strategy would supplant the current practice of only initiating pre-emptive therapy at a specific CMV viraemia threshold, with a view to minimising the clinical and resource implications that arise from reactivation and the subsequent pre-emptive management approach.

Figure 2: Proposed pathway for use of letermovir in CMV prophylaxis



B.1.4 Equality considerations

No equity or equality issues are anticipated with the use of letermovir.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are reported in appendix D.1.

B.2.2 List of relevant clinical effectiveness evidence

A systematic literature review (SLR) was undertaken to identify all relevant published and unpublished randomised control trials (RCTs) relating to letermovir and antiviral agents used in the management of CMV as per the final scope described in Table 1. As the manufacturer, MSD is aware of all relevant clinical trials for letermovir.

The full SLR methodology and results are reported in Appendix D.1. In total three relevant citations were included. This represents two trials reporting letermovir, although only one of these is relevant to the decision problem outlined in Section B.1.1.

The relevant letermovir study was originally identified as an abstract in the searches run in September 2017, and was published in full in December 2017 in the New England Journal of Medicine [23]. This is a phase III, randomised, placebo-controlled trial of letermovir for the prevention of clinically-significant CMV infection in adult R+ allogeneic HSCT recipients.

Table 5: Clinical effectiveness evidence

<table>
<tr><td>Study</td><td colspan="5">A Phase III Randomised, Placebo-controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-8228 (Letermovir) for the Prevention of Clinically Significant Human Cytomegalovirus (CMV) Infection in Adult, CMV-Seropositive Allogeneic Haematopoietic Stem Cell Transplant Recipients [MK-8228 PN001; NCT02137772]
Marty FM et al, 2017 [23]</td></tr>
<tr><td>Study design</td><td colspan="5">Phase III multicentre and multinational randomised, double-blind, placebo-controlled trial</td></tr>
<tr><td>Population</td><td colspan="5">Adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Letermovir 480 mg once-daily (OD, adjusted to 240 mg OD if coadministered with CsA)</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Placebo</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">PN001 is the only available data source for letermovir in this indication and the licensed dosing regimen, and constituted the supporting evidence submitted in the regulatory dossier.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">(Outcomes in bold type are incorporated into the model)
• Clinically-significant CMV infection
• Time to onset of clinically-significant CMV infection
• Initiation of pre-emptive therapy for documented CMV viraemia
• Time to initiation of pre-emptive therapy for documented CMV viraemia
• All-cause mortality
• Reduction of hospital in-patient days (re-hospitalisation for any reason and for CMV reinfection/disease respectively)
• Adverse events
• Health-related quality of life</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">(Outcomes in bold type are incorporated into the model)
• CMV disease
• Opportunistic infections
• Acute and/or chronic GvHD
• Incidence of CMV viraemia
• Time to CMV viraemia
• Incidence of engraftment
• Time to engraftment</td></tr>
</table>

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

2.3.1 PN001 trial overview

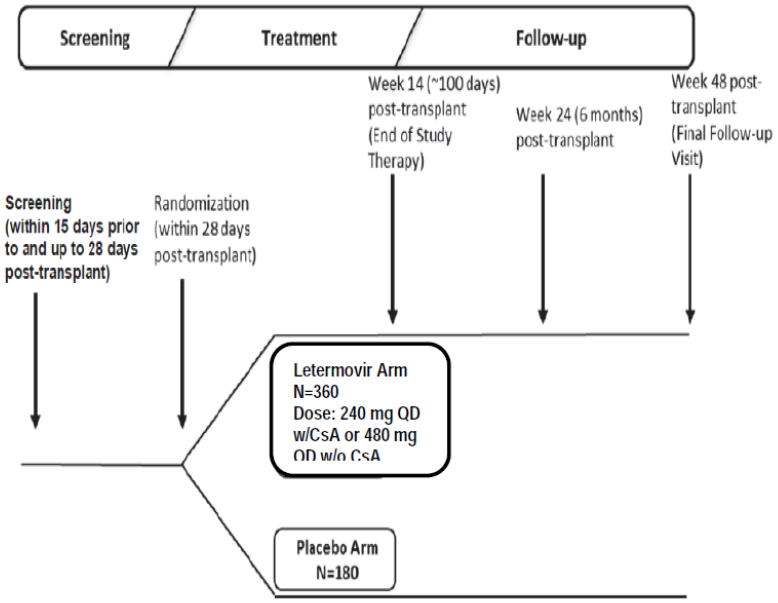
2.3.1.1 Trial design [23]

PN001 was a phase III randomised, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of letermovir compared to placebo for the prevention of clinically-significant human CMV infection in adult, R+ recipients of an allogeneic HSCT.

Patients were randomised centrally via an interactive voice response system (IVRS) and integrated web response system (IWRS) in a 2:1 ratio to receive either letermovir at a dose of 480 mg once daily (adjusted to 240 mg when co-administered with CsA), or placebo (Figure 1). Study medication continued through to week 14 (~100 days) and patients were monitored through to week 24 post-transplant for the primary efficacy endpoint. Patients who completed the trial week 24 post-transplant subsequently entered a follow-up phase from week 24 to week 48 post-transplant to collect data related to CMV disease, health outcomes, and quality of life (QoL) measures.

The design of PN001 is summarised in **Error! Reference source not found.**Figure 3 below:

Figure 3: Study Design of PN001 [24]



CsA= ciclosporin A; QD= every day

PN001 used an external Data Monitoring Committee (eDMC) to monitor safety and efficacy. An interim futility analysis and periodic safety reviews were conducted during the trial, with the option to alter or halt the study if the overall risk/benefit ratio to the study population as a whole was unacceptable.

2.3.1.2 Patient stratification

Randomised patients were stratified by study centre and risk for CMV reactivation in order to balance any effects of these variables on letermovir safety and efficacy across treatment groups. Although this study was performed in CMV-seropositive allogeneic HSCT recipients considered at high risk for CMV reactivation, there is considerable variety across centres and regions worldwide in clinical practice with regards to HSCT (conditioning regimen used, source of stem cell and immunosuppressant regimen used for prevention and/or treatment of GvHD), and considerable variety among HSCT recipients in the risk for CMV reactivation. Therefore, two categories of risk groups were identified for stratification based on available literature [25-28] and input from external experts on the Scientific Advisory Committee (SAC), as follows:

1) High risk: Patients meeting one or more of the following criteria at the time of randomisation:

- Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or –DR
- Haploidentical donor
- Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and –DRB1
- Use of umbilical cord blood as stem cell source
- Use of *ex vivo* T-cell-depleted grafts (including *ex vivo* use of alemtuzumab [Campath™])
- Grade 2 or greater graft-versus host disease (GvHD), requiring the use of systemic corticosteroids (defined as the use of ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid)

2) Low risk: All patients not meeting the definition of high risk

2.3.1.3 Eligibility criteria [29, 30]

Inclusion criteria

In order to be eligible for trial participation, patients must have met all of the following criteria:

1) Been ≥18 years of age on the day of signing informed consent.
2) Had documented seropositivity for CMV (recipient CMV IgG seropositivity [R+]) within 1 year before HSCT.
3) Received a first allogeneic HSCT (bone marrow, peripheral blood stem cell, or cord blood transplant).
4) Had undetectable CMV DNA (as confirmed by the central laboratory) from a plasma sample collected within 5 days prior to randomisation.
5) Been within 28 days post-HSCT at the time of randomisation.
6) Been highly unlikely to become pregnant or to impregnate a partner based on a series of pre-defined criteria (listed on page 78/12041 of the company week 24 clinical study report (CSR [29])).
7) Been able to read, understand, and complete questionnaires and diaries.
8) Understood the study procedures, alternative treatment available, and risks involved with the study, and voluntarily agree to participate by giving written informed consent. The patient could also provide consent for Future Biomedical Research. However, the patient may participate in the main trial without participating in Future Biomedical Research.

Exclusion criteria

Patients who met any of the following criteria were not eligible to participate in the trial:

1) Received a previous allogeneic HSCT (**Note**: Receipt of a previous autologous HSCT was acceptable).
2) Had a history of CMV end-organ disease within 6 months prior to randomisation.
3) Had evidence of CMV viraemia (if tested) at any time from either signing of the informed consent form (ICF) or the HSCT procedure, whichever was earlier, until the time of randomisation. (**Note:** Evidence of CMV viraemia as reported by the central laboratory included reporting of test results as "detectable, not quantifiable" or "detected" with a numeric value provided.).
4) Received within 7 days prior to screening or planned to receive during the study any of the following:
   - ganciclovir
   - valganciclovir
   - foscarnet
   - aciclovir (at doses >3200 mg PO per day or >25 mg/kg IV per day)
   - valaciclovir (at doses >3000 mg PO per day)
   - famciclovir (at doses >1500 mg PO per day)
5) Received within 30 days prior to screening or planned to receive during the study any of the following:
   - cidofovir
   - CMV hyper-immune globulin
   - Any investigational CMV antiviral agent/biologic therapy
6) Had suspected or known hypersensitivity to active or inactive ingredients of letermovir formulations.
7) Had severe hepatic impairment (defined as Child-Pugh Class C, as per

8) Table 6 below) within 5 days prior to randomisation.

Table 6: Child-Pugh Classifications and Interpretations for Severity of Liver Disease

	Scoring by Anomaly		
Signs or symptom	**1 point**	**2 points**	**3 points**
Hepatic encephalopathy[1]	absent	Grade 1 or Grade 2	Grade 3 or Grade 4
Ascites	absent	mild	moderate
Bilirubin (µmol/L)	< 2 mg/dL	2 – 3 mg/dL	> 3 mg/dL
Albumin (g/dL)	> 3.5 g/dL	2.8 – 3.5 g/dL	< 2.8 g/dL
Prothrombin time (INR)	< 1.7	1.7 – 2.3	> 2.3

[1]Hepatic encephalopathy grading:
Grade 1: Altered mood/confusion
Grade 2: Inappropriate behaviour, impending stupor, somnolence
Grade 3: Markedly confused, stuporous but rousable
Grade 4: Comatose/unresponsive

Child Pugh Score Interpretation	
5 – 6 points	Child-Pugh stage A (mild hepatic insufficiency)
7 – 9 points	Child-Pugh stage B (moderate hepatic insufficiency*)
>10 points	Child-Pugh stage C (severe hepatic insufficiency)

*If hypoalbuminemia is the only abnormality noted, the patient will need to have a score of ≥7 to qualify for moderate hepatic insufficiency for this study.

9) Had serum aspartate transaminase (AST) or alanine transaminase (ALT) >5 x the upper limit of normal (ULN) or serum total bilirubin >2.5 x ULN within 5 days prior to randomisation
   - **Note**: Patients who met this exclusion criterion may, at the discretion of the investigator, have had one repeat testing done prior to randomisation. If the repeat value did not meet this criterion, they may have continued in the screening process. Only the specific out of range value should have been repeated (not the entire panel)
10) Had end-stage renal impairment with a creatinine clearance less than 10 mL/min, as calculated by the Cockcroft-Gault equation using serum creatinine within 5 days prior to randomisation

- Creatinine Clearance (Males) = $\frac{\text{(weight in kg) (140 – age)}}{\text{(72) (creatinine in mg/dL)}}$

- Creatinine Clearance (Females) = 0.85 x the value obtained with formula above
- **Note:** Patients who met this exclusion criterion may have, at the discretion of the investigator, had one repeat testing done within 5 days prior to randomisation. If the repeat value did not meet this criterion, they may have continued in the screening process. Only the specific out of range value should have been repeated (not the entire panel)

11) Had both moderate hepatic impairment AND moderate renal impairment
    - **Note**: Moderate hepatic impairment is defined as Child-Pugh Class B (**Error! Reference source not found.**); moderate renal impairment is defined as a creatinine clearance less than 50 mL/min, as calculated by the Cockcroft-Gault equation (as above), respectively
12) Had an uncontrolled infection on the day of randomisation.
13) Required mechanical ventilation or was haemodynamically unstable at the time of randomisation.
14) Had a documented positive result for a human immunodeficiency virus antibody (HIVAb) test at any time prior to randomisation, or for hepatitis C virus antibody (HCV-Ab) with detectable HCV ribonucleic acid (RNA), or hepatitis B surface antigen (HBsAg) within 90 days prior to randomisation.
15) Had active solid tumour malignancies with the exception of localised basal cell or squamous cell skin cancer or the condition under treatment (e.g. lymphomas).
16) Was pregnant or expecting to conceive, was breastfeeding, or planned to breastfeed from the time of consent through 90 days after the last dose of study medication.
17) Was expecting to donate eggs or sperm starting from the time of consent through 90 days after the last dose of study medication.
18) Was currently participating or had participated in a study with an *unapproved* investigational compound or device within 28 days, or 5X half-life of the investigational compound (excluding monoclonal antibodies), whichever was longer, of initial dosing on this study. Patients previously treated with a monoclonal antibody were eligible to participate after a 28-day washout period
    - **Note**: Investigational chemotherapy regimens involving *approved* agents and investigational antimicrobial regimens involving *approved* antibacterial/antifungal/antiviral agents, investigational radiotherapy studies, or other observational studies were allowed

19) Had previously participated in this study or any other study involving letermovir
20) Had previously participated or was currently participating in any study involving administration of a CMV vaccine or another CMV investigational agent, or was planning to participate in a study of a CMV vaccine or another CMV investigational agent during the course of this study
21) Was or had an immediate family member (spouse or child) who was investigational site or Sponsor staff directly involved with this trial
22) Was, at the time of signing informed consent, a user of recreational or illicit drugs or had a recent history (within the last year) of drug or alcohol abuse or dependence
    - **Note:** Patient who had a history of recreational marijuana use which was not deemed excessive by the patient's investigator or did not interfere with the patient's daily function may have participated in the study but must have been instructed to discontinue any further use of recreational marijuana prior to entry into trial and throughout the trial period
23) Had a history or current evidence of any condition, therapy, lab abnormality, or other circumstance that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or would be put at undue risk as judged by the investigator, such that it was not in the best interest of the patient to participate in this study

2.3.1.4 Settings and locations where the data were collected [29]

The study was conducted in 67 transplant centres across 20 countries: Austria, Belgium, Brazil, Canada, Finland, France, Germany, Italy, Japan, Republic of Korea, Lithuania, New Zealand, Peru, Poland, Romania, Spain, Sweden, Turkey, UK and the United States (USA). Approximately half of all patients (n=282; 49.9%) randomised into the study were enrolled from across Europe, of which 12 were enrolled from the 2 participating UK centres.

2.3.1.5 Trial drugs and concomitant medications

Patients were randomised in a 2:1 ratio to receive either letermovir 480 mg once-daily (dose-adjusted to 240 mg once-daily in patients receiving concomitant CsA) or placebo. Study drug was initiated after HSCT (day 0-28 post-transplant) and continued through to week 14 (approximately 100 days) post-transplant (the period of highest risk for CMV infection and/or disease in HSCT recipients), with the primary intent of preventing clinically-significant CMV infection. Study drug was administered at the same time each day and could be given either

via single oral tablet, or IV formulation for patients who could not swallow and/or had a condition that interfered with the absorption of the oral formulation. The dose of letermovir was the same regardless of the route of administration.

The selection of the 480 mg dose was based on modelling and simulation analyses of Phase IIb trial data studying the target population, and available Phase I and II safety data from patients exposed to letermovir doses at or above the selected Phase III dose.
A Phase I trial (PN010) demonstrated that CsA co-administration increases letermovir exposure by 2.3-3.4-fold. Furthermore, modelling and simulation (M&S) analysis of the Phase IIb data (PN020) showed a pronounced impact of CsA co-administration on letermovir exposure. Letermovir $AUC_{tau(24hr)}$ levels were estimated to increase by 2.9-fold with CsA co-administration. Simulations predicted the efficacy target exposure of letermovir $AUC_{tau(24hr)}$ ≥45,000 ng*h/mL could be achieved in >90% of the population with 240 mg of letermovir, when co-administered with CsA. Thus, the dose of letermovir selected for PN001 was 480 mg OD, with a dose adjustment to 240 mg OD when administered in combination with CsA.

Additionally, the trial included a placebo arm designed to mimic pre-emptive therapy, which is the current standard of care (SoC).

The following medications/therapies were permitted in PN001, and could be co-administered with study medication without requiring dose adjustments:

- Standard antimicrobial prophylaxis (e.g. levofloxacin for bacteria, fluconazole/posaconazole for fungi)
- Aciclovir, valaciclovir, or famciclovir for prophylaxis and treatment of herpes simplex virus (HSV) or varicella zoster virus (VZV) infections at doses no greater than prohibited doses of these medications (see exclusion criteria above)
- All types of prior conditioning regimens (including myeloablative, reduced-intensity, or non-myeloablative regimens)
- Prior/ongoing graft manipulation regimens (including various *ex-vivo* or *in-vivo* T-cell depletion or selection regimens)
- GvHD prophylaxis regimens
- Mycophenolate mofetil

As a result of clinical drug-drug interaction studies suggesting that letermovir acts as a weak-to-moderate inhibitor of cytochrome CYP3A4, and pre-clinical data suggesting letermovir acts

as a weak-to-moderate inhibitor of CYP2C8, CYP2B6, and the transporters P-glycoprotein (P-gp), organic anion transporter 3 (OAT3), and organic anion transporter polypeptides OATP1B1 and OATP1B3, medications acting as substrates of these enzymes were permitted for use **with caution**. Additionally, P-gp, OATP1B1 and/or OATP1B3 inhibitors could be administered with caution due to their potential to increase letermovir levels.

Treatments specifically prohibited in the exclusion criteria were not allowed during the study [29].

2.3.2 Outcomes used in the economic model and primary outcome

2.3.2.1 Outcomes included in the economic model

The outcomes clinically-significant CMV infection, initiation of pre-emptive therapy for documented CMV viraemia, all-cause mortality, re-hospitalisation (for any reason and for CMV reinfection/disease respectively), adverse events and health-related quality of life stated in the NICE final scope (Table 1) were included within the economic model as reported in Section B.3.3. All of the aforementioned outcomes were pre-specified in the study protocol.

2.3.2.2 Primary outcome: PN001

The primary endpoint in PN001 was the proportion of patients with clinically-significant CMV infection through Week 24 (~ 6 months) post-transplant, defined as the occurrence of either one of the following outcomes:

- Initiation of anti-CMV pre-emptive therapy based on documented CMV viraemia (as measured by the central laboratory) and the clinical condition of the patient. Initiation of pre-emptive therapy in this study referred to the practice of initiating therapy with ganciclovir, valganciclovir, foscarnet and/or cidofovir

OR

- Onset of CMV end-organ disease

In order to allow standardisation of what constituted 'documented viraemia' in the definition of the primary endpoint, this was defined as any detectable CMV viral DNA on a confirmatory sample obtained immediately prior to (i.e. on the day of) the initiation of treatment for CMV disease or pre-emptive therapy, as measured by a central laboratory using the Roche

COBAS® AmpliPrep/COBAS TaqMan® (CAP/CTM) System. The lower limit of quantification (LLoQ) for this assay is 137 IU/ml, which equates to 151 copies/mL[30].

[redacted]

In the event that the confirmatory result obtained on the day of pre-emptive therapy initiation was not available, a subsequent sample had to be sent to the central laboratory within 7 days after pre-emptive therapy initiation. In the event test results from the central laboratory were not available within the timeframe the investigator wished to initiate pre-emptive therapy, a local laboratory test result could be used in order to make the decision. Due to the current lack of clinically validated viral load thresholds for initiating pre-emptive therapy, further clarification was provided on the guidance regarding viral load threshold for initiation of pre-emptive therapy as per Table 7 below [30]:

Table 7: PN001- Guidance on CMV Viral Load Thresholds for Pre-emptive Therapy Initiation [29, 30]

	Viral DNA level (copies/mL)	
	High risk	**Low risk**
During the study medication period (up to week 14 [~100 days] post-transplant	≥ 150	>300
After week 14 (~100 days) post-transplant	> 300	>300

[redacted]

All suspected cases of CMV disease reported by the Investigator were adjudicated by an independent, blinded Clinical Adjudication Committee (CAC) which reviewed clinical, virological, and histopathological data as well as the investigator's assessments for adjudicating all potential cases of CMV end-organ disease. [redacted]

2.3.2.3 Secondary objectives

(Outcomes in bold type are included in the model)

- **To evaluate the safety and tolerability of letermovir**
- To evaluate the efficacy of letermovir in the prevention of clinically-significant CMV infection through week 14 (~100 days) post-transplant
- To evaluate the efficacy of letermovir as assessed by time to onset of clinically-significant CMV infection through week 24 (~6 months) post-transplant
- **To determine the incidence of CMV disease through week 14 post-transplant and week 24 post-transplant (pre-specified)**
- **To assess the incidence of pre-emptive therapy for CMV viraemia through week 14 post-transplant and week 24 post-transplant (pre-specified)**
- To assess the time to initiation of pre-emptive therapy for CMV viraemia through week 14 post-transplant and week 24 post-transplant

2.3.2.4 Exploratory objectives

(Outcomes in bold type are included in the model)

- To determine the incidence of CMV disease through week 48 post-transplant
- **To determine the incidence of all-cause mortality through week 14 post-transplant, week 24 post-transplant, and week 48 post-transplant**
- **To determine the incidence of opportunistic infection other than CMV infection (i.e., systemic bacterial and invasive fungal infection) through week 14 post-transplant, week 24 post-transplant, and week 48 post-transplant**

- **To determine the incidence of acute and/or chronic GvHD after randomisation through week 14 post-transplant, week 24 post-transplant, and week 48 post-transplant**
- **To determine the incidence of all re-hospitalisations (following initial hospital discharge) and re-hospitalisations for CMV infection/disease through week 14 post-transplant, week 24 post-transplant, and week 48 post-transplant**
- To assess the incidence of CMV viraemia through week 14 post-transplant and week 24 post-transplant
- To assess the time to CMV viraemia through week 14 post-transplant and week 24 post-transplant
- To determine the incidence of engraftment through week 14 post-transplant and week 24 post-transplant. (Engraftment is defined as documented absolute neutrophil counts ≥500/mm^3 on 3 consecutive days.)
- To determine the time to engraftment through week 14 post-transplant and week 24 post-transplant

2.3.3 Summary of trial methodology

Table 8: Comparative summary of trial methodology

Trial number (acronym)	**PN001**
Location	Global study conducted in 20 countries: Austria, Belgium, Brazil, Canada, Finland, France, Germany, Italy, Japan, Korea, Lithuania, New Zealand, Peru, Poland, Romania, Spain, Sweden, Turkey, UK, and USA.
Trial design	Randomised, double-blind, placebo-controlled, phase III trial of oral or IV letermovir prophylaxis versus placebo in adult CMV R+ recipients of an allogeneic HSCT.
Eligibility criteria for participants	• Aged ≥18 years of age on the day of signing informed consent • Documented seropositivity for CMV (recipient IgG seropositivity [R+] within 1 year before HSCT • Received a first allogeneic HSCT (bone marrow, peripheral blood stem cell, or cord blood transplant)

	• Undetectable CMV DNA (as confirmed by central laboratory) from a plasma sample collected within 5 days prior to randomisation • Within 28 days post-HSCT at time of randomisation • Highly unlikely to become pregnant or to impregnate a partner due to meeting at least one of the protocol-specified criteria • Able to read, understand and complete questionnaires and diaries • Understood the study procedures, alternative treatment available, and risks involved with the study, and voluntarily agree to participate by giving written informed consent
Settings and locations where the data were collected	This study was conducted in 67 specialist transplant centres Patients received study treatment both as inpatients and/or outpatients, as necessary.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	Patients were randomised in a 2:1 ratio to receive either oral or IV letermovir 480 mg OD (n= 376), adjusted to 240 mg OD for patients on concomitant CsA; or placebo (n= 194) Permitted concomitant medication: • Standard antimicrobial prophylaxis • Aciclovir, valaciclovir, or famciclovir for prophylaxis and treatment of HSV or VZV infections at doses no greater than prohibited doses of these medications • All types of prior conditioning regimens • Prior/ongoing graft manipulation regimens • GvHD prophylaxis regimens • Mycophenolate mofetil Disallowed concomitant medication: • Antiviral drugs or therapies for prevention/treatment of CMV, including investigational CMV antiviral agents/biologic therapies/vaccines
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint in PN001 was the proportion of patients with clinically-significant CMV infection through to Week 24 (~ 6 months) post-transplant, defined as the occurrence of either one of the following outcomes: • Initiation of anti-CMV pre-emptive therapy based on documented CMV viraemia (as measured by the central laboratory) and the clinical condition of the patient. Initiation of pre-emptive therapy in this study referred to the practice of initiating therapy with ganciclovir, valganciclovir, foscarnet and/or cidofovir

	OR • Onset of CMV end-organ disease
Other outcomes used in the economic model/specified in the scope	• Initiation of pre-emptive therapy for documented CMV viraemia • All-cause mortality • Reduction of hospital in-patient days (re-hospitalisation for any reason and for CMV reinfection/disease respectively) • Adverse events • Health-related quality of life • CMV disease • Opportunistic infections • Acute and/or chronic GvHD
Pre-planned subgroups	Subgroup analyses based on risk categories for CMV reactivation, patient characteristics, and conditioning and concomitant immunosuppressive regimen (CsA-containing and tacrolimus-containing) as per study protocol: • CMV reactivation risk stratum (high risk, low risk) • Stem cell source (peripheral blood, bone marrow) • Donor mismatch (matched related, mismatched related, matched unrelated, mismatched unrelated) • Haploidentical donor (yes, no) • Sex (male, female) • Age (<median (55 years) or ≥median (55 years) • Race (white vs non-white, Asian vs non-Asian) • Ethnicity (Hispanic or Latino, Not Hispanic or Latino) • Region (Europe vs North America, US vs ex-US) • Weight • Days from transplantation to randomisation (<2 weeks, ≥2 weeks) • Conditioning regimen (myeloablative, reduced intensity, non-myeloablative) • Immunosuppressive regimen (CsA, tacrolimus)

2.3.4

Baseline demographics

Patient characteristics were generally balanced between the letermovir and placebo groups (Table 9). The majority of patients were male (327/565 [58%]), white (462/565 [82%]), and with a mean age of around 51 years old. At baseline, 175/565 (31%) of patients were at high risk for reactivation (as defined in the 'Study Design' section above) and 293/565 (52%) were receiving concomitant CsA.

The most common primary reasons for transplant were acute myeloid leukaemia (AML, 142/565 [38%]), myelodysplastic syndrome (MDS, 63/565 [17%]), and lymphoma (47/565 [13%]). The majority of patients had received transplants using peripheral blood stem cells (413/565 [73%]). Baseline aciclovir use for prior HSV prophylaxis was similar across both study groups (311/373 [83%] letermovir group, 152/192 [79%] placebo group; 463/565 [82%] overall).

The median time to starting study drug was 9 days after transplant.

Table 9: PN001- Baseline Characteristics- ASaT Population [24, 29, 30]

	Letermovir n	(%)	Placebo n	(%)	Total n	(%)
Patients in population	373		192		565	
Gender						
Male	211	(56.6)	116	(60.4)	327	(57.9)
Female	162	(43.4)	76	(39.6)	238	(42.1)
Race						
Asian	40	(10.7)	18	(9.4)	58	(10.3)
Black or African	8	(2.1)	4	(2.1)	12	(2.1)
Multi-Racial	22	(5.9)	9	(4.7)	31	(5.5)
Native Hawaiian	1	(0.3)	0	0.0	1	(0.2)
White	301	(80.7)	161	(83.9)	462	(81.8)
Missing	1	(0.3)	0	0.0	1	(0.2)
Age (Years)						
[redacted]						
65 to 74	55	(14.7)	30	(15.6)	85	(15.0)
≥ 75	1	(0.3)	2	(1.0)	3	(0.5)
[redacted]						
Mean	50.8		50.8		50.8	
[redacted]						
Median	53.0		54.0		54.0	
Range	18.0 to 75.0		19.0 to 78.0		18.0 to 78.0	
Ethnicity						
Hispanic or Latino	30	(8.0)	10	(5.2)	40	(7.1)
[redacted]						
Weight (kg)						
[redacted]						
Mean	77.6		74.5		76.6	
[redacted]						
Median	76.2		74.4		75.4	
Range	35.1 to 141.5		40.9 to 113.1		35.1 to 141.5	
BMI (kg/m^2)						

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
[redacted]						
Mean	26.5		25.5		26.2	
[redacted]						
Median	25.6		25.1		25.5	
Range	17.0 to 49.0		16.6 to 44.7		16.6 to 49.0	
Region						
Asia-Pacific	37	(9.9)	16	(8.3)	53	(9.4)
Latin America	7	(1.9)	2	(1.0)	9	(1.6)
Europe	185	(49.6)	97	(50.5)	282	(49.9)
North America	144	(38.6)	77	(40.1)	221	(39.1)
Region Subgroup						
[redacted]						
Stratum[†]						
High Risk	121	(32.4)	54	(28.1)	175	(31.0)
Low Risk	252	(67.6)	138	(71.9)	390	(69.0)
Patients Engrafted at Baseline[‡]						
Yes	132	(35.4)	74	(38.5)	206	(36.5)
[redacted]						
Immunosuppressive Regimen Use[§]						
Ciclosporin A	193	(51.7)	100	(52.1)	293	(51.9)
Tacrolimus	160	(42.9)	79	(41.1)	239	(42.3)
Other	19	(5.1)	10	(5.2)	29	(5.1)
Missing	1	(0.3)	3	(1.6)	4	(0.7)
CMV DNA on Day 1 (when study therapy is initiated)						
Detected	48	(12.9)	22	(11.5)	70	(12.4)
Not detected	325	(87.1)	170	(88.5)	495	(87.6)
Primary Reason for Transplant[‖]						
Acute lymphocytic leukaemia	35	(9.4)	17	(8.9)	52	(9.2)
Acute myeloid leukaemia	142	(38.1)	72	(37.5)	214	(37.9)
Aplastic anaemia	9	(2.4)	11	(5.7)	20	(3.5)
Chronic lymphocytic leukaemia	10	(2.7)	4	(2.1)	14	(2.5)
Chronic myeloid leukaemia	17	(4.6)	6	(3.1)	23	(4.1)
Lymphoma	47	(12.6)	28	(14.6)	75	(13.3)
Myelodysplastic syndrome	63	(16.9)	22	(11.5)	85	(15.0)
Myelofibrosis	9	(2.4)	6	(3.1)	15	(2.7)
Plasma cell myeloma	14	(3.8)	10	(5.2)	24	(4.2)
Other	27	(7.2)	16	(8.3)	43	(7.6)
Donor CMV Serostatus						
Positive	230	(61.7)	114	(59.4)	344	(60.9)
[redacted]						
Donor CMV Serostatus						
[redacted]						
HLA matching and donor type						
Matched related	121	(32.4)	63	(32.8)	184	(32.6)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Mismatched related	63	(16.9)	24	(12.5)	87	(15.4)
Matched unrelated	138	(37.0)	78	(40.6)	218	(38.6)
Mismatched unrelated	51	(13.7)	27	(14.1)	78	(13.8)
Haploidentical related donor	**60**	**(16.1)**	**21**	**(10.9)**	**81**	**(14.3)**
Stem Cell Source						
Peripheral blood	279	(74.8)	134	(69.8)	413	(73.1)
Bone marrow	82	(22.0)	47	(24.5)	129	(22.8)
Cord blood	12	(3.2)	11	(5.7)	23	(4.1)
Conditioning Regimen Use						
Myeloablative	186	(49.9)	97	(50.5)	283	(50.1)
Reduced intensity conditioning	92	(24.7)	54	(28.1)	146	(25.8)
Non-myeloablative	95	(25.5)	41	(21.4)	136	(24.1)
Antithymocyte globulin (ATG) use	**140**	**(37.5)**	**58**	**(30.2)**	**198**	**(35.0)**
Alemtuzumab use	**12**	**(3.2)**	**11**	**(5.7)**	**23**	**(4.1)**
Baseline Acute GvHD (≥ Grade 2)						
Yes	2	(0.5)	1	(0.5)	3	(0.5)
[redacted]						
Days from Transplantation to Randomisation						
< 2 weeks	237	(63.5)	121	(63.0)	358	(63.4)
≥ 2 weeks	136	(36.5)	71	(37.0)	207	(36.6)
[redacted]						
Median	9		9		9	
Days from Transplantation to Randomisation						
Range	0 to 28		0 to 28		0 to 28	

† High- and low-risk criteria as detailed above in the 'Study Design' section.
‡ If the engraftment status at baseline was missing for a patient but an engraftment date was recorded later, the engraftment status at baseline was imputed to be no. NA = not applicable. Patient's absolute neutrophil count did not go below 500/mm^3 at any point after transplantation due to the conditioning regimen received.
§ Patients counted in the CsA row if they received concomitant CsA with or without any other immunosuppressants in the regimen during treatment phase. Tacrolimus containing-regimen included concomitant tacrolimus use with or without any other immunosuppressant use (except CsA). Patients in the Other row received a regimen containing any other immunosuppressants (sirolimus, everolimus, systemic steroids, leflunomide, mycophenolate) except CsA or tacrolimus. The patients in the missing row did not receive any immunosuppressants concomitantly.
‖ Other reasons for transplant are provided in Section 14 of the CSR.
Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with CsA.
n (%) = Number (percent) of patients in each sub-category.

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

Section 2.4 presents the statistical methodology relevant to PN001.

2.4.1 Primary analysis population

The full analysis set (FAS) population served as the primary population for the analysis of the primary outcome in PN001. The FAS consisted of all randomised patients who received at least one dose of study medication and had no detectable CMV viral DNA (measured by the central laboratory) on day 1 (when study medication was initiated) [23, 30].

2.4.2 Statistical tests used in the primary analysis

The statistical methods and analysis strategy for the primary and secondary efficacy endpoints have been summarised in Table 10 below. The study statistician remained blinded to treatment assignment until the final analysis was completed.

The primary efficacy analysis was performed on the FAS population. A sensitivity analysis was carried out to include patients who had detectable CMV viral DNA on study day 1.

Table 10: PN001- Summary of Analyses Performed for Key Efficacy Endpoints [23, 24]

Endpoint/variable (Description, Time point)	Statistical Method	Analysis Population	Primary Missing Data Approach
Primary:			
Proportion of patients with clinically-significant CMV infection through week 24 (~6 months) post-transplant	Stratified Mantel-Haenszel	Full Analysis set	Non-Completer=Failure*
Key Secondary:			
Proportion of patients with clinically-significant CMV infection through week 14 (~100 days) post-transplant	Stratified Mantel-Haenszel	Full Analysis set	Non-Completer=Failure*
Time to onset of clinically-significant CMV infection through week 24 (~6	Kaplan-Meier plot	Full Analysis set	Censored at last assessment

Endpoint/variable (Description, Time point)	Statistical Method	Analysis Population	Primary Missing Data Approach
months post-transplant)			
*Non-completers refer to patients who prematurely discontinued from the study			

2.4.2.1 Primary hypothesis under investigation and power calculation

The primary hypothesis in study PN001 was that letermovir is superior to placebo in the prevention of clinically-significant CMV infection, as assessed by the proportion of patients with CMV end-organ disease or initiation of anti-CMV pre-emptive therapy based on documented CMV viraemia and the patient's clinical condition through to week 24 (approx. 6 months) post-transplant.

To test the primary hypothesis, stratum-adjusted Cochran Mantel-Haenszel weights were used to calculate the overall between-group differences. Letermovir was to be considered superior to placebo if the one-sided p-value was less than or equal to 0.0249.

2.4.2.2 Sample size [23, 24, 29]

A sample size of approximately 540 patients was planned using a 2:1 randomisation ratio (~360 patients in the letermovir arm and ~180 patients in the placebo arm). Excluding 15% patients with detectable CMV DNA on Day 1, the evaluable number of patients in the FAS population was 459 in total (306 in the letermovir arm and 153 in the placebo arm). With this sample size, the study had a 90.5% overall power to detect a treatment difference with a 1-sided p-value less than or equal to 0.0249.

The sample size calculation was based on the following assumptions:

- The incidence rate of clinically-significant CMV infection for patients receiving placebo is approximately 35%
- The letermovir arm reduces this incidence by half to an incidence of approximately 17%
- A dropout rate of about 20% from both treatment arms for reasons other than virologic failure
    - Since the primary missing data approach was non-completer=failure, 20% was added to the expected incidence of clinically-significant CMV infection for the placebo arm (55%) and the letermovir arm (37%) for sample size and power calculations

2.4.2.3 Methods used to account for missing data

The primary missing data approach used for the efficacy analyses in the study was the "non-completer = failure" (NC = F) approach. Non-completers were defined as patients who prematurely discontinued from the study. [redacted]. Patients who discontinued study medication but remained in the study through follow-up were not considered non-completers.

A secondary missing data approach was the "data-as-observed" (DAO) approach. With this approach, any patient with a missing value for a particular endpoint was excluded from the analysis. This approach was used as supportive analysis for the primary endpoint and selected secondary endpoints [redacted]

In response to feedback from external statistical reviewers, a post-hoc multiple imputation model was also carried out within each risk strata to impute the occurrence of clinically-significant CMV infection in patients who either discontinued from the study before Week 24 or were missing a visit in the critical outcome window[30].

Two assumptions for missing data were made: missing-at-random (MAR) and missing-not-at-random (MNAR). Under MAR, the imputation model assumed the clinically significant CMV infection rate = the observed rate for each treatment group. Under MNAR, the imputation model assumed the clinically-significant CMV infection rate for both letermovir and placebo groups = the observed rate in the placebo group. The imputations generated 500 complete datasets, where outcomes were imputed within strata for all patients with missing outcome. A logistic regression model for monotone missing data and a random number generator were used to impute the missing data.

[redacted]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality assessment for PN001 is reported in Appendix D.2.1.

B.2.6 Clinical effectiveness results of the relevant trials

2.6.1 Primary endpoint

The primary endpoint was prevention of clinically-significant CMV infection by week 24 post-transplant, as assessed by the proportion of patients with CMV end-organ disease or initiation of anti-CMV pre-emptive therapy based on documented CMV viraemia and the patient's clinical condition.

In the FAS population fewer patients in the letermovir group (122/325 [37.5%]) developed clinically-significant CMV infection by week 24 post-transplant compared with placebo (103/170 [60.6%]). The stratum-adjusted difference (95% CI) of –23.5% (–32.5%, –14.6%) was statistically significant (one-sided p< 0.0001). This effect was driven by a difference in the rate of initiation of pre-emptive therapy based on documented CMV viraemia (16.0% vs. 40.0% at 24 weeks for letermovir (52/325) vs. placebo (68/170), respectively; Table 11). CMV disease rates were low in both treatment groups, and rates of discontinuation and missing outcomes were similar between letermovir and placebo (Table 11).

Table 11: PN001- Analysis of Proportion of Patients with Clinically Significant CMV Infection by week 24 Post-Transplant (NC=F Approach, FAS Population)

Parameter	Letermovir (n = 325) n (%)	Placebo (n = 170) n (%)
Primary efficacy endpoint (proportion of patients who failed prophylaxis by Week 24)[a]	**122 (37.5)**	**103 (60.6)**
Clinically significant CMV infection by week 24[b]	57 (17.5)	71 (41.8)
Initiation of pre-emptive therapy based on documented CMV viraemia	52 (16.0)	68 (40.0)
CMV end-organ disease	5 (1.5)	3 (1.8)

Parameter	Letermovir (n = 325) n (%)	Placebo (n = 170) n (%)
Discontinued from study before week 24	56 (17.2)	27 (15.9)
Missing outcome in week 24 visit window	9 (2.8)	5 (2.9)
Stratum-adjusted treatment difference (letermovir-placebo)[c]		
Difference (95% CI)	–23.5 (–32.5 to –14.6)	
P value	<0.0001	

CI = confidence interval; CMV = cytomegalovirus; FAS = full analysis set; NC = F = non-completer = failure.
[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.
[b] Clinically significant CMV infection was defined as CMV end-organ disease or initiation of pre-emptive therapy based on documented CMV viraemia and the clinical condition of the patient.
[c] 95% CIs and *P* value for the treatment differences in percentage of response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A 1-sided *P* value ≤ 0.0249 was used for declaring statistical significance.
Note: Approach to handling missing values: With NC = F approach, failure was defined as all patients who developed clinically-significant CMV infection or prematurely discontinued from the study or had a missing outcome through week 24 post-transplant visit window.

2.6.2 Secondary analyses of the primary endpoint

[redacted]

Using the MAR approach, the stratum-adjusted treatment difference was -30.7 between letermovir and placebo (95% CI: -34.8, -26.5; p<0.0001). The point estimate for the failure rate among letermovir patients was 21.7% (95% CI: 16.7, 26.7) and the point estimate for the failure rate among placebo patients was 51.7 (95% CI: 42.0, 60.0).

Using the MNAR approach, the stratum-adjusted treatment difference is -24.5 (95% CI: -28.4, -20.7, p<0.0001). The point estimate for the failure rate among letermovir patients is 28.1% (95% CL: 22.3, 33.7) and the point estimate for the failure rate among placebo patients is 51.8 (95% CL: 43.6, 60.1).

The efficacy of letermovir on reducing the incidence of clinically significant CMV infection

through Week 24 post-transplant was also demonstrated based on an analysis of *only* patients who were positive on Day 1 (a subset of the All Randomised and Treated patients which includes only randomised patients who received at least 1 dose of study medication and had detectable CMV viral DNA on Day 1, i.e., excluding the FAS Population), using the NC=F approach. A lower proportion of patients with detectable CMV viral DNA on Day 1 developed clinically-significant CMV infection in the letermovir group (64.6%) compared to the placebo group (90.9%) through Week 24 post-transplant (95% CI -26.1% (-45.9%, -6.3%), nominal one-sided p-value <0.0048).

2.6.3 Secondary outcomes included in the model

2.6.3.1 Proportion of patients with CMV disease by week 14 post-transplant and week 24 post-transplant

All suspected cases of CMV disease reported by study investigators were adjudicated by an independent and blinded Clinical Adjudication Committee (CAC). Only CAC-confirmed CMV end-organ disease cases were included in the analyses of endpoints that included CMV end-organ disease.

Overall, study investigators reported 10 patients as having suspected CMV end-organ disease through week 24 post-transplant. All cases were adjudicated by the CAC; 8 were confirmed as having CMV end-organ disease (all gastrointestinal disease), and 2 were not confirmed (including 1 case of suspected pneumonia in the letermovir group and 1 case of suspected hepatitis in the placebo group).

The overall incidence of CMV end-organ disease (FAS population) was low through both the week 14 and week 24 post-transplant time points, with only 8 patients adjudicated through week 24 post-transplant as discussed above. Because of this low incidence, the DAO approach for missing data was used to evaluate results directly so as not to classify patients who discontinued before week 24 post-transplant or had missing data as failures, which could lead to potentially misleading estimates of CMV end-organ disease rates. Using this approach, the rates of CMV end-organ disease were comparable between the groups at both time points.

Three of the 8 patients developed CMV end-organ disease through week 14 post-transplant; 1/285 (0.4%) in the letermovir group and 2/145 (1.4%) in the placebo group. The estimated

difference (95% CI) between treatment groups was -1.0 (-3.5, 1.5) with a nominal one-sided p-value of 0.2258. An additional 5 patients developed CMV end-organ disease through week 24 post-transplant for a total of 8 patients (5/285 [2.0%] in the letermovir group and 3/145 [2.4%] in the placebo group). The estimated difference (95% CI) between treatment groups was -0.4% (-4.0%, 3.2%), with a nominal one-sided p-value of 0.4056.

2.6.3.2 Initiation of pre-emptive therapy for documented CMV viraemia by week 14 post-transplant and week 24 post-transplant

Letermovir was also associated with a lower proportion of patients who initiated pre-emptive therapy for documented CMV viraemia through week 14 post-transplant (18.8%) compared to the placebo group (49.4%). The estimated difference (95% CI) was -31.0 (-39.6%, 22.4%), with a nominal one-sided p-value <0.0001.

Similarly, the proportion of patients who initiated pre-emptive therapy for CMV viraemia through week 24 post-transplant was lower for the letermovir (16.0%) group compared to the placebo group (40.0%) (Table 12).

Table 12: Proportion of Patients with Initiation of Pre-emptive Therapy for Documented CMV Viraemia by week 24 Post-Transplant (NC=F Approach, FAS Population)

Parameter	Letermovir (n=325) N (%)	Placebo (n=170) N (%)
Failures	**119 (36.6)**	**101 (59.4)**
Initiation of pre-emptive therapy based on documented CMV viraemia	52 (16.0)	68 (40.0)
Discontinued from study before week 24	57 (17.5)	28 (16.5)
Missing outcome in week 24 visit window	10 (3.1)	5 (2.9)
Stratum-adjusted treatment difference (Letermovir-Placebo)		
Difference (95% CI)	-23.3 (-32.3, -14.3)	
p-value	<0.0001	

† The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.
‡ 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A nominal one-sided p-value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.
Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all patients who initiated pre-emptive therapy or prematurely discontinued from the study or had a missing outcome through week 24 post-transplant visit window.
N = number of patients in each treatment group. n (%) = Number (percent) of patients in each sub-category.

In order to be included in the primary analysis of clinically-significant CMV infection, the protocol definition for pre-emptive therapy initiation required confirmation of CMV viraemia by

the central laboratory using a sample obtained immediately prior to/on the day of pre-emptive therapy initiation (but no later than within 7 days of pre-emptive therapy initiation). While the protocol provided guidance for viral load thresholds for pre-emptive therapy (as per Table 7 above) using the central laboratory assay, sites were permitted to initiate pre-emptive therapy based on local laboratory test results as there are no universally accepted guidelines for viral load thresholds for pre-emptive therapy initiation and institutional practice varies widely across sites. However, sites were required to obtain a confirmatory CMV DNA polymerase chain reaction (PCR) result based on central laboratory testing prior to initiation of pre-emptive therapy in such instances.

[redacted]

[redacted]

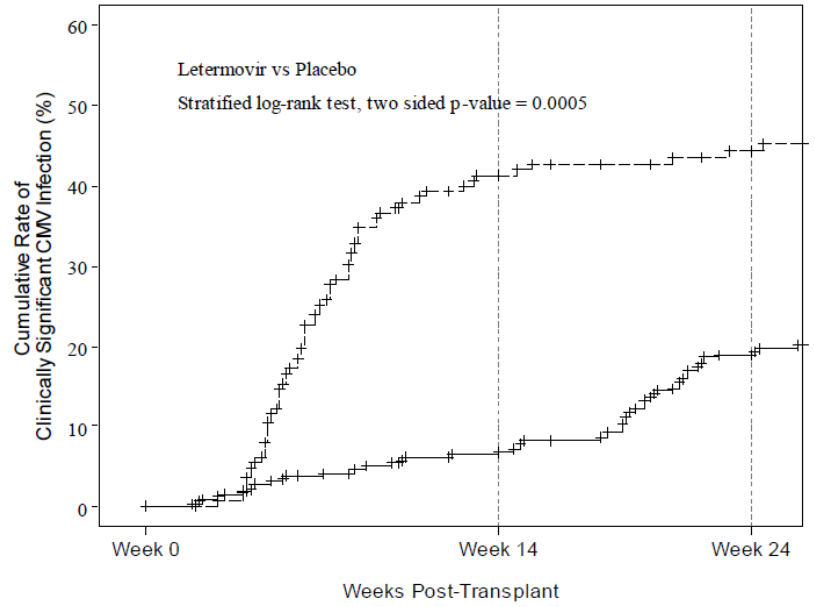
2.6.4 Other secondary endpoints

2.6.4.1 Time to onset of clinically-significant CMV infection by week 24 post-transplant

The time to onset of clinically-significant CMV infection through week 24 post-transplant was summarised using Kaplan-Meier (K-M) plots. At week 24 post-transplant, the event rate (95% CI) for clinically-significant CMV infection was 18.9% (14.4%, 23.5%) in the letermovir group versus 44.3% (36.4%, 52.1%) in the placebo group. The distribution of time to event significantly differed between the letermovir and placebo groups (nominal two-sided

p=0.0005), after controlling for stratification of high and low risk of CMV end-organ disease at baseline. There was a large separation between the curves from day 0 to week 14 while patients were on study drug. Once medication was discontinued at week 14, there was a small rebound effect in the letermovir group (Figure 4). Factors associated with CMV DNAemia after cessation of letermovir prophylaxis up to Week 24 post-transplant included high baseline risk for CMV reactivation, GvHD, corticosteroid use and receipt of a transplant from a seropositive donor (D+).

Figure 4: K-M Plot of Time to Onset of Clinically Significant CMV Infection by week 24 Post-Transplant (FAS Population)



2.6.5 Exploratory Endpoints included in the model

2.6.5.1 All-cause mortality

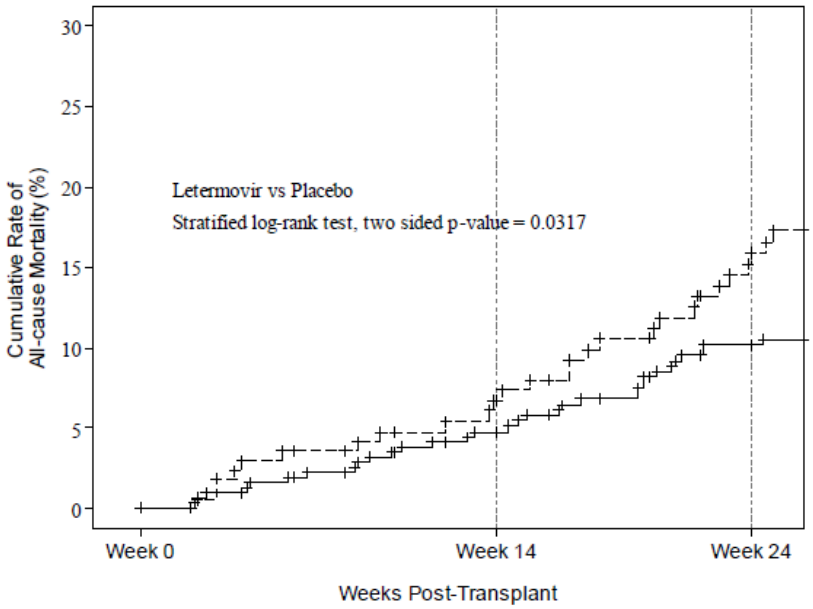
Letermovir was associated with a lower proportion of all-cause mortality in the FAS population when compared with placebo at weeks 14, 24, and 48 post-transplant.

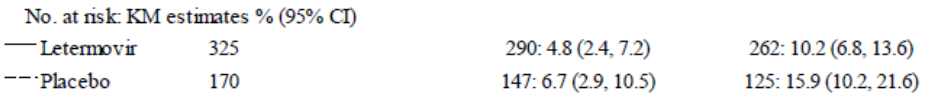
At week 14 post-transplant the observed incidence of all-cause mortality was 5.2% (17/325) for the letermovir group (95% CI; 3.1, 8.2) compared with 7.1% (12/170; 95% CI; 3.7, 12.0) for

the placebo group; and the distribution of time to all-cause mortality at this time-point was again lower in the letermovir group (K-M event rate 4.8; 95% CI; 2.4, 7.2) versus the placebo group (K-M event rate 6.7; 95% CI; 2.9, 10.5).

Mortality incidence remained lower in the letermovir group (9.8% [32/325]; 95% CI 6.8, 13.6) compared to placebo (15.9% [27/170]; 95% CI 10.7, 22.3) at week 24 post-transplant. The distribution of time to all-cause mortality between the letermovir and placebo groups through the week 24 post-transplant for the FAS population was evaluated using the K-M method (Figure 5). The K-M event rate (95% CI for the difference) was lower for the letermovir group (10.2%; 95% CI 6.8, 13.6) compared to the placebo group (15.9%; 95% CI; 10.2, 21.6), and the distribution of time to all-cause mortality between the letermovir and placebo groups through the week 24 post-transplant for the FAS population was evaluated using the K-M method (Figure 5). The K-M event rate (95% CI for the difference) was lower for the letermovir group (10.2%) [95% CI, 6.8 to 13.6] compared to the placebo group (15.9%[23]), and the distribution of time to all-cause mortality through week 24 was substantially different between the letermovir and placebo groups (nominal two-sided log-rank p-value=0.0317, not controlled for multiplicity).

Figure 5: K-M Plot of Time to All-cause Mortality Through to Week 24 Post-Transplant





At week 48 post-transplant incidence of all-cause mortality (FAS population) remained lower for the letermovir group (20.9%, 95% CI: 16.2% to 25.6%) compared to the placebo group (25.5%, 95% CI: 18.6% to 32.5%). Similarly, the distribution of time to all-cause mortality through week 48 differed substantially between the letermovir and placebo groups (nominal two-sided p=0.1224, stratified log-rank test).

A number of post-hoc analyses were conducted to further explore the significant mortality benefit observed at the time of primary endpoint. An analysis was conducted that included vital status for 58 of the 76 patients who prematurely withdrew from the trial with unknown mortality status, resulting in vital status availability for 96.8% of patients (547/565) in the ASaT population [30].

The full patient disposition in this analysis for both the ASaT and FAS populations is presented in Table 13 and Table 14.

Table 13: Patient disposition including patients who withdrew from the study prior to Week 48 post-transplant (All Randomised Patients)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	376		194		570	
Status for Trial Through 24 Weeks Post-transplant						
Randomised but not treated	3	(0.8)	2	(1.0)	5	(0.9)
Completed 24 weeks Post-transplant	295	(78.5)	136	(70.1)	431	(75.6)
Discontinued Through Week 24 Post-transplant (Death)	37	(9.8)	28	(14.4)	65	(11.4)
Discontinued Through Week 24 Post-transplant (other reasons)	41	(10.9)	28	(14.4)	69	(12.1)
Post-study status: Alive	25	(6.6)	17	(8.8)	42	(7.4)
Post-study status: Death	10	(2.7)	8	(4.1)	18	(3.2)
Post-study status: Unknown	6	(1.6)	3	(1.5)	9	(1.6)
Status for Trial Through 48 Weeks Post-transplant						
Completed 48 weeks Post-transplant	244	(64.9)	119	(61.3)	363	(63.7)
Discontinued Through Week 48 Post-transplant (Death)	71	(18.9)	44	(22.7)	115	(20.2)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Discontinued Through Week 48 Post-transplant (other reasons)	58	(15.4)	29	(14.9)	87	(15.3)
Post-study status: Alive	22	(5.9)	10	(5.2)	32	(5.6)
Post-study status: Death	22	(5.9)	15	(7.7)	37	(6.5)
Post-study status: Unknown	14	(3.7)	4	(2.1)	18	(3.2)
n (%) = Number (percent) of patients in each sub-category.						

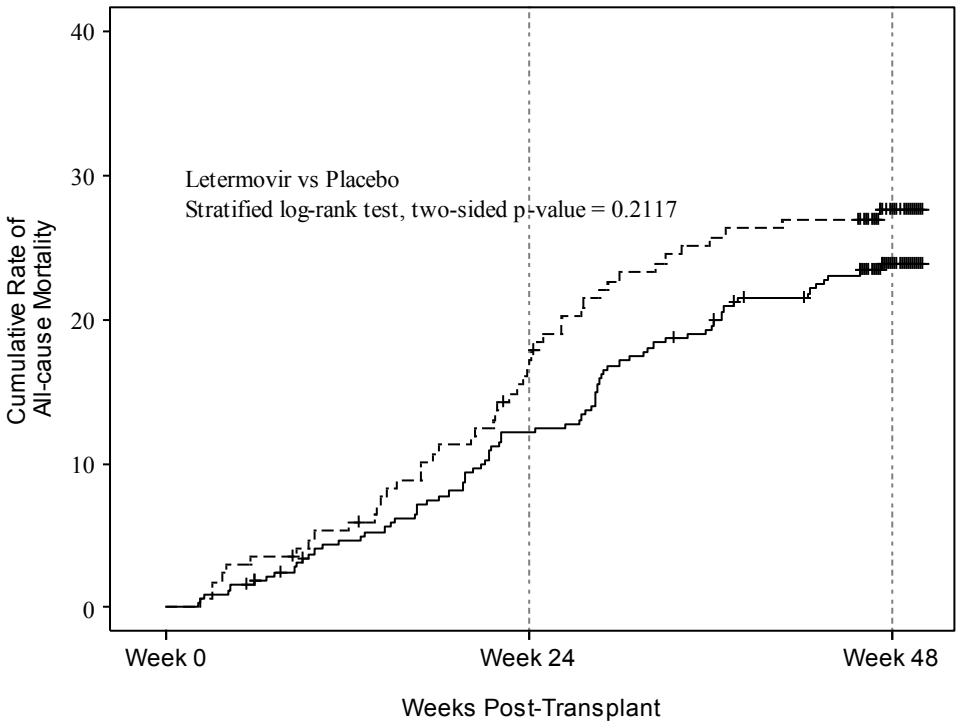
Table 14: Patient disposition including patients who withdrew prior to Week 48 post-transplant (Full Analysis Set)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	325		170		495	
Status for Trial Through 24 Weeks Post-transplant						
Randomised but not treated	0	(0.0)	0	(0.0)	0	(0.0)
Completed 24 weeks Post-transplant	261	(80.3)	123	(72.4)	384	(77.6)
Discontinued Through Week 24 Post-transplant (Death)	31	(9.5)	26	(15.3)	57	(11.5)
Discontinued Through Week 24 Post-transplant (other reasons)	33	(10.2)	21	(12.4)	54	(10.9)
Post-study status: Alive	20	(6.2)	12	(7.1)	32	(6.5)
Post-study status: Death	9	(2.8)	6	(3.5)	15	(3.0)
Post-study status: Unknown	4	(1.2)	3	(1.8)	7	(1.4)
Status for Trial Through 48 Weeks Post-transplant						
Completed 48 weeks Post-transplant	219	(67.4)	109	(64.1)	328	(66.3)
Discontinued Through Week 48 Post-transplant (Death)	60	(18.5)	39	(22.9)	99	(20.0)
Discontinued Through Week 48 Post-transplant (other reasons)	46	(14.2)	22	(12.9)	68	(13.7)
Post-study status: Alive	17	(5.2)	9	(5.3)	26	(5.3)
Post-study status: Death	19	(5.8)	9	(5.3)	28	(5.7)
Post-study status: Unknown	10	(3.1)	4	(2.4)	14	(2.8)
n (%) = Number (percent) of patients in each sub-category.						

The absolute difference in K-M mortality event rates between letermovir and placebo was maintained through week 24 (letermovir, 12.1%; placebo 17.2%; p=0.0401) and week 48 (letermovir, 23.8%; placebo 27.6%; p=0.2117) post-transplant (Figure 6).

Finally, the mortality benefit was explored when stratified by prior CMV infection in an additional ad-hoc analysis. This analysis suggested a lower mortality rate in the letermovir group (9/57 [15.8%]) versus the placebo group (22/71 [31.0%]) among patients with clinically-significant CMV infection through week 24; and similar mortality rates between the letermovir (52/268 [19.4%]) and placebo (18/99 [18.2]) groups in patients without clinically-significant CMV infection through Week 24. Since significantly fewer letermovir-treated versus placebo-treated patients developed clinically-significant CMV infection, the decrease in all-cause mortality observed with letermovir is likely due to prevention of CMV viraemia post-transplant [24, 31, 32]

Figure 6: K-M plot of time to all-cause mortality at Week 48 post-transplant (including vital status collected post-study, FAS population)



No. at risk: KM estimates % (95% CI)			
Letermovir	325	282: 12.1 (8.6, 15.7)	165: 23.8 (19.1, 28.5)
Placebo	170	139: 17.2 (11.5, 22.9)	81: 27.6 (20.8, 34.4)

2.6.5.2 Health-Related Quality of Life [23, 30, 31]

To assess QoL in this study, patients completed two validated tools of patient-reported outcomes (PROs) - the EQ-5D (Version 3L) and the FACT-BMT (Version 4) - at the time of randomisation, week 14, week 24, and week 48 post-transplant. An assessment was also conducted upon CMV infection onset or at the early discontinuation visit, if applicable.

[redacted]

[redacted]

[redacted]

2.6.6 Other exploratory endpoints included in the economic model

The results for GvHD, re-hospitalisation and opportunistic infections are reported in Table 15.

Table 15: Summary of the efficacy analyses for non-mortality exploratory endpoints (FAS population) [24]

Exploratory Endpoints	Letermovir (N=325)		Placebo (N=170)	
	n	% (95% CI)	n	% (95% CI)
Bacterial and/or Fungal opportunistic infection through Week 14 post-transplant	78	24.0 (19.5, 29.0)	37	21.8 (15.8, 28.7)
Bacterial and/or Fungal opportunistic infection through Week 24 post-transplant	87	26.8 (22.0, 31.9)	43	25.3 (19.0, 32.5)
GvHD through Week 14 post-transplant	126	38.8 (33.4, 44.3)	71	41.8 (34.3, 49.6)
GvHD through Week 24 post-transplant	159	8.9 (43.4, 54.5)	93	54.7 (46.9, 62.3)
Re-hospitalisation through Week 14 post-transplant	118	6.3 (31.1, 41.8)	81	47.6 (39.9, 55.4)
Re-hospitalisation for CMV infection/disease through Week 14 post-transplant	2	0.6 (0.1, 2.2)	12	7.1 (3.7, 12.0)
Re-hospitalisation through Week 24 post-transplant	158	8.6 (43.1, 54.2)	94	55.3 (47.5, 62.9)
Re-hospitalisation for CMV infection/disease through Week 24 post-transplant	10	3.1 (1.5, 5.6)	13	7.6 (4.1, 12.7)
Documented CMV viraemia through Week 14 post-transplant	103	1.7 (26.7, 37.1)	118	69.4 (61.9, 76.2)
Documented CMV viraemia through Week 24 post-transplant	186	7.2 (51.7, 62.7)	124	72.9 (65.6, 79.5)

N = Number of patients in analysis population.
n = Number of patients with outcome.

B.2.7 Subgroup analysis

The consistency of the treatment effect of letermovir in PN001 was assessed across various subgroups (FAS population) based on risk categories for CMV reactivation (risk stratum, stem cell source, degree of donor mismatch, haploidentical transplantation), patient characteristics (age, gender, weight, region, time of randomisation from the day of transplantation), and conditioning and concomitant immunosuppressive regimen (CsA-containing and tacrolimus-containing) used.

Overall, the treatment effect consistently favoured letermovir across subgroups based on patient baseline, epidemiological and clinical characteristics (Table 16-Table 18) [29].

The corresponding forest plots for the above analyses are presented in Appendix E. All analyses were pre-planned.

Table 16: Patients with clinically-significant CMV infection at Week 24 post-transplant by risk categories (NC=F approach, FAS population)

Risk category	Letermovir		Placebo		Letermovir vs. Placebo Difference in % (95% CI)†
	n/N	% (95% CI)	n/N	% (95% CI)	
[redacted]					

Table 17: Patients with clinically-significant CMV infection at Week 24 post-transplant by Patient Characteristic Subgroup (NC=F approach, FAS population)

Patient characteristic subgroup	Letermovir		Placebo		Letermovir vs. Placebo Difference in % (95% CI)[†]
	n/N	% (95% CI)	n/N	% (95% CI)	

[redacted]

Patient Characteristic Subgroup	Letermovir		Placebo		Letermovir vs. Placebo Difference in % (95% CI)[†]
	n/N	% (95% CI)	n/N	% (95% CI)	
[redacted]					

Table 18: Proportion of patients with clinically-significant CMV infection through Week 24 post-transplant by conditioning regimen and immunosuppressive regimen (NC=F approach, FAS population)

Subgroup	Letermovir		Placebo		Letermovir vs. Placebo Difference in % (95% CI)[†]
	n/N	% (95% CI)	n/N	% (95% CI)	
[redacted]					

B.2.8 Meta-analysis

Not applicable due to a variety of doses in the two trials reporting outcomes for letermovir (Table 19 and section B.2.9).

The remainder of section 2.8 presents a qualitative overview of the individual studies.

2.8.1 Study treatments

The three studies included in the SLR are summarised in Table 19. All were multicentre RCTs; two were multinational and one was conducted only in the USA.

The Phase III trial (Duarte et al 2017) [23] ran between June 2014 and March 2016 and was only available as a conference abstract at the time of the search, and thus only limited information on study details and outcome data were available. The full study results, which now constitute the evidence base for this submission, were published in the New England Journal of Medicine in December 2017 [23], after the SLR was conducted.

Table 19: Summary of included studies and study treatments

Author, year	Phase	Trial dates	Intervention	Dose	Regime	Treatment length	Study conclusion
Burns, 2002	NR	NR	Ganciclovir	5 mg/kg	1x daily, Mon-Fri	100 days	No statistically significant difference between ganciclovir and aciclovir when used as part of an overall strategy for prevention of CMV antigenaemia and disease in HSCT, although fewer side-effects occurred with aciclovir treatment
			Aciclovir	800 mg	5x daily		
Chemaly, 2014	Phase II	Mar 2000 – Oct 2011	Letermovir	60 mg 120 mg 240 mg	1x daily	84 days	Letermovir, as compared with placebo, was effective in reducing the incidence of CMV infection in recipients of allogeneic haematopoietic-cell transplants. The highest dose (240 mg/day) had the greatest anti-CMV activity, with an acceptable safety profile.
			Placebo	-	1x daily		
Duarte, 2017	Phase III	Jun 2014 – Mar 2016	Letermovir	480 mg (240 mg if on CsA)	1x daily	100 days	Letermovir prophylaxis was effective in reducing clinically-significant CMV infection, was overall well-tolerated, and provides a new approach to CMV prevention after HSCT.
			Placebo	-	1x daily		
CsA= ciclosporin A; NR= not reported							

2.8.2 Patient characteristics

Patient characteristics are presented in Table 20 and Table 21 below. Population sizes were similar across two of the three studies (Burns et al 2002 and Chemaly et al 2014) [33, 34]. The modified intention-to-treat (mITT) populations, defined as all patients who received at least one dose of the study drug and had at least one measurement of the CMV viral load during the study, were also reported by Chemaly et al 2014 [34]. Duarte et al 2017 [35] reported that 565 patients received study treatment and were randomised 2:1 to letermovir and placebo. Study arm populations reported for outcomes were 325 for letermovir and 170 for placebo. The number of patients who completed the full treatment course, the safety population and the per-protocol population was only reported by Chemaly et al 2014 [34].

Gender proportions, average age and age range were not reported by Duarte et al 2017. The average age of patients was lower in Burns et al 2002 (20 and 34 years for ganciclovir and aciclovir, respectively) than in the Chemaly et al 2014 study (53-57 years) [33, 34]. However, the reported average age and age range was for the entire treatment arm populations which included patients under the age of 18, and thus does not represent the average age of the adult-only population. The proportion of male patients, CMV-seropositive donor status, and proportion of patients who received a bone marrow or peripheral blood HSCT was reported by Burns et al 2002 and Chemaly et al 2014 [33, 34], although these data were only reported by Burns et al 2002 for the entire treatment arm population. The majority of patients in the Chemaly et al 2014 study[34] received a peripheral blood HSCT (94-100%), compared to the Burns et al., 2002 study[33] in which more patients were recipients of a bone marrow HSCT (67-76%).

Table 20: Patient characteristics of included studies

Author, year	Intervention	Dose	n randomised	n ITT	n mITT	n clinically evaluable	n completed	n safety population	n per protocol
Burns, 2002	Ganciclovir	5 mg/kg	30	NR	NR	NR	NR	NR	NR
	Aciclovir	800 mg	29						
Chemaly, 2014	Letermovir	60 mg 120 mg 240 mg	33 33 34	NR	33 31 34	NR	13 15 20	31 28 32	31 28 32
	Placebo	-	33		33		5	28	28
Duarte, 2017	Letermovir	480 mg	NR	NR	565	325	NR	NR	NR
	Placebo	-				170			
ITT= intention to treat; mITT= modified intention-to-treat; NR= not reported; n= number of patients									

Table 21: Patient characteristics of included studies

Author, year	Intervention	Dose	Male participants, n (%)	Average age (range)	CMV seropositive donor status, n (%)	Bone marrow HSCT, n (%)	Peripheral blood HSCT, n (%)
Burns, 2002	Ganciclovir	5 mg/kg	24 (53)*	20 (1.1-55)*	21 (47)*	34 (76)*	11 (24)*
	Aciclovir	800 mg	30 (65)*	34 (1.1-55)*	20 (44)*	31 (67)*	15 (33)*
Chemaly, 2014	Letermovir	60 mg 120 mg 240 mg	14(42) 22 (71) 22 (65)	55 (24-69) 57 (22-68) 53.5 (25-67)	13 (39) 17 (55) 21 (62)	1 (3) 0 (0) 1 (3)	32 (97) 31 (100) 33 (97)
	Placebo	-	19 (58)	53 (24-71)	19 (58)	2 (6)	31 (94)
Duarte, 2017	Letermovir	480 mg	NR	NR	NR	NR	NR
	Placebo	-					
NR= not reported; HSCT= haematopoietic stem cell transplant *= data reported for entire treatment arm population (including patients <18 years old)							

2.8.3 Efficacy outcomes

Clinical endpoints for the three included trials are presented in Table 22 below. The number and percentage of patients who developed clinically-significant CMV infection (defined as CMV antigenaemia or detection of viral DNA) was the only clinical endpoint comparable between Burns et al., 2002 and the Phase II letermovir trial (Chemaly et al 2014) [33, 34].

The comparable clinical outcomes between the two letermovir studies were the percentage of patients with all-cause prophylaxis failure (defined by Chemaly et al 2014 as patients who discontinued the study drug because of virologic failure or for any other reason such as an adverse event, non-adherence or withdrawal of consent [34]) and mortality and patients who developed GvHD. All-cause prophylaxis failure was similar between the two letermovir studies. All-cause mortality ranged between 3-6% in Chemaly et al 2014, and 10-15% in Duarte et al 2017, and patients who developed GvHD ranged between 12-16% in Chemaly et al 2014 and was 39% for both letermovir and placebo arms in Duarte et al 2017 [35]. Although the higher mortality and GvHD rate was not addressed by Duarte et al 2017, this study had only been presented as a conference abstract at the time of the SLR. As other efficacy outcomes reported by Burns et al 2002 were not stratified for the adult-only population, these data were not extracted from the study for comparison with letermovir.

No study reported either the number of patients who developed CMV disease (although Burns et al 2002 reported CMV disease, this was not stratified for adult patients [33]), any pre-emptive therapy outcomes, or any hospital admission outcomes.

Table 22: Efficacy outcomes of included studies

Author (year)	Intervention	Dose	CS-CMV infection, n (%)	Time to onset of CS-CMV (days)	All-cause prophylaxis failure, n (%)	All mortality, n (%)	CMV-related mortality, n (%)	Non-CMV, non-drug mortality, n (%)	GvHD, n (%)	Infection or infestation, n (%)
Burns, 2002	Ganciclovir	5 mg/kg	8 (27)	NR†	NR	NR†	NR	NR	NR	NR†
	Aciclovir	800 mg	14 (48)	NR†		NR†				NR†
Chemaly, 2014	Letermovir	60 mg 120 mg 240 mg	7 (21) 6 (19) 2 (6)	1-42 1-15 1-8	16 (48) 10 (32) 10 (29)	2 (6) 0 (0) 1 (3)	0 (0) 0 (0) 0 (0)	2 (6) 0 (0) 1 (3)	4 (12) 5 (16) 4 (12)	17 (52) 18 (58) 23 (68)
	Placebo	-	12 (36)	1-21	21 (64)	1 (3)	0 (0)	1 (3)	5 (15)	25 (76)
Duarte, 2017	Letermovir	480 mg	NR	NR	122 (38)	(10)	NR	NR	(39)	NR
	Placebo	-			103 (61)	(15)			(39)	
CS-CMV= clinically-significant CMV infection; GvHD= graft-versus-host disease; NR= not reported										

2.8.4 Safety outcomes

Of the three included studies, only Chemaly et al 2014 presented comprehensive safety outcomes [34]. Although adverse events were reported by Burns et al 2002, these were not reported stratified for the adult-only population [33]. Duarte et al 2017 reported the percentage of patients who experienced diarrhoea, nausea and vomiting (gastrointestinal disorders), as well as oedema (general and site administration disorders) and atrial arrhythmia (cardiovascular disorders) [35].

Health-related quality of life was not reported by any study.

2.8.5 Risk of bias within studies

The risk of bias in each of the included studies was assessed using according to criteria for assessment of risk of bias suggested by the Centre for Reviews and Dissemination (CRD) [36]. Full details of the quality assessment are tabulated within Appendix D.1.

All three included studies randomised patients using different methods. Burns et al 2002 randomised patients into groups with stratification for related vs unrelated donor transplant, Chemaly et al 2014 reported that patients were allocated into treatment groups by use of block randomisation, and Duarte et al 2017 randomised patients stratified by study site and high or low CMV disease risk [33-35]. Only Burns et al 2002 reported p-values for differences between patient characteristics and stated that no statistically significant difference was found between groups [33]. Patient demographics and baseline characteristics were reported by Chemaly et al 2014 and were broadly similar across treatment groups [34]. No patient characteristics were reported by Duarte et al 2017 although the authors stated that study arms were balanced; however, the conference abstract form of this study prevented a more detailed disclosure. There were no unexpected imbalances in drop-outs between groups for any of the studies, and no evidence to suggest that the authors measured more outcomes than they reported.

Concealment of treatment allocation was not addressed by any of the three studies. Blinding of treatment allocation was reported by Chemaly et al., 2014, which stated that all trial site, staff and team members were unaware of the treatment assignments[34]. Although Duarte et al 2017 did not report blinding of treatment allocation, the clinicaltrials.gov record for this trial reported that triple masking of patients, investigators and outcomes assessors was performed (NCT02137772).

The analysed population of Burns et al 2014 used the patients randomised to the study drugs [33]. Chemaly et al 2014 [34] analysed the mITT population, which included all patients who received at least one dose of the study drug and had at least one measurement of the CMV viral load during the

study (Chemaly et al 2014). Descriptions of the analysed population of Duarte et al 2017 were not stated, although the total population size of the treatment arms was reported and was lower than the number of patients who received study treatment.

2.8.6 Summary of main results

This SLR identified three studies assessing the efficacy and safety of letermovir, ganciclovir and aciclovir; although only one clinical endpoint (clinically-significant CMV infection) could be compared between letermovir and the other two agents. As there was no common comparator between the single letermovir trial and the single ganciclovir/aciclovir trial reporting this endpoint, a network meta-analysis could not be performed.

Four additional studies that were considered of interest were identified at the full-text screening stage. These studies did not fit the inclusion criteria as they contained patients under the age of 18, but were flagged as potentially of interest as their non-adult populations were limited to those aged above 13 years (Ljungman et al 2002, Winston et al 2003), 14 years (Winston et al 1993), or 17 years (Li et al 1994). Although adherence to the original PICOS and inclusion/exclusion criteria required these studies to be excluded, the corresponding authors for these studies were contacted requesting information on how many of these patients were under the age of 18; however, no responses were received. Another study, Prentice et al 1994, was excluded as it randomised patients aged under 18 as well as seronegative patients. However, this citation was subsequently identified as potentially of interest due to the BSH guidelines citing it as supporting evidence for aciclovir use [20], despite some concerns about the robustness of the data [3]. Attempts to obtain separate data on the adult seropositive subpopulation of this study were also unsuccessful.

B.2.9 Indirect and mixed treatment comparisons

An attempt was made to form a network connecting the studies identified in the systematic review in order to perform a mixed treatment comparison (MTC).

The only clinical endpoint able to be compared across letermovir and other antiviral agents was the proportion of patients who developed clinically-significant CMV infection, which was reported by two studies [33, 34]. However, no network could be built for this endpoint. Chemaly et al 2014 compared letermovir to placebo, while Burns et al 2002 compared aciclovir and ganciclovir, with no placebo arm included. Thus, with a lack of a common comparator used to anchor a comparison, a network meta-analysis was not feasible. A diagram of the attempted network is presented in Appendix D.1.

Although an NMA was not feasible, other indirect comparisons could be attempted to compare the clinically-significant CMV infection endpoint of the two studies. When no common comparator is available, the options for an adjusted analysis are hierarchical Bayesian modelling, simulated treatment comparison or matching-adjusted indirect comparison (MAIC). Both simulated treatment comparison and matching-adjusted indirect comparison require individual patient-level data for one treatment, while hierarchical Bayesian modelling does not require individual patient-level data as historical controls are commonly used.

If individual patient level data (IPLD) reporting clinically-significant CMV infection is available from the Phase II trial (Chemaly et al) then a MAIC of letermovir versus aciclovir or ganciclovir may be feasible, providing that average baseline characteristics for adult patients receiving aciclovir or ganciclovir in the Burns et al., (2002) study are available (these data were not reported in the manuscript). As reported in section 2.8.6 above, attempts were made to follow up with study authors to obtain IPLD that would facilitate an MAIC, but these data were not made available.

Finally, a standard meta-analysis pooling data from the Phase II and Phase III letermovir versus placebo trials would not be recommended as four different doses were utilised 60 mg, 120 mg, 240 mg and 480 mg, and a clear dose-response relationship was observed [23, 34, 35].

2.9.1 Uncertainties in the indirect and mixed treatment comparisons

Not applicable, please refer to section B.2.9 above.

B.2.10 Adverse reactions

2.10.1 Safety analysis population

The All Subjects as Treated (ASaT) population (n=565) was used for safety analyses in PN001 and consisted of all randomised patients who received at least one dose of study medication. For this analysis patients were included in the treatment group corresponding to the study medication they actually received.

[redacted]

[redacted]

Table 23: Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.10.2 Results of safety analysis

Data are presented over the following time periods:

- Treatment phase: AEs collected from time of study drug initiation through to 14 days following the last dose of study medication. The AE reporting period for Treatment Phase is directly linked to study medication exposure and is longer in the letermovir group than in placebo
- Through to week 24 post-transplant: AEs collected from time of study drug initiation through to week 16 post-transplant. From weeks 16-24 post-transplant, only drug-related SAEs and SAEs leading to death are reported. Tabulated AE data after week 16 post-transplant also contain any other types of AEs that were passively reported. The AE reporting period through week 24 post-transplant is the same for both treatment groups

(Note: drug-related SAEs and SAEs leading to death were also collected through to week 48).

2.10.3 Study drug exposure

Within the ASaT population the mean duration of exposure (mean days on therapy) in the letermovir [redacted] group [redacted] was 69.4 days [redacted]

Table 24: Extent of Exposure to Letermovir or Placebo by Route of Administration [24, 29]

	Letermovir			Placebo		
	Any route of administration	IV	Oral	Any route of administration	IV	Oral
Patients in population	373	99	367	192	[redacted]	[redacted]
[redacted]						
Mean	69.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	82	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] Patients may be counted in multiple columns if they received different routes of administration. IV= intravenous [redacted]						

2.10.4 Adverse Events- Treatment Phase

Overall, the AE profile was similar in the letermovir and placebo groups with the exception of AEs leading to discontinuation of study medication for which there was a numerical imbalance favouring letermovir (19.3% letermovir; 51.0% placebo, Table 25). This was primarily due to a greater proportion of patients discontinuing due to the AE of CMV infection in the placebo group (6.2% in letermovir group compared to 39.1% in the placebo group). The most commonly reported AEs, namely graft-versus-host disease (GvHD), nausea, vomiting, diarrhoea, pyrexia and rash, occurred at comparable frequency in patients receiving letermovir or placebo. There were no drug-related deaths in either treatment group.

Table 25: Analysis of Adverse Event Summary- Treatment Phase (ASaT Population)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI) †
Patients in population	373		192		

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI) †
With one or more adverse events	365	(97.9)	192	(100.0)	-2.1 (-4.2, -0.2)
With no adverse event	8	(2.1)	0	(0.0)	2.1 (0.2, 4.2)
With drug-related‡ adverse events	63	(16.9)	23	(12.0)	4.9 (-1.4, 10.6)
With serious adverse events	165	(44.2)	90	(46.9)	-2.6 (-11.3, 6.0)
With serious drug-related adverse events	3	(0.8)	3	(1.6)	N/A
Who died	38	(10.2)	17	(8.9)	1.3 (-4.2, 6.2)
Discontinued§ due to an adverse event	72	(19.3)	98	(51.0)	-31.7 (-39.7, -23.6)
Discontinued due to a drug-related adverse event	18	(4.8)	7	(3.6)	1.2 (-2.9, 4.5)
Discontinued due to a serious adverse event	35	(9.4)	27	(14.1)	-4.7 (-10.9, 0.7)
Discontinued due to a serious drug-related adverse event	3	(0.8)	3	(1.6)	N/A

† Based on Miettinen & Nurminen method.
‡ Determined by the investigator to be related to the drug.
§ Study medication withdrawn
n= Number of patients randomised and treated in each treatment group.
Note: Treatment phase is defined as the time of first dose through 14 days following the last dose of study treatment.
Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with ciclosporin A.

The incidences of commonly-reported AEs were generally comparable in the letermovir and placebo groups, with the exception of the AE of CMV infection (8.3% letermovir vs. 45.8% placebo, Table 26).

The most commonly reported AEs (letermovir vs. placebo) during the Treatment Phase were GvHD (39.1% vs. 38.5%), diarrhoea (26.0% vs. 24.5%), nausea (26.5% vs. 23.4%), vomiting (18.5% vs. 13.5%), rash (20.4% vs. 21.4%), and pyrexia (20.6% vs. 22.4%).

Table 26: Analysis of Patients With Adverse Events (Incidence ≥ 4 Patients in One or More Treatment Groups)- Treatment Phase (ASaT Population)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Patients in population	373		192		
With one or more adverse events	365	(97.9)	192	(100.0)	-2.1 (-4.2, -0.2)
With no adverse events	8	(2.1)	0	(0.0)	2.1 (0.2, 4.2)
Blood and lymphatic system disorders	**98**	**(26.3)**	**51**	**(26.6)**	**-0.3 (-8.2, 7.2)**
Anaemia	25	(6.7)	10	(5.2)	1.5 (-3.1, 5.4)
Eosinophilia	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Febrile neutropaenia	31	(8.3)	18	(9.4)	-1.1 (-6.6, 3.6)
Leukopaenia	11	(2.9)	7	(3.6)	-0.7 (-4.6, 2.2)
Neutropaenia	14	(3.8)	7	(3.6)	0.1 (-3.9, 3.2)
Pancytopaenia	7	(1.9)	6	(3.1)	-1.2 (-4.9, 1.3)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Thrombocytopaenia	25	(6.7)	11	(5.7)	1.0 (-3.8, 4.9)
Cardiac disorders	**47**	**(12.6)**	**12**	**(6.3)**	**6.4 (1.1, 11.0)**
Atrial fibrillation	13	(3.5)	2	(1.0)	2.4 (-0.5, 5.0)
Atrial flutter	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Cardiac failure	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Sinus tachycardia	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Tachycardia	15	(4.0)	4	(2.1)	1.9 (-1.5, 4.8)
Eye disorders	**62**	**(16.6)**	**32**	**(16.7)**	**-0.0 (-6.9, 6.2)**
Dry eye	22	(5.9)	10	(5.2)	0.7 (-3.9, 4.5)
Gastrointestinal disorders	**261**	**(70.0)**	**129**	**(67.2)**	**2.8 (-5.1, 11.0)**
Abdominal pain	44	(11.8)	18	(9.4)	2.4 (-3.3, 7.5)
Abdominal pain upper	15	(4.0)	16	(8.3)	-4.3 (-9.4, -0.3)
Constipation	27	(7.2)	20	(10.4)	-3.2 (-8.8, 1.5)
Diarrhoea	97	(26.0)	47	(24.5)	1.5 (-6.3, 8.8)
Dry mouth	20	(5.4)	6	(3.1)	2.2 (-1.7, 5.6)
Dyspepsia	20	(5.4)	7	(3.6)	1.7 (-2.4, 5.1)
Nausea	99	(26.5)	45	(23.4)	3.1 (-4.6, 10.3)
Stomatitis	23	(6.2)	9	(4.7)	1.5 (-3.0, 5.2)
Vomiting	69	(18.5)	26	(13.5)	5.0 (-1.7, 11.0)
General disorders and administration site conditions	**211**	**(56.6)**	**100**	**(52.1)**	**4.5 (-4.2, 13.1)**
Asthenia	23	(6.2)	7	(3.6)	2.5 (-1.6, 6.1)
Fatigue	50	(13.4)	21	(10.9)	2.5 (-3.6, 7.8)
Mucosal inflammation	46	(12.3)	24	(12.5)	-0.2 (-6.4, 5.3)
Oedema peripheral	54	(14.5)	18	(9.4)	5.1 (-0.8, 10.4)
Pyrexia	77	(20.6)	43	(22.4)	-1.8 (-9.2, 5.2)
Hepatobiliary disorders	**22**	**(5.9)**	**15**	**(7.8)**	**-1.9 (-7.0, 2.3)**
Immune system disorders	**153**	**(41.0)**	**80**	**(41.7)**	**-0.6 (-9.3, 7.8)**
Graft versus host disease	146	(39.1)	74	(38.5)	0.6 (-8.0, 8.9)
Infections and infestations	**241**	**(64.6)**	**139**	**(72.4)**	**-7.8 (-15.5, 0.4)**
Bacteraemia	20	(5.4)	4	(2.1)	3.3 (-0.3, 6.4)
Cytomegalovirus infection	31	(8.3)	88	(45.8)	-37.5 (-45.1, -30.0)
Pneumonia	20	(5.4)	5	(2.6)	2.8 (-1.0, 6.0)
Viraemia	11	(2.9)	11	(5.7)	-2.8 (-9.1, 2.8)
Injury, poisoning and procedural complications	**42**	**(11.3)**	**27**	**(14.1)**	**-2.8 (-9.1, 2.8)**
Investigations	**133**	**(35.7)**	**60**	**(31.3)**	**4.4 (-3.9, 12.4)**
Alanine aminotransferase increased	24	(6.4)	16	(8.3)	-1.9 (-7.1, 2.4)
Aspartate aminotransferase increased	19	(5.1)	13	(6.8)	-1.7 (-6.5, 2.2)
Blood creatinine increased	36	(9.7)	13	(6.8)	2.9 (-2.3, 7.4)
Metabolism and nutrition disorders	**134**	**(35.9)**	**63**	**(32.8)**	**3.1 (-5.3, 11.2)**
Decreased appetite	38	(10.2)	22	(11.5)	-1.3 (-7.2, 3.9)
Hyperglycaemia	25	(6.7)	10	(5.2)	1.5 (-3.1, 5.4)
Hyperkalaemia	27	(7.2)	4	(2.1)	5.2 (1.4, 8.6)
Hypokalaemia	22	(5.9)	11	(5.7)	0.2 (-4.5, 4.0)
Hypomagnesaemia	23	(6.2)	15	(7.8)	-1.6 (-6.8, 2.6)
Hyponatraemia	21	(5.6)	10	(5.2)	0.4 (-4.1, 4.1)
Musculoskeletal and connective tissue disorders	**121**	**(32.4)**	**57**	**(29.7)**	**2.8 (-5.5, 10.6)**
Arthralgia	26	(7.0)	10	(5.2)	1.8 (-2.9, 5.7)
Back pain	23	(6.2)	14	(7.3)	-1.1 (-6.1, 3.0)
Myalgia	19	(5.1)	3	(1.6)	3.5 (0.2, 6.5)

	Letermovir n	(%)	Placebo n	(%)	Difference in % vs Placebo Estimate (95% CI)†
Pain in extremity	19	(5.1)	11	(5.7)	-0.6 (-5.2, 3.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**39**	**(10.5)**	**17**	**(8.9)**	**1.6 (-4.0, 6.5)**
Nervous system disorders	**137**	**(36.7)**	**64**	**(33.3)**	**3.4 (-5.0, 11.5)**
Dizziness	25	(6.7)	11	(5.7)	1.0 (-3.8, 4.9)
Headache	52	(13.9)	18	(9.4)	4.6 (-1.3, 9.8)
Tremor	27	(7.2)	8	(4.2)	3.1 (-1.3, 6.9)
Psychiatric disorders	**78**	**(20.9)**	**30**	**(15.6)**	**5.3 (-1.6, 11.6)**
Anxiety	20	(5.4)	5	(2.6)	2.8 (-1.0, 6.0)
Insomnia	34	(9.1)	10	(5.2)	3.9 (-0.9, 8.1)
Renal and urinary disorders	**81**	**(21.7)**	46	(24.0)	-2.2 (-9.8, 4.9)
Acute kidney injury	36	(9.7)	25	(13.0)	-3.4 (-9.5, 1.9)
Cystitis haemorrhagic	4	(1.1)	6	(3.1)	-2.1 (-5.7, 0.2)
Dysuria	11	(2.9)	6	(3.1)	-0.2 (-3.9, 2.7)
Haematuria	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Nocturia	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Pollakiuria	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Renal failure	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Renal impairment	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Urinary retention	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
[redacted]	[redacted]		[redacted]		[redacted]
Respiratory, thoracic and mediastinal disorders	**147**	**(39.4)**	**71**	**(37.0)**	**2.4 (-6.1, 10.7)**
Cough	53	(14.2)	20	(10.4)	3.8 (-2.2, 9.2)
Dyspnoea	30	(8.0)	6	(3.1)	4.9 (0.8, 8.6)
Dyspnoea exertional	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Epistaxis	23	(6.2)	11	(5.7)	0.4 (-4.3, 4.3)
Haemoptysis	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Hypoxia	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Nasal congestion	8	(2.1)	1	(0.5)	1.6 (-0.9, 3.7)
Oropharyngeal pain	28	(7.5)	15	(7.8)	-0.3 (-5.5, 4.1)
Pleural effusion	10	(2.7)	3	(1.6)	1.1 (-2.0, 3.6)
Productive cough	5	(1.3)	2	(1.0)	0.3 (-2.5, 2.2)
Pulmonary oedema	6	(1.6)	4	(2.1)	-0.5 (-3.8, 1.8)
Respiratory failure	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Rhinorrhoea	12	(3.2)	9	(4.7)	-1.5 (-5.7, 1.7)
Upper-airway cough syndrome	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Skin and subcutaneous tissue disorders	**179**	**(48.0)**	**80**	**(41.7)**	**6.3 (-2.4, 14.8)**
Dry skin	26	(7.0)	8	(4.2)	2.8 (-1.6, 6.6)
Erythema	33	(8.8)	11	(5.7)	3.1 (-1.8, 7.4)
Pruritus	26	(7.0)	11	(5.7)	1.2 (-3.5, 5.2)
Rash	76	(20.4)	41	(21.4)	-1.0 (-8.4, 5.9)
Vascular disorders	**69**	**(18.5)**	**40**	**(20.8)**	**-2.3 (-9.6, 4.4)**
Haematoma	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Hypertension	31	(8.3)	21	(10.9)	-2.6 (-8.4, 2.3)
Hypotension	14	(3.8)	9	(4.7)	-0.9 (-5.2, 2.4)
Orthostatic hypotension	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)

† Based on Miettinen & Nurminen method. Every patient is counted a single time for each applicable row and column.

	Letermovir n (%)	Placebo n (%)	Difference in % vs Placebo Estimate (95% CI)†
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. System organ class groups are presented in bold, preferred adverse terms in regular font.			

Based on the Tier 2 analysis, the incidences of AEs in the Cardiac Disorders System Organ Class (SOC) and Ear and Labyrinth Disorders SOC, and AEs of myalgia, hyperkalaemia, and dyspnoea were higher in the letermovir group compared to the placebo group. A brief summary of these AEs is provided below:

- Cardiac Disorders SOC: (12.6% letermovir vs.6.3% placebo; 6.4% difference [95% CI: 1.1, 11.0]). The incidence of cardiac AEs by SOC was higher in the letermovir group compared to the placebo group and the 95% CI of the difference in percentage excluded zero by Tier 2 analysis. The percentage of patients with specific AEs by PT reported in this SOC (atrial fibrillation, atrial flutter, cardiac failure, sinus tachycardia, and tachycardia) were numerically higher in the letermovir and placebo groups, but their corresponding 95% CI of the difference in percentage included zero. No patients in the letermovir group experienced a drug-related Cardiac Disorders SOC AE
- Ear and Labyrinth Disorders SOC: (4.6% letermovir vs. 1.0% placebo; 3.5% difference [95% CI: 0.5, 6.3]). The incidence of Ear and Labyrinth SOC AEs was higher in the letermovir group than placebo, and the 95% CI of the difference excluded zero by Tier 2 analysis. A numerically higher percentage of patients with specific AEs by PT reported in this SOC (ear pain and vertigo) were observed, but the corresponding 95% CI of the difference in percentages included zero
- Myalgia: 5.1% letermovir vs. 1.6% placebo; 3.5% difference (95% CI: 0.2%, 6.5%)
- Hyperkalaemia: 7.2% letermovir vs. 2.1% placebo; 5.2% difference (95% CI: 1.4%, 8.6%)
- Dyspnoea: 8.0% letermovir vs. 3.1% placebo; 4.9% difference (95% CI: 0.8%, 8.6%)

Notably, the proportions of patients with Renal and Urinary Disorders SOC AEs and the acute kidney injury PT AE were numerically lower in the letermovir group compared to the placebo group. The proportion of patients with AE PT of renal failure and renal impairment was generally comparable between the treatment groups.

The incidence of the following AEs was lower in the letermovir group compared to the placebo group and the corresponding 95% CI for the difference in percentage excluded zero:

- CMV infection: 8.3% letermovir vs. 45.8% placebo; -37.5% difference (95% CI: -45.1%, -30.0%)

- Upper abdominal pain: 4.0% letermovir vs. 8.3% placebo; -4.3% difference (95% CI: -9.4%, -0.3%)
- Gastroesophageal reflux disease (GORD): 1.1% letermovir vs. 4.7% placebo; -3.6% difference (95% CI: -7.7%, -1.0%)
- Myopathy: 0.5% letermovir vs. 2.6% placebo; -2.1% difference (95% CI:-5.5%, -0.1%)
- Dehydration: 0.5% letermovir vs. 2.6% placebo; -2.1% difference (95% CI: -5.5%, -0.1%)
- Presyncope: 0.3% letermovir vs. 2.1% placebo; -1.8% difference (95% CI: -5.0%, -0.2%)

2.10.5 Serious Adverse Events

Overall, the proportions of patients with SAEs reported during the Treatment Phase were similar in the treatment groups (44.2% letermovir vs. 46.9% placebo; difference -2.6 [95% CI -11.3%, 6.0%]). SAEs that occurred most frequently in patients in the letermovir and placebo groups were GvHD (9.9% vs. 10.4%), recurrent acute myeloid leukaemia (2.9% vs. 3.6%), CMV infection (2.7% vs. 6.8%), acute kidney injury (1.3 % vs. 4.7%), pneumonia (2.1% vs. 1.6%), and pyrexia (1.9% vs. 2.1%).

The incidence of CMV infection was lower in the letermovir group (2.7%) compared to the placebo group (6.8%; -4.1% difference [95% CI: -8.8%, -0.6%]). Similarly, the incidence of acute kidney injury was lower in the letermovir group (1.3%) compared to placebo group (4.7%; -3.3% difference [95% CI: -7.4%, -0.6%]).

Cardiac Disorders SOC were reported as SAEs by 6 patients (1.6%) in the letermovir group and 1 (0.5%) in the placebo group. There were no SAEs reported in the Ear and Labyrinth Disorder SOC, or SAEs of hyperkalaemia, dyspnoea or myalgia.

2.10.6 Adverse events through to week 24 Post-Transplant

A summary of the overall AE profile of patients through to week 24 post-transplant is presented in Table 27 below. Overall, the AE profile was similar to the profile during the Treatment Phase.

At week 24 post-transplant, the proportion of patients with SAEs had increased from 44.2% to 51.7% in the letermovir group and 46.9% to 56.8% in the placebo group.

The proportion of patients who died was also increased at week 24 post-transplant in each treatment group; from 10.2 % to 16.4% in the letermovir group and 8.9% to 19.8% in the placebo group, respectively. Neither of these increased rates is unexpected given the additional safety follow-up through to week 24 post-transplant.

There were no additional reports of drug-related AEs or SAEs, and discontinuations due to an AE, a drug-related AE or drug-related SAEs through week 24 post-transplant compared to the Treatment Phase, which was expected, since patients did not take study medication from the end of the Treatment Phase (week 14, ~Day 100) to week 24 post-transplant.

Overall, the results of the Tier 2 analysis of AEs through week 24 post-transplant were similar to those previously described for the Treatment Phase. There were no changes in the proportions of patients with AEs or SAEs leading to discontinuation of study medication in either treatment group by week 24 post-transplant compared to the Treatment Phase.

Table 27: Adverse Event Summary Through to 24 weeks Post-Transplant (ASaT Population) [23, 29]

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	373		192		565	
With one or more adverse events	366	(98.1)	192	(100.0)	558	(98.8)
With no adverse event	7	(1.9)	0	(0.0)	7	(1.2)
With drug-related† adverse events	63	(16.9)	23	(12.0)	86	(15.2)
With non-serious adverse events	364	(97.6)	190	(99.0)	554	(98.1)
With serious adverse events	193	(51.7)	109	(56.8)	302	(53.5)
With serious drug-related adverse events	3	(0.8)	3	(1.6)	6	(1.1)
Who died	61	(16.4)	38	(19.8)	99	(17.5)
Who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to an adverse event	72	(19.2)	98	(51.0)	170	(30.1)
Discontinued due to a drug-related adverse event	18	(4.8)	7	(3.6)	25	(4.4)
Discontinued due to a serious adverse event	35	(9.4)	27	(14.1)	62	(11.0)
Discontinued due to a serious drug-related adverse event	3	(0.8)	3	(1.6)	6	(1.1)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
n= Number of patients randomised and treated in each treatment group
Note: All AEs are reported from the time of initiation of study treatment through to week 24 post-transplant
Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with ciclosporin A.

Table 28 below summarises the number and percentage of patients with specific AEs that occurred at an incidence ≥5% in one or more treatment groups through to week 24 post-transplant.

In general, the AE profile by treatment group through week 24 post-transplant is similar to the AE profile during the Treatment Phase. As in the Treatment Phase, the incidence of CMV infection was lower in the letermovir group (62/373 [16.6%]) compared to the placebo group (90/192 [46.9%]) through week 24 post-transplant.

The most commonly reported AEs by SOC through week 24 post-transplant were Gastrointestinal (GI) Disorders (72.9% letermovir vs. 71.4% placebo), and Infections and Infestations (70.8% letermovir vs. 75.5% placebo).

The most commonly reported AEs were also similar, but increased in frequency compared to the Treatment Phase, which is expected due the longer duration of safety follow-up through week 24 post-transplant. These events included (letermovir vs. placebo): GvHD (44.5% vs. 49.5%), diarrhoea (28.2% vs. 27.1%), and nausea (27.3% vs. 26.0%), pyrexia (23.1% vs. 26.0%), CMV infection (16.6% vs. 46.9%), rash (23.1% vs. 25.0%), and vomiting (19.8% vs. 16.7%).

The Tier 2 analysis of AEs at week 24 post-transplant reported higher incidences of the following AEs in the letermovir group:

- Ear and Labyrinth Disorders SOC: 5.6% letermovir vs. 1.0% placebo; 4.6% difference (95% CI: 1.5%, 7.6)
- Hyperkalaemia: 7.5% letermovir vs. 2.1% placebo; 5.4% difference (95% CI: 1.7%, 8.9%)
- Blurred vision: 3.2% letermovir vs. 0.5% placebo; 2.7% difference (95% CI: 0.1%, 5.1%)

Table 28: Patients With Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) Through 24 Weeks Post-Transplant (ASaT Population) [29]

	Letermovir n	(%)	Placebo n	(%)	Total n	(%)
[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Letermovir n (%)		Placebo n (%)		Total n (%)	
[redacted]						

	Letermovir n (%)		Placebo n (%)		Total n (%)	
[redacted]						

2.10.7 Drug-related AEs/SAEs

[redacted]

2.10.8 AEs leading to fatal outcomes

[redacted]

2.10.9 Exposure to IV Formulation

[redacted]

2.10.10 Engraftment [24, 29]

Another aspect of assessment for myelotoxicity that was examined in this trial was the incidence and time to engraftment for patients who received study medication prior to engraftment. Overall, the majority of these patients engrafted in both treatment groups with more patients engrafting in the letermovir group (95.4%) compared to the placebo group (91.3%). [redacted]

B.2.11 Ongoing studies

There are currently no ongoing studies for the indication being appraised.

B.2.12 Innovation

Letermovir is the first new anti-CMV molecule to be successfully developed in more than 15 years. It is a first-in-class agent with high specificity against human CMV, targeting the pUL56 subunit of the viral terminase complex in order to inhibit virion maturation. This unique mode of action means that no cross-resistance is expected with older antiviral agents targeting the viral DNA polymerase, allowing for letermovir to be used in patients who may have resistance to pre-emptive therapy agents. As letermovir has no human target, it is anticipated that many of the toxicities associated with pre-emptive therapy may be avoided.

Letermovir will be available in both oral and IV formulations, with the latter preparation available for patients with gastrointestinal complications that may compromise swallowing and absorption of the oral formulation. The two formulations are interchangeable at the discretion of the initiating physician, and no dose-adjustment is required; this allows for greater flexibility of use in patients that may be transitioning between inpatient and outpatient settings. Letermovir was designated as an orphan drug in 2011, with the EMA recognising its potential to delay the use of pre-emptive therapy [37].

B.2.13 Interpretation of clinical effectiveness and safety evidence

Results from PN001 demonstrate that letermovir had superior efficacy over placebo in the primary endpoint analysis, as a lower proportion of patients in the letermovir group (37.5%) developed clinically-significant CMV infection compared to the placebo group (60.6%) by Week 24 post-transplant, primarily driven by significantly more placebo-arm patients initiating pre-emptive therapy.

Letermovir is well-tolerated in the target population. The most commonly-reported AEs, including GvHD, nausea and vomiting, occurred at a comparable frequency in both treatment arms and exemplify some of the morbidities typically experienced in this patient population. Notably, a numerically lower incidence of renal disorder AEs was seen in the letermovir group compared to the placebo group, although incidences of renal failure or impairment were comparable between study groups. The incidence of drug-related AEs and SAEs was also low overall and comparable between study groups.

The PN001 findings can be considered to have internal validity based on the nature of the randomised, double-blind trial design and the balance of the treatment arms at baseline. A quality assessment of PN001 according to the CRD criteria is reported in Appendix D.2.1. Although the subgroup analyses reported in Section B.2.7 and Appendix E demonstrated a consistent benefit of letermovir over placebo, the small sizes of some of the subgroups mean that results should be interpreted with caution.

The PN001 patient population can be considered broadly representative from a UK perspective. Despite the wide heterogeneity in local and international CMV management practices, the baseline characteristics, CMV risk factors, and indications for allogeneic HSCT are relevant to UK practice, and the reported clinical endpoints (particularly CMV viraemia, pre-emptive therapy initiation, GvHD and opportunistic infections) are aligned to the key post-transplant morbidities associated with this patient population. Reporting of the study outcomes using a variety of missing data approaches also allows for a clear assessment of the true treatment effect observed in PN001 in patients known to have taken study medication versus other approaches that require missing values to be considered as treatment failures.

Although PN001 may be considered to have strong external validity, it should be noted that only 12 patients from 2 UK centres were enrolled in the study, and only a small proportion of patients were receiving ATG or alemtuzumab at baseline for T-cell depletion; both these drugs are commonly used in the UK for this subpopulation. Additionally, the doses and sequences of pre-emptive therapy were not reported, which may have varied across countries.

The overall findings from PN001 demonstrate that letermovir is a novel and effective treatment option, and has the potential to address the significant and well-characterised clinical unmet need that remains in this patient population.

The demonstrated benefits of letermovir do not meet end-of-life criteria; therefore, a corresponding table has not been included with the submission.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

3.1.1 Identification of economic evaluation studies

A systematic literature review was conducted on 23rd October 2017, to identify relevant published cost-effectiveness studies for the prophylaxis and/or treatment of CMV infection. Given the limited information known about CMV, and the relatively unchanged treatment landscape, electronic database searches and additional hand-searches did not have a restricted time frame.

Of the 2,446 studies identified in the SLR, no cost-effectiveness studies assessing letermovir prophylaxis for CMV reactivation and disease were found that met the inclusion criteria.
Thus, a summary list of the included cost-effectiveness studies has not been compiled and a quality assessment was not possible; a de-novo model was therefore required to assess the cost-effectiveness of letermovir against current standard of care in UK clinical practice.

The SLR was conducted following the methodology and established international guideline for conducting systematic reviews published in 2009 by the CRD (University of York)[36], and further details have been reported in Appendix G.

B.3.2 Economic analysis

Due to the lack of previous technology appraisals for CMV, a de-novo cost-utility model was built to evaluate the clinical and economic value of letermovir in the prophylaxis of clinically-significant CMV infection under various scenarios. The model is based on good research practices recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [38] and guidance from NICE [39].

3.2.1 Patient population

The patient population considered in the economic evaluation reflects the licence for letermovir and aligns to the final NICE scope for this appraisal outlined in Table 1. Letermovir received marketing authorisation from the EMA on 8th January 2018 for the prophylaxis of clinically-significant CMV reactivation and disease in CMV R+ adults undergoing an allogeneic HSCT [40].

The main body of clinical evidence relating to letermovir and Standard of Care (SoC) was derived from PN001 [23], where the patients included reflect the marketing authorisation and population specified in the final NICE scope.

The baseline characteristics of patients included in the model are presented in Table 29 below.

Table 29: Baseline patient characteristics included in the model

Patient characteristic	Mean	Source
Age (years)	50.8	EPAR [24]
Weight (kg)	76.6	

3.2.2 Model structure

3.2.2.1 Type of analysis

In order to determine the cost-effectiveness of introducing letermovir into NHS clinical practice in England, a decision analytic model was used to evaluate the clinical progression of CMV infection and the related outcomes. The model was populated by clinical endpoints (measured at weeks 14, 24 and 48) from PN001 [23], and simulates CMV reactivation and the associated costs and health outcomes post-allogeneic HSCT. The primary outcome of interest for this economic evaluation is clinically-significant CMV infection, as defined by initiation of pre-emptive therapy based on documented CMV viraemia or CMV end-organ disease. [23]

3.2.2.2 Justification for the model structure and ability to capture the disease

The model was structured akin to a decision tree, populated by the clinical endpoints (14 weeks, 24 weeks and 48 weeks) from PN001. [23] As shown in Figure 7 and as aligned to the clinical pathway, adult CMV-seropositive allogeneic HSCT recipients enter the decision model and are treated with letermovir or SoC (placebo) at the blue decision node. Pre-emptive therapy based on documented CMV viraemia, CMV disease, re-hospitalisations, opportunistic infection and GvHD was accounted for using cumulative probabilities from the trial at each time point (i.e. all events up to that time point). Adverse events (AEs) were conditional on having confirmed CMV viraemia or CMV end-organ disease. Life-years and QALYs estimation used probabilities from successive time points to estimate outcomes using an area under the curve (AUC) approach.

Life expectancy, QALYs, and costs for a 5 year, 10 year, 20 year and lifetime analysis based on 24 week or 48 week outcomes were estimated to perform analyses over an appropriate time horizon to assess all important differences in costs and effects.

The base case analysis used a lifetime horizon based on 24 week trial data, the primary endpoint in the clinical trial, and the latest time point where data on pre-emptive therapy initiation and occurrence of CMV end-organ disease were available. Beyond this, only secondary and exploratory outcomes were followed up. A lifetime horizon is appropriate for the model given the potential mortality differences and differences in accrual of benefits and costs when using different treatment strategies against CMV reactivation.

In the lifetime analysis, costs and outcomes beyond one year were discounted at the annual discount rate of 3.5% per annum.[39]

3.2.2.3 Cycle length and half-cycle correction

The length of the decision tree is one year to capture the safety and efficacy outcomes associated with the introduction of letermovir. Long-term cost-effectiveness of prophylaxis extended the model from the end of the trial time period using estimates of life expectancy for those still alive at the end of the trial.

Life-years were estimated for survivors and non-survivors during the 14-week, 24-week or 48-week trial period. Life-years for non-survivors were estimated by applying Kaplan-Meier curves from PN001, providing points of actual death throughout the trial period. Overall-survival (OS) curves were not deemed appropriate to estimate OS as the conservative assumption is applied where there are no residual gains in mortality for the acute intervention. Appendix P displays the attenuation between the curves over time.

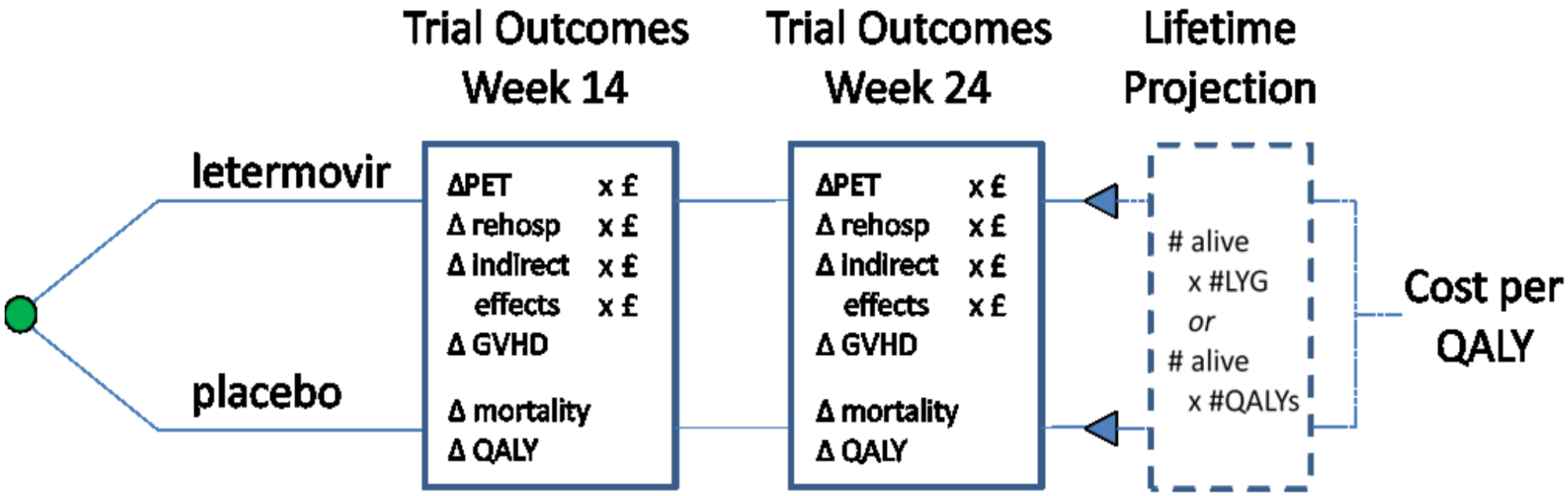
Life-years for survivors beyond the trial period were estimated by calculating the remaining life expectancy for these patients.

Patients who survive through the 24-week or 48-week trial period are assumed to survive to one year post-allogeneic HSCT. Life expectancy was estimated by applying a weighted average of the adjusted (age, sex, nationality, and ethnicity) annual relative risk of mortality [41], adjusted for the underlying indication, to the post-transplant life expectancies of the general population annual mortality rates from the 2014-2016 National Life Table England [42].

Excess risk of mortality data in Wingard et al. (2011) [41] was calculated from two years post-transplant to 15 years post-transplant. The model assumed that the relative risk of death at one year post-transplant is equal to the relative risk at two years post-transplant for each underlying disease. This assumption was also applied to the week 24 lifetime analysis to account for the remaining 28 weeks

of the first year of the analysis and is therefore likely to be conservative. The excess risk after 15 years post-allogeneic HSCT was assumed to remain static, and was calculated by taking the average of the excess risks from year 10 through to 15 for each underlying disease. Chronic myelogenous leukaemia (CML) and chronic lymphocytic leukaemia (CLL) data were not present in the Wingard et al. (2011) analysis. Therefore, the excess risk for the severe aplastic anaemia (SAA) disease group was used as a proxy. Myelofibrosis and plasma cell myeloma syndrome (PCM) were not presented in the Wingard et al (2011) analysis [41]; therefore the excess risk for the MDS group was used as a proxy.

Figure 7: Decision model structure



Abbreviations: CMV=cytomegalovirus; GvHD=graft-versus-host-disease; HSCT=haematopoietic stem cell transplant; LYG= life year gained; PET=pre-emptive therapy; QALY=quality-adjusted life year

3.2.3 Main features and justifications of the analysis

The main features of the de-novo analysis are displayed in Table 30.

Table 30: Features of the de-novo analysis

Factor	Previous appraisal	Current appraisal	Justification
	Chosen value	Chosen value	
Time horizon	N/A	Lifetime analysis based on week 24 outcomes.	This time horizon is sufficient to reflect the relevant cost and benefit differences between letermovir and SoC, as suggested by the NICE Decision Support Unit (DSU) [43].
Type of economic evaluation	N/A	Cost-utility analysis (CUA) with the direct health effects expressed in terms of QALYs.	This is the preferred form of economic evaluation recommended by the NICE reference case [39].
Treatment waning effect	N/A	N/A	To account for a treatment waning effect is not suitable for this technology appraisal or for against the reactivation of CMV post-allogeneic HSCT. Letermovir is taken for up-to 100 days post-transplant, as this is the duration that patients are most immuno-compromised.
Annual discount rate	N/A	3.5% for both health utilities and costs.	This is the annual discount rate recommended by the NICE reference case for costs and benefits [44].
Source of utilities	N/A	The sources of utilities were obtained from PN001 trial data [23] and were collected using FACT-BMT and the EQ-5D. Aligned to the NICE reference case, the utilities derived from the EQ-5D were applied in the model. The direct health effects for patients are expressed in terms of QALYs.	This is the perspective recommended by the NICE reference case when characterising and comparing potential health benefits between treatments.[39]

Factor	Previous appraisal	Current appraisal	Justification
	Chosen value	Chosen value	
Source of costs	N/A	Costs have been sourced from the NHS reference costs [44] and the PSSRU [45]. Costs have been applied using the perspective of NHS England And the Personal Social Services (PSS).	This is the perspective recommended for analysis by the NICE reference case.[39] Please note that the costs to the NHS were included, but PSS costs have not been considered due to the unavailability of data to incorporate this into the model.

CMV=cytomegalovirus; CUA=cost-utility analysis; DSU=decision support unit; FACT-BMT=Functional Assessment of Cancer Therapy – Bone Marrow Transplant; HSCT=haematopoietic stem cell transplant; N/A=not-applicable; NHS=National Health Service; NICE=national institute of health and care excellence; PSS=personal social services; PSSRU=personal social services research unit; QALY=quality-adjusted life years; SoC=standard of care

3.2.4 Intervention technology and comparators.

3.2.4.1 Alignment to the marketing authorisation

The cost-effectiveness model compared the use of letermovir prophylaxis against SoC (no treatment). The intervention of interest, letermovir, has been assessed as part of this submission and is to be considered for the prophylaxis of CMV reactivation and disease in patients who have undergone an allogeneic HSCT [1].

Letermovir was implemented into the model as the licensed dose of 480 mg (adjusted to 240 mg if given concomitantly with CsA), administered daily either as an oral tablet or an IV infusion.

MSD are proposing a simple rebate scheme for the indication considered within this submission, equating to a [redacted] on the list price of letermovir. The NHS acquisition costs (excl. VAT) at PAS prices for each formulation are as follows

The letermovir cost breakdown is displayed in Table 31 below.

Table 31: Letermovir cost breakdown

Letermovir	Oral		IV infusion	
	240mg (concomitant CsA)	480mg	240mg (concomitant CsA)	480mg
List price	[redacted]	[redacted]	[redacted]	[redacted]

Letermovir	Oral		IV infusion	
	240mg (concomitant CsA)	480mg	240mg (concomitant CsA)	480mg
PAS price	[redacted]	[redacted]	[redacted]	[redacted]

CsA=ciclosporin A; IV=intravenous; PAS=patient access scheme

The licence establishes that letermovir should be started no later than 28 days post-allogeneic HSCT and should be administered for up to 100 days post-transplant.

The SoC arm of the model closely resembles a pre-emptive strategy, where patients initiate antivirals based on CMV viraemia levels or onset of CMV disease [22]. This was deemed to be a pragmatic approach that would allow comparisons of letermovir with a strategy similar to initiation of antivirals for pre-emptive therapy based on documented CMV viraemia. The antiviral agents ganciclovir, valganciclovir and foscarnet are currently used in English clinical practice as pre-emptive therapy. Currently there are no routine treatment options for the prophylaxis of CMV reactivation.

In contrast to the final scope, aciclovir and valaciclovir are not considered relevant comparators due to their lack of comparative evidence, meaning no meta-analysis could be formed (please see Section 2.8). Aciclovir and valaciclovir do not have marketing authorisation in the indication addressed in this submission. In addition, they are regarded as unsuitable use in clinical practice for CMV prophylaxis due to dose related toxicities. Finally, aciclovir and valaciclovir were equally utilised in both study arms of PN001 for the prophylaxis of HSV as detailed in Table 1.

Twice-weekly CMV viral load monitoring has been applied to both the letermovir and SoC arms of the model. Outcomes related to the initiation of pre-emptive therapy were included through modelling cost inputs related to real-world clinical practice in England.

3.2.4.2 Continuation rules

The EMA marketing authorisation for letermovir does not mandate any futility rules [1], and there is no clinical evidence to support its use beyond 100 days.

B.3.3 Clinical parameters and variables

3.3.1 Clinical data use in the model

PN001[23] served as the primary data source for the economic model and was the basis for treatment decisions and outcomes in the model. As shown in Table 32, the model includes probabilities of the initiation of pre-emptive therapy for CMV infection, CMV disease, and the subsequent outcomes that may occur after the development of clinically-significant CMV infection based on natural progression. The probabilities of events occurring were obtained from the week 24 and week 48 CSRs [29, 31]. All probabilities were assumed to be cumulative up to the specified time point.

3.3.1.1 Outcome measures collected

The trial primary endpoint for clinically-significant CMV infection as determined by pre-emptive therapy initiation or CMV disease at week 24 was collected, and the probability of these events were obtained from Table 11-3 of the week 24 CSR [29].
The probabilities of initiation of pre-emptive therapy based on clinically-significant CMV infection and CMV disease at week 48 were assumed to be equal to the probabilities at week 24, as these data points were collected until the primary endpoint of the study period (week 24) and not the extended period (week 48).

The probabilities of CMV-related re-hospitalisation at weeks 14, 24, and 48 were obtained from Table 14.2-23 of the week 48 CSR [31] based on the proportion of patients in the FAS that were re-hospitalised for CMV infection or CMV disease up through weeks 14, 24, and 48 post-allogeneic HSCT. These estimates are based on the number of patients who were re-hospitalised but were not adjusted for censoring and as such may be a slight underestimate. These also do not capture any CMV-related increased length of stay during the initial hospitalisation for allogeneic HSCT.

The probabilities for opportunistic infections and GvHD were obtained in the same way. The probabilities of opportunistic infection at week 14, 24 and 48 were obtained from Table 14.2-24 of the week 48 CSR as the percentage of patients with opportunistic infections up through the time period post-transplant. The probabilities of GvHD were obtained from Table 14.2-26 of the week 48 CSR [31].

For all-cause mortality data, K-M estimators at each time point (weeks 14, 24, and 48) in the FAS were used to reflect the mortality of the at-risk population and allow survival over time to be more accurately reflected in the model for area-under the curve (AUC) calculation of life-years and QALYs [31].

The primary data used in the model is the data point of week 24 from PN001. Week 24 data was used to inform the lifetime horizon of the model as the primary endpoint of clinically significant CMV infection was captured up until this time (Section 2.3.2). Scenario analysis has been conducted where the week 48 data is used to inform the lifetime horizon. Using this data set, an assumption is applied where the probability of clinically significant CMV infection, or CMV end-organ disease occurring is equal to the probability seen at week 24.

As discussed in Section 2.4.2.3, the primary approach for censoring in the trial was based on a NC=F approach. For initiation of pre-emptive therapy due to CMV viraemia or CMV end-organ disease, the secondary approach for missing data, the DAO approach in the FAS population at weeks 14 and 24 was used to reflect the likely cumulative proportion of patients up to each time point that experience events and to most accurately reflect the likely magnitude of healthcare resource use required. With this approach, any subject with a missing value for a particular endpoint was excluded from the analysis and data was assumed to be missing at random. At 24 weeks, a large proportion of censoring was due to deaths (32 in the letermovir arm (9.8%), 27 in the placebo arm (14.4%)). Discontinuation constituted a relatively comparable proportion in each arm (patient withdrawal: 6.2% and 8.2%; physician decision: 2.4% and 2.6%, in the letermovir and placebo arms respectively) (Please see Appendix M). Scenario analysis of the base case was conducted using data based on a NC=F approach for pre-emptive therapy initiation.

The clinical outcome probabilities used in the model are presented in Table 32 below.

Table 32: Clinical outcome probabilities used in the model

Clinical outcome	24 weeks		48 weeks		Reference
	Letermovir	Standard of care	Letermovir	Standard of care	
Initiation of pre-emptive therapy due to CMV infection	[redacted]	[redacted]	[redacted]	[redacted]	Table 11-3/11-6 week 24 CSR
CMV disease	[redacted]	[redacted]	[redacted]	[redacted]	Table 11-3/11-6 week 24 CSR
CMV-related re-hospitalisation	[redacted]	[redacted]	[redacted]	[redacted]	Table 14.2-23 week 48 CSR
Pre-emptive therapy-related AEs	[redacted]	[redacted]	[redacted]	[redacted]	Table 14.2-24 week 48 CSR
GvHD	[redacted]	[redacted]	[redacted]	[redacted]	Table 14.2-26 week 48 CSR
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]	Figure 11-1 week 48 CSR

AEs=adverse events; CMV=cytomegalovirus; GvHD=graft-versus-host-disease

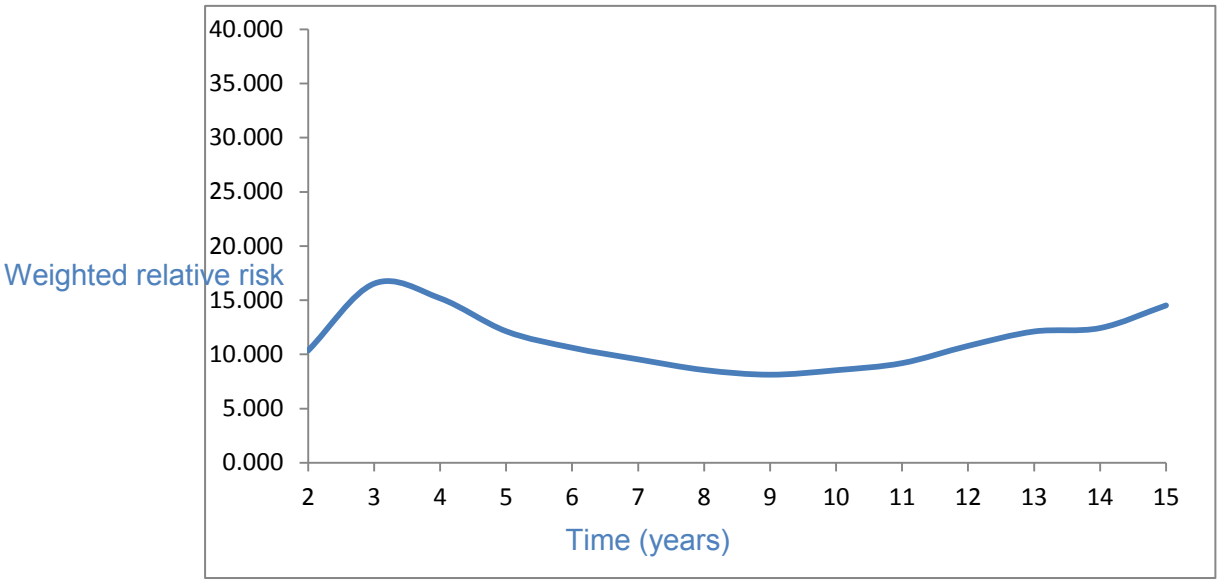
According to the NHS England Clinical Commissioning Policy on the treatment options available for GvHD[46], patients who have undergone an allogeneic HSCT are predisposed to GvHD [46]. Acute GvHD (aGvHD) is expected to start in the first 100 days post-allogeneic HSCT when a patient's immune system is compromised, and chronic GvHD (cGvHD) is expected to start at any time beyond the first 100 days [46]. After one year post-allogeneic HSCT the risk of contracting cGvHD is 30% [46], therefore the model assumes the risk of cGvHD occurring remains constant at 30% beyond the period of the trial.

A pre-defined exploratory endpoint included in the economic model was the difference in all-cause mortality seen between the letermovir arm of the trial and the SoC arm at weeks 24 and 48 post-allogeneic HSCT. All-cause mortality included subjects who died for any reason throughout the duration of the study.
The population of interest for all-cause mortality was the FAS population, where the K-M curve was plotted by treatment-group, with a p-value for the between group difference (please refer to Section 2.6.5 for greater detail).

Beyond the end of the trial (24 or 48-week observed mortality) survival was extrapolated to the full time horizon of the model (i.e. lifetime) using relative risks obtained from Wingard et al (2011)[41] applied to general population probability of mortality. This approach assumes no further survival or life-year gains from letermovir beyond the trial follow-up, as the same long-term mortality probabilities are applied to both arms. The difference in survival across model arms thus attenuates over the lifetime horizon of the model (Appendix P). To calculate relative risks of mortality patients in the ASaT population were stratified by primary condition for the allogeneic HSCT (acute lymphocytic leukaemia (ALL); AML; CLL, etc.), based on the percentages in the clinical trial. From year two post-allogeneic HSCT, the standardised mortality ratio (SMR) for the underlying primary reason for transplant, as calculated in Wingard et al (2011) [41], was applied. For the underlying conditions that Wingard et al (2011) [41] did not report, assumptions were made: for CML, CLL and Other the SMR was assumed equal to the SMR of SAA, and the rate of mortality for myelofibrosis and plasma cell myeloma (PCM) were assumed equal to the SMR for MDS. 'Other' accounted for less than 2 percent of the underlying indications for allogeneic HSCT.

The progression over time of the calculated weighted relative mortality risk by underlying cause for allogeneic HSCT is presented in Figure 8 below.

Figure 8: Relative risk of mortality as projected through the model



It was assumed that the excess risk of mortality at two years was equal to one year.

Using the percentages calculated with respect to the underlying conditions, a weighted average of the SMRs was applied to the National Life Table for England [42], and were used to obtain the age and sex dependent probabilities of mortality. The excess risk of mortality calculated using Wingard et al (2011) [41] was applied to the survivors in either arm of the model to estimate the mortality rate of patients beyond the end of the trial. After 15 years it was assumed the excess risk of mortality post-allogeneic HSCT stabilised, and remained a constant rate for the remainder of the model.

Further details on the all–cause mortality reported in PN001, is included in Section 2.6.5 of the submission.

Several post-hoc analyses were conducted to explore the mortality benefit associated with the introduction of letermovir and observed at the primary endpoint. Please see Supplementary Material 12 [30] for the post-study mortality analysis requested by the FDA, with full details also reported in Section 2.6.5.

3.3.2 Inputs validated with clinical experts

Given the lack of published UK data available in this specific treatment setting, clinical expertise was sought to provide guidance on UK clinical practice and validate individual parameters. MSD consulted with numerous experts [12, 22, 47] who were selected based on one or more of the following criteria:

- Author of British guideline on management of CMV in allogeneic stem cell transplant
- Investigator(s) in PN001
- Clinical experts in the highly specialised allogeneic transplant centres

The following inputs were validated with English clinical experts as no sources could be found in the published literature:

- The proportion of patients administered oral versus IV letermovir;
- The proportion of patients treated with CsA as an immunosuppressant;
- The proportion of ganciclovir, valganciclovir, and foscarnet used as pre-emptive therapy;
- The expected average treatment duration of pre-emptive therapy to be 21 days;
- The treatment setting for ganciclovir
- The treatment setting for GvHD

3.3.2.1 Declaration of potential conflicts of interest from experts

- Professor Antonio Pagliuca received funding from the manufacturer for research, advisory board participation, and conference travel.
- Professor Karl Peggs received funding from the manufacturer for advisory board participation.

B.3.4 Measurement and valuation of health effects

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

3.4.1.1 Method of elicitation and valuation

Health-related quality of life (HRQoL) was evaluated in PN001 [23] using the EuroQoL EQ-5D-3L approach, and the FACT-BMT. Aligned to NICE's preferred measure of HRQoL, utilities derived from the EQ-5D scores collected in PN001 were used in the cost-effectiveness modelling. This consisted of five general health questions and a visual analogue scale [31] and was collected at each significant time point within the trial. The trial was not powered to detect statistically significant differences in QoL scores between the treatment arms. All HRQoL analyses conducted for the purpose of this submission were derived from PN001, with the estimated utilities used in the cost-effectiveness analysis. Evaluation of HRQoL using EQ-5D directly from patients is consistent with the NICE reference case.[39]

3.4.1.2 Point in time when measurements were made

In PN001, the EQ-5D questionnaire was administered at the time points of weeks 0, 14, and 24, during the primary study period,[23, 30] and at the conclusion of the follow-up period (week 48) to estimate the treatment-specific utility weights. HRQoL was measured if early discontinuation or infection occurred. A mean of the utilities collected at each time point, based on the UK EQ-5D index, was used to estimate the time point specific utility measure. The change from baseline mean at each time point was applied to provide the utilities for the letermovir and the placebo arms in the model.

3.4.1.3 Appropriateness for cost-effective analysis

Baseline utilities for the letermovir [redacted] and placebo arm [redacted] were combined with the number of patients in each arm to create a weighted average (0.649) that is conservatively applied to both arms at baseline. Baseline utility is combined with the change from baseline seen at each time point, to estimate time point utility weights. The treatment-specific change from baseline values at each time point represent the mean change in EQ-5D Index experienced by patients.

3.4.1.4 Results with confidence intervals

The utilities included in the model and ICER calculations are reported in Table 33 below, with the standard deviation.

Table 33: Utilities as reported in the CSR versus the model

	As reported in the CSR [Mean (SD)]		As reported in the model [Mean (SD)]	
	Letermovir	SoC	Letermovir	SoC
N	325	170	N/A	N/A
EQ-5D index at baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change at Week 14	[redacted]	[redacted]	[redacted]	[redacted]
Change at week 24	[redacted]	[redacted]	[redacted]	[redacted]
Change at week 48	[redacted]	[redacted]	[redacted]	[redacted]

EQ-5D=EuroQol-5 Dimension; N/A=not-applicable; SoC=standard of care

3.4.2 Mapping

Mapping was not applicable as the HRQoL scores applied in the model were derived directly from results of the EQ-5D taken from PN001. Additionally FACT-BMT was collected to measure utilities. As no difference was seen in either arm, and FACT-BMT is not the preferred tool for utility measurement, the results have not been applied to the model.

3.4.3 Health-related Quality of life studies

In line with the NICE guide to the methods of technology appraisal [39], an SLR was conducted to identify any relevant studies reporting utility values for CMV-infection post allogeneic HSCT.

Due to the limited scope of information for the treatment of CMV, none of the retrieved studies examined HRQoL as an outcome. However, a number of studies were identified as having potentially useful information despite not meeting the inclusion criteria for the systematic review. Full details of the SLR and the potentially relevant identified studies can be found in Appendix H.

3.4.4 Adverse events

The impact of AEs on HRQoL was investigated by exploring the recent technology appraisals for ALL and AML[48, 49]. No studies were found relating to the disutility of the post-allogeneic HSCT CMV associated AEs.

As utilities in PN001 were collected at time points irrespective of whether patients had experienced AEs, it is assumed that the utilities estimated based on EQ-5D data already reflect the disutility related to adverse events occurring within this study. To avoid double-counting, no further disutilities have been applied within the cost-effectiveness model.

The most commonly seen haematological adverse events in allogeneic-HSCT patients are neutropaenia, thrombocytopaenia, and leukopaenia, which all are components of myelosuppression, and are seen to be associated with the initiation of pre-emptive therapy. The incidence of these AEs has been derived from the week 24 CSR and is reported in Table 34 below.

Table 34 : Myelosuppression adverse events

Myelosuppression AE	Incidence		Reference
	Letermovir	Standard of Care	
Neutropaenia	[redacted]	[redacted]	Week 24 CSR Table 12-8 (MSD, 2017a)
Thrombocytopaenia	[redacted]	[redacted]	
Leukopaenia	[redacted]	[redacted]	

AE=adverse event

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

3.4.5.1 Health related quality of life for the different health states

In PN001, once a patient had documented CMV viraemia he or she was excluded from the analysis as having met the primary end point [23]. HRQoL data were not collected after this point, and the presumed utility decrement from experiencing the CMV infection is not applied to the effected patients in the model.

The utility estimates included in the base case scenario are taken from the CSR and were collected and reported at four main time-points of treatment: day 1, week 14, week 24 and week 48. EQ-5D analyses based on the PN001 data show that patients in the standard of care arm had a lower HRQoL than patients in the letermovir arm.

3.4.5.2 Baseline utility

The model used EQ-5D utility inputs based on the time point in the trial for each comparator, to adjust life-years based on patient health-related quality of life. The baseline utility at each time point was assumed to be the weighted average EQ-5D index at baseline for letermovir and placebo from PN001.

A baseline utility value of [redacted] is calculated by collating the mean at time point, with the proportion in each arm of the trial, as seen in Table 35 below.

Table 35 EQ-5D index at baseline

	Number of patients	Baseline EQ-5D index mean (SD)
Letermovir	325	[redacted]
Standard of care	170	[redacted]
EQ-5D=EuroQol-5 Dimension; SD=standard deviation		

3.4.5.3 Utility adjustment from base case

The weighted baseline utility is conservatively applied to both arms of the model, with the change at each time point providing the change in utility gain for either arm. Treatment-specific change from baseline values at each time point represent the mean change in EQ-5D index from PN001.

The utility inputs used in the model, and the corresponding time points of interest are listed in Table 36 and Table 37, below.

Table 36: Utility inputs

Time point	Baseline utility	Change from baseline		Reference
		Letermovir (SD)	Standard of care (SD)	
Week 14	[redacted]	[redacted]	[redacted]	Table 11-12 Week 48 CSR PN001 [31]
Week 24				
Week 48				
SD=standard deviation				

The utility is seen to increase with time, throughout the various time points of the trial, until the first year of the analysis (week 48).

Beyond the first year of the analysis, the model estimates life years by applying the adjusted life expectancy for survivors to the patients who are alive. A post-trial utility using the lowest

value of either 0.82 from an AML population who underwent a HSCT (Leunis et al., 2014) [50], or the age-specific general population utility (Ara et al., 2011) [51], was applied to estimate the QALYs beyond year one for survivors. Age-specific utility values are shown in Table 38.

Table 37: Utility time point weights

Time point	Letermovir	Standard of care	Reference
Week 14	[redacted]	[redacted]	MSD week 48 CSR [31]
Week 24	[redacted]	[redacted]	MSD week 48 CSR [31]
Week 48	[redacted]	[redacted]	MSD week 48 CSR [31]
Post-trial utility	0.82	0.82	Leunis et al. 2014 [50]

Table 38: General (UK) population utility values

Age	Utility value EQ-5D (95% CI)	Reference
60 to ≤ 65	0.8072 (0.793,0.821)	Ara et al., (2011) [51]
65 to ≤ 70	0.8041 (0.790, 0.817)	
70 to ≤ 75	0.7790 (0.766,0.791)	
75 to ≤ 80	0.7533 (0.739,0.767)	
80 to ≤ 85	0.6985 (0.677,0.719)	
> 85	0.65497 (0.624,0.675)	
CI=confidence interval; EQ-5D=EuroQol-5 Dimension		

The annual age-related utility decrement applied in the model is based on the age-specific UK general population utility norms presented by Ara et al (2011), [51] which reported the average utility values used in the model from the age range of 60-65 to > 85 years. It is assumed that the utility values for > 85 apply to all patients who are aged over 85 years, and no further age-related decrement was applied. This means that patients aged 85 years and above had the same age-related utility decrement in the model.

A scenario analysis was conducted to specifically account for the loss in quality of life from contracting GvHD after the end of the PN001. This disutility may be reflected to an extent in the long-term estimate acquired from the post-HSCT AML population utility source, [50] as a proportion would be expected to be suffering from symptoms of cGvHD but the data was not reported. SF-36 QoL data from a study by Pidala et al (2011) [52] was converted into EQ-5D disutility using an algorithm by Ara and Brazier (2008). [51] The disutility (0.09) was applied in year 1 and 2 after the trial period for 30% of survivors.

3.4.5.4 Clinical expert validation

An English clinical expert assessed the applicability of utility values estimated from the trial and deemed them to be reasonable [22].

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

3.5.1 Parameters used in the cost-effectiveness analysis

A summary of the variables used in the cost-effectiveness estimation is presented in Table 39.

Table 39: Summary of the variables used in the cost-effectiveness analyses

Variable	Parameter		Reference	Rationale
Time horizon	Life time based on week 24 data		NICE reference case [39]	The time horizon is sufficiently long to reflect the costs and benefits that may be accrued through the introduction of letermovir
Mean age	50.8 years		Table 10-6 Week 24 CSR (MSD, 2017a)	N/A
Mean weight	76.6 kg		Table 10-6 Week 24 CSR (MSD, 2017a)	N/A
Discount rate	3.5%		NICE reference case	The preferred discounting after year one applied to both health outcomes and costs
Week 14 outcomes				
	Letermovir	SoC		
Initiation of pre-emptive therapy based on documented CMV viraemia	[redacted]	[redacted]	Table 11-6 (MSD, 2017a).	N/A
CMV end-organ disease	[redacted]	[redacted]	Table 11-6 (MSD, 2017a).	N/A
CMV-related re-hospitalisation	[redacted]	[redacted]	Table 14.2-23 (MSD, 2017b).	N/A
Opportunistic infections	[redacted]	[redacted]	Table 14.2-24 (MSD, 2017b).	N/A
GvHD	[redacted]	[redacted]	Table 14.2-26 (MSD, 2017b).	N/A
All-cause mortality	[redacted]	[redacted]	Figure 11-5 (MSD, 2017a)	N/A
Week 24 outcomes				
	Letermovir	SoC		
Initiation of pre-emptive therapy based on	[redacted]	[redacted]	Table 11-3 (MSD, 2017a).	N/A

Variable	Parameter		Reference	Rationale
documented CMV viraemia				
CMV end-organ disease	[redacted]	[redacted]	Table 11-3 (MSD, 2017a).	N/A
CMV-related re-hospitalisation	[redacted]	[redacted]	Table 14.2-23 (MSD, 2017b).	N/A
Opportunistic infections	[redacted]	[redacted]	Table 14.2-24 (MSD, 2017b).	N/A
GvHD	[redacted]	[redacted]	Table 14.2-26 (MSD, 2017b).	N/A
All-cause mortality	[redacted]	[redacted]	Figure 11-1 (MSD, 2017b).	N/A
Week 48 outcomes				
	Letermovir	SoC		
Initiation of pre-emptive therapy based on documented CMV viraemia	[redacted]	[redacted]	Assumed equal to 24-week outcome.	N/A
CMV end-organ disease	[redacted]	[redacted]	Assumed equal to 24-week outcome.	N/A
CMV-related re-hospitalisation	[redacted]	[redacted]	Table 14.2-23 (MSD, 2017b).	N/A
Opportunistic infections	[redacted]	[redacted]	Table 14.2-24 (MSD, 2017b).	N/A
GvHD	[redacted]	[redacted]	Table 14.2-26 (MSD, 2017b).	N/A
All-cause mortality	[redacted]	[redacted]	Figure 11-1 (MSD, 2017b).	N/A
Treatment costs				
Daily cost of letermovir	[redacted]		Calculation	Calculated based on the pricing assumptions in Section 3.5.4.1.
Total cost of pre-emptive therapy	£11,077		Calculation	Calculated based on the pricing assumptions for pre-emptive therapy reported in Section 3.5.4.2

Variable	Parameter	Reference	Rationale
CMV disease cost	£11,077	Calculation	Assumption based on BSH guidelines
Opportunistic infection			
% of patients with FUO	63.7%	Kruger et al. (1999) [53]	
% of patients with pneumonia	18.7%	Kruger et al. (1999)	
% of patients with septicaemia	17.6%	Kruger et al. (1999)	
FUO cost	£1,020	NHS Reference Costs 2015/16 (WJ07A-D Weighted Average of Elective & Non-elective & Day Case & Regular Day/Night Admissions) [44]	
Pneumonia cost	£1,905	NHS Reference Costs 2015/16 (DZ11K-V Weighted Average of Elective & Non-elective & Day Case & Regular Day/Night Admissions)	
Septicaemia cost	£2,164	NHS Reference Costs 2015/16 (WJ06A-J Weighted Average of Elective & Non-elective & Day Case & Regular Day/Night Admissions)	
Total cost of opportunistic infection	£1,387		
Rehospitalisation			
Average extra days re-hospitalisation due to pre-emptive therapy	13.9 days	Jain et al. (2014) [15]	Validated with English clinicians

Variable	Parameter	Reference	Rationale
Inpatient excess bed day cost	£305.72	NHS Reference Costs 2015/16 (EL_XS and NEL_XS Weighted Average of Elective & Non-elective Inpatients Excess Bed Days Unit Cost)	
CMV-related re-hospitalisation cost	£4,250	Calculated	
GvHD			
aGVHD cost	£9,548	BNF (methylprednisolone); Dignan et al. (2012a) [54]	IV methylprednisolone (£2.52 for a 76.6kg patient at 2mg/kg), administered daily for 40 days.
% of patients who develop cGvHD	30%	NHS England Clinical Commissioning Policy: Treatments for GvHD following HSCT [46]	Although the commissioning policy gives a range between 30% – 40%, on the understanding that there may be some double counting of cGvHD occurring, the 30% figure was applied to the model.
Annual cost to treat once year survivors (cGvHD cost)	£12,983	BNF (methylprednisolone); Dignan et al. (2012b) [55]	1mg/kg administered in the first year on alternate days, 0.5mg/kg administered in the second year on alternate days. This figure is multiplied by percent of patients expected to develop cGvHD (30%).
Pre-emptive therapy related adverse events			
Neutropaenia rate	[redacted]	Table 14.3-2 (MSD, 2017b)	The pre-emptive therapy related AEs are applied to both arms of the model via a weighted average; neutropaenia (5.1% and 5.7%); thrombocytopaenia (8.0% and 7.3%); leukopaenia (3.8% and 4.2%) for the letermovir and SoC arms of the trial.
Thrombocytopaenia rate	[redacted]	Table 14.3-2 (MSD, 2017b)	
Leukopaenia rate	[redacted]	Table 14.3-2 (MSD, 2017b)	

Variable	Parameter		Reference	Rationale
Neutropaenia cost	£1,142.90		NHS Reference Costs 2015/16 (Weighted average SA08G-SA08J)	N/A
Thrombocytopaenia cost	£636.19		NHS Reference Costs 2015/16 (Weighted average SA12G – SA12K)	N/A
Leukopaenia cost	£1,142.90		NHS Reference Costs 2015/16 (Weighted average SA08G-SA08J)	N/A
Utility				
	Letermovir	SoC		
Week 14	[redacted]	[redacted]	Table 11-12 Week 48 CSR (MSD, 2017b)	N/A
Week 24	[redacted]	[redacted]	Table 11-12 Week 48 CSR (MSD, 2017b)	N/A
Week 48	[redacted]	[redacted]	Table 11-12 Week 48 CSR (MSD, 2017b)	N/A
Post-trial utility	0.820		Leunis et al. (2014)	Post-trial utility using the lowest value from either the post-trial utility of an AML population who underwent a HSCT (Leunis et al., 2014) or the age-specific general population utility (Ara et al., 2011).
General population 60 to ≤ 65 years	0.807		Ara et al. (2011)	
General population 65 to ≤ 70 years	0.804		Ara et al. (2011)	
General population 70 to ≤ 75 years	0.779		Ara et al. (2011)	
General population 75 to ≤ 80 years	0.753		Ara et al. (2011)	
General population 80 to ≤ 85 years	0.699		Ara et al. (2011)	
General population > 85 years	0.650		Ara et al. (2011)	

aGvHD=acute graft-versus-host-disease; cGVHD=chronic graft-versus-host-disease; CMV=cytomegalovirus; FUO=fever of unknown origin; GvHD=graft-versus-host-disease; SoC=standard of care

Full details of the SLR conducted for the identification of relevant cost and healthcare resource use data, used to populate the cost-effectiveness model can be found in Appendix I.

3.5.2 Resource identification, measurement and valuation

The model includes inputs related to the costs of prophylaxis treatment (letermovir), pre-emptive therapy, CMV disease monitoring, and treatment for clinical outcomes. Where possible, England-specific data were sought, either on components of resource use (e.g. length of treatment, dosing) or unit costs. In particular, 2015/16 NHS Reference Costs [44] were used for hospital stay related costs, and the British National Formulary [56] informed the unit cost of medicines. Costs are expressed in 2017 prices or 2015/16 prices and where necessary were inflated using published indices [45].

There are no NHS reference costs or payment-by-results (PbR) tariffs specific for costing letermovir. Details about the cost estimation of treatment with letermovir in terms of acquisition and administration are reported below.

5.5.3 Input from clinical experts

The administration and costing method applicable to letermovir and the pre-emptive therapy options has been validated with clinical experts as seen in Section The trial primary endpoint for clinically-significant CMV infection as determined by pre-emptive therapy initiation or CMV disease at week 24 was collected, and the probability of these events were obtained from Table 11-3 of the week 24 CSR [29].

The probabilities of initiation of pre-emptive therapy based on clinically-significant CMV infection and CMV disease at week 48 were assumed to be equal to the probabilities at week 24, as these data points were collected until the primary endpoint of the study period (week 24) and not the extended period (week 48).

The probabilities of CMV-related re-hospitalisation at weeks 14, 24, and 48 were obtained from Table 14.2-23 of the week 48 CSR [31] based on the proportion of patients in the FAS that were re-hospitalised for CMV infection or CMV disease up through weeks 14, 24, and 48 post-allogeneic HSCT. These estimates are based on the number of patients who were re-hospitalised but were not adjusted for censoring and as such may be a slight underestimate. These also do not capture any CMV-related increased length of stay during the initial hospitalisation for allogeneic HSCT.

The probabilities for opportunistic infections and GvHD were obtained in the same way. The probabilities of opportunistic infection at week 14, 24 and 48 were obtained from Table 14.2-24 of the week 48 CSR as the percentage of patients with opportunistic infections up through the time period post-transplant. The probabilities of GvHD were obtained from Table 14.2-26 of the week 48 CSR [31].

For all-cause mortality data, K-M estimators at each time point (weeks 14, 24, and 48) in the FAS were used to reflect the mortality of the at-risk population and allow survival over time to be more accurately reflected in the model for area-under the curve (AUC) calculation of life-years and QALYs [31].

The primary data used in the model is the data point of week 24 from PN001. Week 24 data was used to inform the lifetime horizon of the model as the primary endpoint of clinically significant CMV infection was captured up until this time (Section 2.3.2). Scenario analysis has been conducted where the week 48 data is used to inform the lifetime horizon. Using this data set, an assumption is applied where the probability of clinically significant CMV infection, or CMV end-organ disease occurring is equal to the probability seen at week 24.

As discussed in Section 2.4.2.3, the primary approach for censoring in the trial was based on a NC=F approach. For initiation of pre-emptive therapy due to CMV viraemia or CMV end-organ disease, the secondary approach for missing data, the DAO approach in the FAS population at weeks 14 and 24 was used to reflect the likely cumulative proportion of patients up to each time point that experience events and to most accurately reflect the likely magnitude of healthcare resource use required. With this approach, any subject with a missing value for a particular endpoint was excluded from the analysis and data was assumed to be missing at random. At 24 weeks, a large proportion of censoring was due to deaths (32 in the letermovir arm (9.8%), 27 in the placebo arm (14.4%)). Discontinuation constituted a relatively comparable proportion in each arm (patient withdrawal: 6.2% and 8.2%; physician decision: 2.4% and 2.6%, in the letermovir and placebo arms respectively) (Please see Appendix M). Scenario analysis of the base case was conducted using data based on a NC=F approach for pre-emptive therapy initiation.

The clinical outcome probabilities used in the model are presented in Table 32 below.

Table 32: Clinical outcome probabilities used in the model

Clinical outcome	24 weeks		48 weeks		Reference
	Letermovir	Standard of care	Letermovir	Standard of care	
Initiation of pre-emptive therapy due to CMV infection	[redacted]	[redacted]	[redacted]	[redacted]	Table 11-3/11-6 week 24 CSR
CMV disease	[redacted]	[redacted]	[redacted]	[redacted]	Table 11-3/11-6 week 24 CSR
CMV-related re-hospitalisation	[redacted]	[redacted]	[redacted]	[redacted]	Table 14.2-23 week 48 CSR
Pre-emptive therapy-related AEs	[redacted]	[redacted]	[redacted]	[redacted]	Table 14.2-24 week 48 CSR
GvHD	[redacted]	[redacted]	[redacted]	[redacted]	Table 14.2-26 week 48 CSR
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]	Figure 11-1 week 48 CSR

AEs=adverse events; CMV=cytomegalovirus; GvHD=graft-versus-host-disease

According to the NHS England Clinical Commissioning Policy on the treatment options available for GvHD[46], patients who have undergone an allogeneic HSCT are predisposed to GvHD [46]. Acute GvHD (aGvHD) is expected to start in the first 100 days post-allogeneic HSCT when a patient's immune system is compromised, and chronic GvHD (cGvHD) is expected to start at any time beyond the first 100 days [46]. After one year post-allogeneic HSCT the risk of contracting cGvHD is 30% [46], therefore the model assumes the risk of cGvHD occurring remains constant at 30% beyond the period of the trial.

A pre-defined exploratory endpoint included in the economic model was the difference in all-cause mortality seen between the letermovir arm of the trial and the SoC arm at weeks 24 and 48 post-allogeneic HSCT. All-cause mortality included subjects who died for any reason throughout the duration of the study.
The population of interest for all-cause mortality was the FAS population, where the K-M curve was plotted by treatment-group, with a p-value for the between group difference (please refer to Section 2.6.5 for greater detail).

Beyond the end of the trial (24 or 48-week observed mortality) survival was extrapolated to the full time horizon of the model (i.e. lifetime) using relative risks obtained from Wingard et al (2011)[41] applied to general population probability of mortality. This approach assumes no further survival or life-year gains from letermovir beyond the trial follow-up, as the same long-term mortality probabilities are applied to both arms. The difference in survival across model arms thus attenuates over the lifetime horizon of the model (Appendix P). To calculate relative risks of mortality patients in the ASaT population were stratified by primary condition for the allogeneic HSCT (acute lymphocytic leukaemia (ALL); AML; CLL, etc.), based on the percentages in the clinical trial. From year two post-allogeneic HSCT, the standardised mortality ratio (SMR) for the underlying primary reason for transplant, as calculated in Wingard et al (2011) [41], was applied. For the underlying conditions that Wingard et al (2011) [41] did not report, assumptions were made: for CML, CLL and Other the SMR was assumed equal to the SMR of SAA, and the rate of mortality for myelofibrosis and plasma cell myeloma (PCM) were assumed equal to the SMR for MDS. 'Other' accounted for less than 2 percent of the underlying indications for allogeneic HSCT.

The progression over time of the calculated weighted relative mortality risk by underlying cause for allogeneic HSCT is presented in Figure 8 below.

Figure 8: Relative risk of mortality as projected through the model

It was assumed that the excess risk of mortality at two years was equal to one year.

Using the percentages calculated with respect to the underlying conditions, a weighted average of the SMRs was applied to the National Life Table for England [42], and were used to obtain the age and sex dependent probabilities of mortality. The excess risk of mortality calculated using Wingard et al (2011) [41] was applied to the survivors in either arm of the model to estimate the mortality rate of patients beyond the end of the trial. After 15 years it was assumed the excess risk of mortality post-allogeneic HSCT stabilised, and remained a constant rate for the remainder of the model.

Further details on the all–cause mortality reported in PN001, is included in Section 2.6.5 of the submission.

Several post-hoc analyses were conducted to explore the mortality benefit associated with the introduction of letermovir and observed at the primary endpoint. Please see Supplementary Material 12 [30] for the post-study mortality analysis requested by the FDA, with full details also reported in Section 2.6.5.

3.3.2 Inputs validated with clinical experts.

3.5.4 Intervention and comparators' costs and resource use

The drug acquisition costs per treatment are presented below, with the unit costs for the unlicensed treatment options sourced from the British National Formulary and quantified in their licensed indications. If the drug costs are not reported in the BNF, they have been sourced from the literature and inflated using the PSSRU inflation index [45].

3.5.4.1 Letermovir

The prophylaxis cost inputs include the letermovir cost per day and the letermovir treatment length in days. To calculate the total cost per day for the use of letermovir as prophylaxis of CMV infection, the costs have been adjusted based on assumptions of letermovir length of treatment, the use of IV or oral formulations, and the proportion of patients expected to be on concomitant CsA. The letermovir price per day used in the model was [redacted] based on

weighted oral and IV therapy. Both the list price calculation and PAS price calculation is tabulated below (Table 40).

Data from PN001 was used to inform the mean duration of letermovir therapy experienced by patients. From PN001, the mean duration was for patients using oral and IV letermovir was 69.4 days, with the mean being anchored to the start of treatment. [29]

A small proportion of patients who cannot initially tolerate oral administration are administered letermovir intravenously for a temporary period [redacted]. Letermovir will be available in both oral and IV formulations, with the latter preparation available for patients with gastrointestinal complications that may compromise swallowing and absorption of the oral formulation. The two formulations are interchangeable at the discretion of the initiating physician, and no dose-adjustment is required; this allows for greater flexibility of use in patients that may be transitioning between inpatient and outpatient settings. An assumption of oral (95%) and intravenous infusion (5%) letermovir use was used in the cost-effectiveness model, based on the administration route observed in the UK trial population (100% PO; MSD, Data on file (25)) and after discussing with UK clinical experts the likely mode of administration seen in clinical practice.

The mean duration of letermovir IV treatment has been informed by the population in PN001 (Table 12-1, week 24 CSR), [29] where after [redacted] days on IV treatment, patients who were initiated on IV letermovir, were switched to oral letermovir. As there were no IV formulations administered in the UK cohort, scenario analysis has been conducted to reflect varying lengths of IV use seen in clinical practice.

Based on personal correspondence with an English clinician, [22] few patients are expected to be treated with tacrolimus, and instead are treated with concomitant CsA. Based on this insight into English clinical practice, whilst 100% of the UK cohort in PN001 was on the 240 mg dosing regimen, a conservative assumption of 95% of patients on concomitant CsA was applied in the analyses. This is further supported by an internal report using EBMT data, which displayed high levels of CsA use for the prevention of GvHD.[57] To mitigate the uncertainty, sensitivity analysis has been conducted to understand the influence on the ICER of increasing and decreasing the proportion of patients concomitantly using CsA by 25% of the base case.

Patients were treated for up to 100 days post-allogeneic HSCT with adjustments made for those that discontinued from the study. To explore this a sensitivity analysis was conducted to enable analysis of lengthening the treatment duration of letermovir to 100 days.

Based on the assumptions above for the combined IV and oral therapy price, and average duration of treatment, a letermovir price per day was calculated as seen below (Table 40, Table 41and Table 42). The letermovir price per day was multiplied by the treatment length to estimate the total cost of prophylaxis for patients in the model.

Table 40: List price and PAS price of oral and IV letermovir

Prophylaxis cost component	NHS list price	Discounted price	Reference
Letermovir 240mg (Oral) unit cost	[redacted]	[redacted]	MSD
Letermovir 480mg (Oral) unit cost	[redacted]	[redacted]	MSD
Letermovir 240mg (IV) unit cost	[redacted]	[redacted]	MSD
Letermovir 480mg (IV) unit cost	[redacted]	[redacted]	MSD
Discount	[redacted]		MSD

IV=intravenous; NHS=National Health Service

Table 41: Letermovir cost per day PAS applied

Prophylaxis Cost	Unit cost per day at PAS price	Letermovir cost per day	Reference
Letermovir 240 mg (Oral)	[redacted]	[redacted]	N/A
Letermovir 480 mg (Oral)	[redacted]		N/A
Letermovir 240 mg (IV)	[redacted]	[redacted]	N/A
Letermovir 480 mg (IV)	[redacted]		N/A
IV administration cost	£236.19		NHS Reference costs 15/16 (SB12Z – Day Case & Outpatient & other – weighted average) [44]
% of patients on CsA[i]	95%		Assumption based on clinical practice in England
CsA=ciclosporin A; IV=intravenous; N/A=not-applicable; NHS=National Health Service; PAS=patient access scheme			

i those patients who are on CsA have a dose adjustment of letermovir to 240 mg

The cost of administration for the IV infusion formulation at £236.19 [44] has been taken from a weighted average of NHS reference costs code SB12Z for Day Case & Outpatient & Other [44] and is applied to both IV infusion forms of letermovir and pre-emptive therapy.

Table 42: Letermovir weighted cost per day, based on proportion of oral and intravenous administration

Letermovir Cost component	Proportion of administration (%)	Mean Duration Therapy	Letermovir cost per day	Source
Percent of patients on letermovir oral therapy	95%		-	Assumption based on clinical practice in England
Percent of patients on letermovir IV therapy	5%		-	
Letermovir (PO) cost		69.4 days	[redacted]	Mean duration of letermovir therapy– Table 12-1 Week 24 CSR
Letermovir (IV)		[redacted]	[redacted]	Mean duration of letermovir therapy– Table 12-1 Week 24 CSR
Letermovir (IV) continues (PO) 240 mg		[redacted]	[redacted]	NA
Weighted IV cost per day			[redacted]	NA
Weighted letermovir cost per day		69.4 days	[redacted]	NA
IV=intravenous; PO=per oral				

3.5.4.2 Pre-emptive therapy costs

If a patient develops clinically-significant CMV infection, all patients are treated with pre-emptive therapy following the detection of CMV viraemia or clinically-significant CMV infection. The model assumes the use of three pre-emptive therapy CMV antivirals (ganciclovir, valganciclovir and foscarnet) based on PN001 and English clinical practice. [12, 22, 47] Cidofovir used as a pre-emptive therapy in PN001 has been excluded from the analysis due to the lack of use in English clinical practice, the similarity to outcomes seen with other pre-emptive therapy agents, and its use as a rescue after the failure of other pre-emptive therapy options. Cidofovir also had its European marketing authorisation withdrawn in 2014 [19] and any current use is likely to be in rare circumstances. It was not possible to conduct a scenario analysis including the use of cidofovir because no list price from the BNF was available.

Inpatient and outpatient costs per day are applied to the respective treatment and length of exposure, and a weighted average is calculated based on proportions seen in English clinical practice, and a total pre-emptive therapy cost is estimated. After speaking with an English clinical expert[22], it was noted that foscarnet is used primarily in the inpatient setting, while valganciclovir and ganciclovir are used primarily in the outpatient setting.

From discussions with clinical experts[12, 22], it was ascertained that pre-emptive therapy would be initiated based on CMV viraemia levels for two weeks induction dose and then continued as appropriate or with additional maintenance treatment until two satisfactory PCR tests are received. In the model, it has been conservatively assumed that patients remain on pre-emptive therapy for 21 days based on clinical feedback. This is in contrast to PN001, where pre-emptive therapy was maintained for a mean of 59.3 days (Table 11-29, (MSD, 2017a)). Results were comparable across both arms with the letermovir arm displaying pre-emptive therapy duration of 60.4 days for patients who received pre-emptive therapy and the SoC arm reporting pre-emptive therapy duration of 58.5 days.

The inpatient cost per day is assumed to be the NHS indicative price of foscarnet 60 mg/kg every 8 hours [58] from British National Formulary Online (2017) based on a patient weight of 76.6 kg [29]. A weighted average of day case, outpatient and other drug administration costs (SB12Z - £236.19) are applied to a weighted average of elective and non-elective excess bed days (£305.72) to account for hospital stay, obtained from the NHS Reference Costs 2015/16 [44].

The outpatient pre-emptive therapy cost per day was assumed to be a weighted average of the NHS indicative price of ganciclovir 5 mg/kg daily administered every 12 hours [59] based on a patient weight of 76.6 kg [29], and NHS indicative price of valganciclovir 900mg per day (Valcyte PI, 2017) [60] from British National Formulary Online (2017).

Using PN001 the summary of antiviral use for pre-emptive therapy was estimated to be 39.2% ganciclovir, 10.8% foscarnet, and 51.7% valganciclovir (Table 11-29; [29]), where it should be noted that the total use of pre-emptive therapy exceeds 100% due to a minority of patients receiving a combination of pre-emptive therapy. However, based on discussions with English clinical experts [47] the likely proportion of use seen in clinical practice is 37.5% ganciclovir; 37.5% valganciclovir, and 25% foscarnet. Length of treatment for inpatient and outpatient

treatment were estimated by applying the percentage of use to the mean duration of treatment of 21 days, concordant with clinical practice in England as confirmed by clinical opinion.

The pre-emptive therapy costing and assumptions are presented in Table 43, Table 44 and Table 45 below.

Table 43: Pre-emptive therapy therapies

Pre-emptive therapy therapies	Dosing	Source	Market share (MSD, CSR week 24 Table 11-29) [29]
Valganciclovir	900 mg twice daily for 21 days (induction)	eMC SmPC Valcyte (valganciclovir) [61]	37.5%
Ganciclovir	5 mg/kg infusion once every 12 hours (twice daily)	eMC SmPC Cymevene (ganciclovir) [62]	37.5%
Foscarnet	60 mg/kg infusion once every 8 hours (thrice daily)	eMC SmPC Foscavir (foscarnet) [63]	25%
Mean pre-emptive therapy duration	21 days	Assumption based on correspondence with an English clinical expert [12, 22]	

eMC=electronic Medicines Compendium; SmPC=Summary of Product Characteristics

Table 44: Pre-emptive therapy cost per day break down

Pre-emptive therapy	Dose (mg)	Cost	Reference
Ganciclovir acquisition cost per day	5 (IV) twice daily	£45.60*	BNF [59]
Foscarnet acquisition cost per day	60 (IV) thrice daily	£275.42*	BNF [58]
Valganciclovir acquisition cost per day	900 (PO) once daily	£28.84	BNF [60]
Drug administration cost (IV) per day	-	£236.19	NHS Reference costs 15/16 [44]
Foscarnet administration cost per day	-	£708.75	NA
Inpatient bed cost per day	-	£305.72	NHS Reference costs 15/16
Pre-emptive therapy inpatient cost per day	-	£1,289.71	NA
Pre-emptive therapy outpatient cost per day	-	£273.41	NA

IV=intravenous; PO=per oral

*Based on patient weight of 76.6 kg obtained from PN001 week 24 CSR [29]

Table 45: Pre-emptive therapy Model inputs

Input	Value	Source
Pre-emptive therapy inpatient cost per day	£1,289.71	NHS indicative price and dosing of foscarnet from the British National Formulary Online (2017) [26,27] and percentage use and weight estimates from the letermovir clinical trial (20). Drug administration cost (£236.19) and excess bed day cost (£305.72) from NHS Reference Costs 2015/16 [21] were also included.
Pre-emptive therapy inpatient length (days)	5.25 days	Estimated by applying the percentage use of inpatient pre-emptive therapy (foscarnet) to the mean pre-emptive therapy duration from the letermovir clinical trial [20]
Pre-emptive therapy outpatient cost per day	£273.41	NHS indicative price and dosing of outpatient pre-emptive therapy (valganciclovir and ganciclovir) from the British National Formulary Online (2017) [28] and percentage use and weight estimates from the letermovir clinical trial (20). Drug administration cost (£236.19) from NHS Reference Costs 2015/16 [21] were also included.
Pre-emptive therapy outpatient length (days)	15.75 days	Estimated by applying the percentage use of outpatient pre-emptive therapy (valganciclovir and ganciclovir) to the mean pre-emptive therapy duration from the letermovir clinical trial [20].
Pre-emptive therapy total	£11,077	

3.5.5 Health state unit costs and resource use

The model applies costs to the possible complications that can occur from the onset of clinically-significant CMV infection. These included CMV disease, CMV-related re-hospitalisation, opportunistic infection and the costs associated with GvHD, and were applied to the patients that experienced the respective outcomes.

3.5.5.1 CMV end-organ disease

The cost of CMV end-organ disease was assumed to be equal to the total cost of pre-emptive therapy based on both inpatient and outpatient treatments and durations, as per the British guidelines on CMV management [20]. This is likely to be an underestimate of the true costs associated with CMV disease, as it is expected that patients are treated with more intensive medicines, such as IV immunoglobulin and IV pre-emptive therapy monotherapy [20]. With intensive pre-emptive therapy there are toxicities that may occur such as renal damage [15] and cytopaenia, which require further treatment and hospitalisation. These outcomes and associated costs were not applied in the model. However, given the relatively low occurrence

of events these costs constitute a small proportion of total expected costs, and this assumption is conservative in estimating cost-effectiveness.

3.5.5.2 CMV-related re-hospitalisation

CMV-related hospitalisation costs were estimated using the average additional days in hospital associated with pre-emptive therapy of 13.9 days [15] and multiplied by the cost of an additional bed day (£305.72), obtained from Jain et al (2014) [15] and the NHS Reference costs 2015/15 excess bed day cost respectively. The average cost of an excess bed day in NHS reference costs 2015/16 [44] represents a proxy for the additional costs, but does not include specific treatments or procedures relating to CMV. Hence this may be an underestimate of the true cost, and be conservative in estimating the cost-effectiveness of letermovir.

3.5.5.3 Opportunistic infections

The cost of opportunistic infections was estimated using the percentage of allogeneic patients who had the most common three opportunistic infections, obtained from the study by Kruger et al (1999) [53]. NHS Reference Costs 2015/16 for fever of unknown origin (FUO), pneumonia and septicaemia were applied to generate a weighted cost [44].

The incidence and costs of opportunistic infections were applied to both arms of the model which is a conservative assumption as CMV reactivation and a compromised immune system predispose patients to opportunistic infections.

3.5.5.4 Graft-versus-host-disease

Estimates of the cost of graft-versus-host disease were based on first line treatment of advanced grade (III-IV) acute GvHD. This included drug acquisition and administration cost of methylprednisolone 2 mg/kg per day (IV) taken from BNF and NHS Reference Costs 2015/16 [44, 54], assuming a treatment duration of 40 days inferred from UK guidelines [64].

Costs of chronic GvHD (cGvHD) (onset 100 days after transplant) were based on a proportion of patients receiving 2 years of immunosuppressive agent treatment. A proportion of these cGvHD costs are likely to be already reflected in week 24 trial data and hence are likely to be conservative due to higher survival rates for letermovir. UK estimates suggest 30% of HSCT recipients will develop cGvHD, with guidelines indicating average treatment duration of 2-3 years and first line systemic steroid dosing involves tapering over the course of treatment [46, 55]. In the model the dose in year one was assumed to be 1mg/kg on alternate days and in year two 0.5mg/kg on alternate days, as informed by British guidelines on the diagnosis and

management of GvHD [55, 64]. The cost of methylprednisolone per day is assumed at £1.26, based on a patient weighing 76.6kg, as taken from PN001. Appropriate BNF costs and NHS reference costs of administration were applied and an annual cost of £12,983 was applied for survivors beyond the trial follow-up.

The costs associated with the clinical outcomes are presented below in Table 46.

Table 46: Costs associated with clinical outcomes

Health states	Items	Value	Reference in submission
CMV disease	Valganciclovir	£227.12	Section 3.5.4.2
	Ganciclovir	£359.11	Section 3.5.4.2
	Foscarnet	£1,445.96	Section 3.5.4.2
	Staff	N/A	N/A
	Hospital costs – ganciclovir administration cost	£3,719.99	Section 3.5.4.2
	Hospital costs – foscarnet administration cost	£3,719.99	Section 3.5.4.2
	Excess bed day cost	£1,605.03	Section 3.5.4.2
	Total	£11,077	N/A

Health states	Items	Value	Reference in submission
CMV related re-hospitalisation	Average extra days in hospital due to pre-emptive therapy	13.9 days	Jain et al (2014) [15]
	Inpatient excess bed cost per day	£305.72	NHS Reference Costs 2015/16 [44]
	Total	£4,250	N/A
Opportunistic infections	Percentage of patients with FUO	63.7%	Kruger et al. (1999) [30]
	Percentage of patients with pneumonia	18.7%	Kruger et al. (1999) [30]
	Percentage of patients with septicaemia	17.6%	Kruger et al. (1999) [30]
	Cost of FUO	£1,020	NHS Reference Costs 2015/16 [21] (WJ07A-D Elective & Non-elective & Day Case & Regular Day/Night Admissions - Weighted Average)
	Cost of pneumonia	£1,905	NHS Reference Costs 2015/16 [21] (DZ11K-V Elective & Non-elective & Day Case & Regular Day/Night Admissions - Weighted Average)
	Cost of septicaemia	£2,164	NHS Reference Costs 2015/16 [21] (WJ06A-J Elective & Non-elective & Day Case & Regular Day/Night Admissions - Weighted Average)
	Total	£1,387	N/A
GvHD	Methylprednisolone dose (mg/kg)	2 mg/kg (IV) once daily	Dignan et. al (2012) [32]
	Methylprednisolone cost per day	£2.52	BNF [22]

Health states	Items	Value	Reference in submission
	Administration cost per day	£236.19	NHS Reference Costs 2015/16 [21] (SB12Z – Day Case & Outpatient & Other - Weighted Average)
	Methylprednisolone mean duration of therapy	40 days	Dignan et. al (2012) [32]
	Total	£9,548	N/A
cGvHD (1-year survivors)	Methylprednisolone dose (mg/kg) 1st year	1 mg/kg (IV) alternate days	Dignan et. al (2012) [64]
	Methylprednisolone dose (mg/kg) 2nd year	0.5 mg/kg (IV) alternate days	
	Methylprednisolone cost per day - 1st year	£1.26	BNF [22]
	Methylprednisolone cost per day - 2nd year	£0.63	
	IV drug administration cost (per day)	£236.19	NHS Reference Costs 2015/16, as above [21]
	Percent of survivors developing cGvHD	30%	NHS England (2017) [33]
	Total	£12,983	NA

3.5.6 Adverse reaction unit costs and resource use

Neutropaenia, thrombocytopaenia, and leukopaenia are components of myelosuppression and have been included in the model as the most commonly occurring pre-emptive therapy-related AEs. As shown in Table 47 below, the model considers the incidence of these events for patients who receive pre-emptive therapy and applies the costs of treating these events. The default incidence rates for these inputs were assumed to average across the arms in the trial, a conservative assumption given that differential rates are likely to be observed in each arm. The cost values were obtained from the NHS Reference Costs 2015/16 [44] and are presented in Table 47.

Table 47: Adverse events

Adverse event	Event rate (%)	Reference	Cost	Reference
Neutropaenia	[redacted]	Table 14.3-2 CSR (19)	£1,142.90	NHS Reference cost 15/16* [21]
Thrombocytopaenia	[redacted]	Table 14.3-2 CSR (19)	£636.19	NHS Reference cost 15/16† [21]
Leukopaenia	[redacted]	Table 14.3-2 CSR (19)	£1,142.90	NHS Reference cost 15/16* [21]

*Obtained from the NHS Reference Costs 2015/16 (SA12G-SA12K weighted average)
† Obtained from the NHS Reference Costs 2015/16 (Elective & Non-elective & Day Case & Regular Day/Night Admissions – weighted average)

3.5.7 Miscellaneous unit costs and resource use

To accurately represent CMV viraemia monitoring, the model assumes that patients in both treatment arms were regularly observed for the development of CMV disease. Based on clinical practice in England [22], monitoring occurs twice-weekly for patients in both arms. The default CMV disease monitoring cost was £32.62, the cost of a PCR test, and was obtained from the NHS Nottingham University Hospital [65]. Monitoring costs were included in the model conditional on survival, whereby morality half-way through the period based on linear increases was used to estimate the average proportion of patients in each arm being monitored.

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

Summary of base-case analysis inputs

3.6.1 Variables used in the cost-effectiveness analysis

The cost-effectiveness analysis was run using base-case values as described in Sections 3.1 to 3.5 over a lifetime horizon. As per the primary endpoint of PN001, the 24-week outcomes were used in the base case to estimate the outcomes and costs over the trial period. Trial data from follow-up at 48-weeks was used as a scenario analysis. Additional scenario analyses were run using 5, 10 and 20 year time horizons using both the week 24 and week 48 outcomes.

The primary outcome measure for the economic evaluation was the incremental cost per QALY gained from letermovir compared to SoC.

Deterministic and probabilistic sensitivity analysis methods were employed to investigate the robustness of results. Values, ranges and distribution used are presented in Appendix N and Appendix O.

A full list of the variables applied in the economic model is presented in Table 39, Section 3.5.1.

3.6.2 Base case

A list of the values used in the base case of the economic analysis can be found in Table 48 and an overview of the assumptions included can be found in Table 49.

Table 48: Base case inputs

Variable	Value		Source/Rationale
Key variables			
Time horizon	Life time based on 24 weeks		NICE Reference Case
Model length	One year		N/A
Discount rate	3.5% per annum		NICE Reference case
Age (years)	50.8		MSD, 2017a
Weight	76.6kg		MSD, 2017a
Clinical inputs			
Week 14			
	Letermovir	SoC	
Initiation of pre-emptive therapy based on documented viraemia	[redacted]	[redacted]	Table 11-6 (MSD, 2017a)
CMV end-organ disease	[redacted]	[redacted]	Table 11-6 (MSD, 2017a)
CMV-related re-hospitalisation			Table 14.2-23 (MSD, 2017b)
Opportunistic infection			Table 14.2-24 (MSD, 2017b)
GvHD			Table 14.2-26 (MSD, 2017b)
All-cause mortality			Figure 11-5 (MSD, 2017a)
Week 24			
Initiation of pre-emptive therapy based on documented viraemia	[redacted]	[redacted]	Table 11-3 (MSD, 2017a)
CMV end-organ disease	[redacted]	[redacted]	Table 11-3 (MSD, 2017a)
CMV-related re-hospitalisation			Table 14.2-23 (MSD, 2017b)
Opportunistic infection			Table 14.2-24 (MSD, 2017b)
GvHD			Table 14.2-26 (MSD, 2017b)
All-cause mortality			Figure 11-1 (MSD, 2017b)
Week 48			
Initiation of pre-emptive therapy based on documented viraemia	[redacted]	[redacted]	Assumed equal to 24-week outcome
CMV end-organ disease	[redacted]	[redacted]	Assumed equal to 24-week outcome
CMV-related re-hospitalisation			Table 14.2-23 (MSD, 2017b)
Opportunistic infection			Table 14.2-24 (MSD, 2017b)

Variable	Value		Source/Rationale
GvHD	[redacted]	[redacted]	Table 14.2-26 (MSD, 2017b)
All-cause mortality	[redacted]	[redacted]	Figure 11-1 (MSD, 2017b)
Cost inputs			
Letermovir cost per day	[redacted]		Reflects proportion of patients receiving oral and intravenous preparations, and 240 mg or 480 mg dose of letermovir
CMV viraemia monitoring cost	£32.62		Cost of PCR Test. NHS Nottingham University Hospitals [65]
Pre-emptive therapy cost per day	£11,077		Calculated based on inpatient and outpatient use
CMV disease cost	£11,077		Assumed to be equal to the total cost of pre-emptive therapy (inpatient plus outpatient)
CMV-related re-hospitalisation	£4,250		Extra days: Jain et al. (2014); Unit cost: NHS Reference Costs 2015/16 (Elective & Non-elective weighted average)
Total opportunistic infection cost	£1,387		Calculated
GvHD	£9,548		Calculated
chronic GvHD	£12,983		Calculated
Adverse events			
Rates			
Neutropaenia	[redacted]		Calculated rate from table 14.3-3 of week 24 CSR
Thrombocytopaenia	[redacted]		Calculated rate from table 14.3-3 of week 24 CSR
Leukopaenia	[redacted]		Calculated rate from table 14.3-3 of week 24 CSR
Costs			
Neutropaenia	£1,142.90		NHS Reference Costs 2015/16 (Weighted average SA08G-SA08J)
Thrombocytopaenia	£636.19		NHS Reference Costs 2015/16 (Elective & Non-elective & Day Case & Regular Day/Night Admissions weighted average)
Leukopaenia	£1,142.90		NHS Reference Costs 2015/16 (Weighted average SA08G-SA08J)
Utilities			
Baseline	[redacted]		Baseline utilities are assumed to be the weighted average EQ-5D index at baseline for letermovir and placebo
Letermovir		Placebo	
Letermovir week 14	[redacted]	[redacted]	Change from baseline at each time point from the treatment-specific mean change in EQ-5D index (MSD, 2017b) [31]

Variable	Value		Source/Rationale
Letermovir week 24	[redacted]	[redacted]	Change from baseline at each time point from the treatment-specific mean change in EQ-5D index (MSD, 2017b)
Letermovir week 48	[redacted]	[redacted]	Change from baseline at each time point from the treatment-specific mean change in EQ-5D index (MSD, 2017b)
Post-trial utility	0.82		Leunis et al (2014) [50]
General UK population utility			
60 to ≤ 65 years	0.807		Ara et al. (2011) [51]
65 to ≤ 70 years	0.804		
70 to ≤ 75 years	0.779		
75 to ≤ 80 years	0.753		
80 to ≤ 85 years	0.699		
> 85 years	0.650		
CMV=cytomegalovirus; CSR=clinical study report; GvHD=graft-versus-host-disease			

3.6.3 Assumptions

Due to the limited published material available regarding the treatment of CMV, assumptions were made based on English clinical expertise. The assumptions used to inform the cost-effectiveness analysis are presented in Table 49 below.

Table 49: Assumptions used in the cost-effectiveness model

Assumption used	Trial reported	Rationale
95% concomitant CsA use	51.9% concomitant CsA use	The most frequently used immunosuppressant in the UK is CsA whereas the trial reported a high proportion of tacrolimus use. The value used in the cost-effectiveness analysis has been validated with clinical experts.
95% of patients initiate with oral letermovir	73% initiate with oral letermovir	Based on UK clinical practice validated by multiple experts, it is expected that only a maximum of 5% of patients will be administered with IV. Additionally, none of the 6 UK patients allocated to the letermovir arm in PN001 received the IV formulation.
Average duration of pre-emptive therapy was 21 days	Average duration of pre-emptive therapy was 59 days	After validation with clinicians, it was understood that on average clinicians administer pre-emptive therapy treatments for the induction period (2 weeks) and then the weeks thereafter until two negative PCR tests were attained.
Two PCR tests per week applied to both arms of the model	N/A	Clinical opinion was sought regarding frequency of PCR testing for CMV disease in clinical practice
37.5% ganciclovir 37.5% valganciclovir 25% foscarnet	39.17% ganciclovir 51.6% valganciclovir 10.83% foscarnet	English clinical advice was sought for the prescribing pattern commonly seen for the different pre-emptive therapy options. PN001 figures from Table 11-29 week 24 CSR.

Assumption used	Trial reported	Rationale
CMV disease equal to the total cost of pre-emptive therapy	N/A	Due to the lack of published information regarding the costs of CMV disease, it was assumed that, aligned to the BSH guidelines, all patients developing CMV disease would be treated with pre-emptive therapy.
The relative risk of mortality at two years from Wingard et al (2011) is equal to the relative risk at one year.	N/A	Due to the dearth of published information regarding the mortality of post-transplant patients at one year, it has been assumed that the relative risk at one and two years is equal.
Relative risk of mortality for CML, CLL and other assumed equal to SAA. Relative risk of mortality for myelofibrosis and PCM assumed equal to MDS.	N/A	Due to the limited published information regarding the relative risks of mortality post-transplant and the similar characteristics between the unreported underlying diseases.
Opportunistic infections treated in the outpatient setting	N/A	Due to the limited published information on opportunistic infections it has been conservatively assumed that patients will either be treated as outpatients, or will be treated as inpatients due to other complications.
Methylprednisolone IV administration for GvHD takes place in the outpatient setting	N/A	Based on clinical expertise, IV or oral methylprednisolone is normally treated in an outpatient setting; if patients receive IV methylprednisolone as an inpatient, it is because they are already either in the hospital or will be admitted due to the severity of illness.
Post-trial utility of 0.82 (Leunis et al (2014)) or the general population utility, whichever is lower	N/A	An assumption was made that the utility expected for survivors beyond one year of a transplant would not exceed that of the general population of the same age.

B.3.7 Base-case results

Results of the base-case analysis are presented below in **Error! Reference source not found.**Section 3.7.1 Base-case incremental cost-effectiveness analysis results, with the probabilistic sensitivity analysis (PSA) results and one and two-way sensitivity analyses presented in Section 3.8.1 and Section 3.8.2. Exploratory analysis considering alternative time horizons is presented in Section 3.8.3. Disaggregated base-case results for costs and outcomes are presented in Appendix J.

3.7.1 Base-case incremental cost-effectiveness analysis results

The base-case cost-effectiveness results are deterministic model outputs based on the model inputs and are presented per patient over a lifetime horizon based on 24-week cost and outcomes data. The base case incremental results are presented, both including and excluding the PAS. The corresponding incremental cost-effectiveness ratio (ICER) when letermovir is compared to SoC is £10,904.

The base-case model results are presented in tabular form with disaggregated expected costs and expected outcomes presented in Appendix J.

Table 50: Base case results (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	£28,805	7.91	6.73	-	-	-	-
Letermovir	£33,891	8.43	7.19	£5,014	0.52	0.46	£10,904

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

B.3.8 Sensitivity analyses

3.8.1 Probabilistic sensitivity analysis

The PSA input distributions and parameters are shown in Appendix N, and were informed by measures of precision computed from PN001 data, where possible, or based on large standard errors (10% of mean). Appropriate distributions were used for costs (Gamma: long tail and positive skew), probabilities and utilities (Beta: bound by 0 and 1). In the absence of information on the likely characteristics of a distribution, a normal distribution was utilised.

The results of 10,000 iterations of the PSA are summarised in tabular format (Table 51), and in graphical format in a cost-effectiveness scatter plot and a cost-effectiveness acceptability curve (CEAC) calculated from the net monetary benefit statistic across a range of willingness-to-pay (WTP) thresholds for each treatment option within each scenario (Figure 10). The treatment with the greatest monetary net benefit at each specific WTP threshold is considered the most cost-effective option.

As shown in the PSA results (Table 51), the ICER for the introduction of letermovir is £10,913, which is comparable to the ICER obtained in the base-case £10,904. Letermovir has a higher net monetary benefit than SoC and this statistic is higher for letermovir compared with SoC in 89.49% and 81.92% of the iterations at a WTP threshold of £30,000 and £20,000 per QALY respectively.

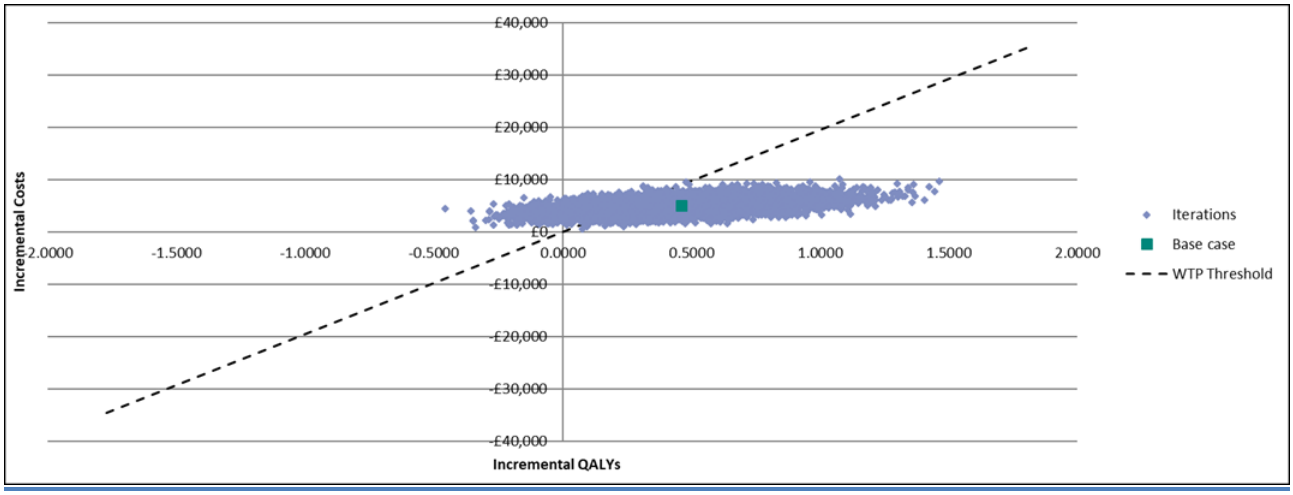
The scatter plot (Figure 9) shows that the majority of the ICERs from iterations comparing letermovir with standard of care fall below the willingness-to-pay threshold of £20,000 per QALY gained and the cost-effectiveness acceptability curve (Figure 10) shows that the probability of letermovir being cost-effective compared with standard of care increases as the WTP threshold increases.

Table 51: Probabilistic sensitivity analysis (PSA) results

Outcome	Letermovir	Standard of care
Total cost		
Mean	£33,826	£28,790
Standard deviation	£945	£847
QALYs		
Mean	7.19	6.72
Standard deviation	0.17	0.24
ICER for letermovir vs SoC	£10,913	
Net monetary benefit £20,000	£109,885	£105,691
Net monetary benefit £30,000	£181,740	£172,932
P (cost-effectiveness) £20,000	81.92%	18.08%
P (cost-effectiveness) £30,000	89.49%	10.51%

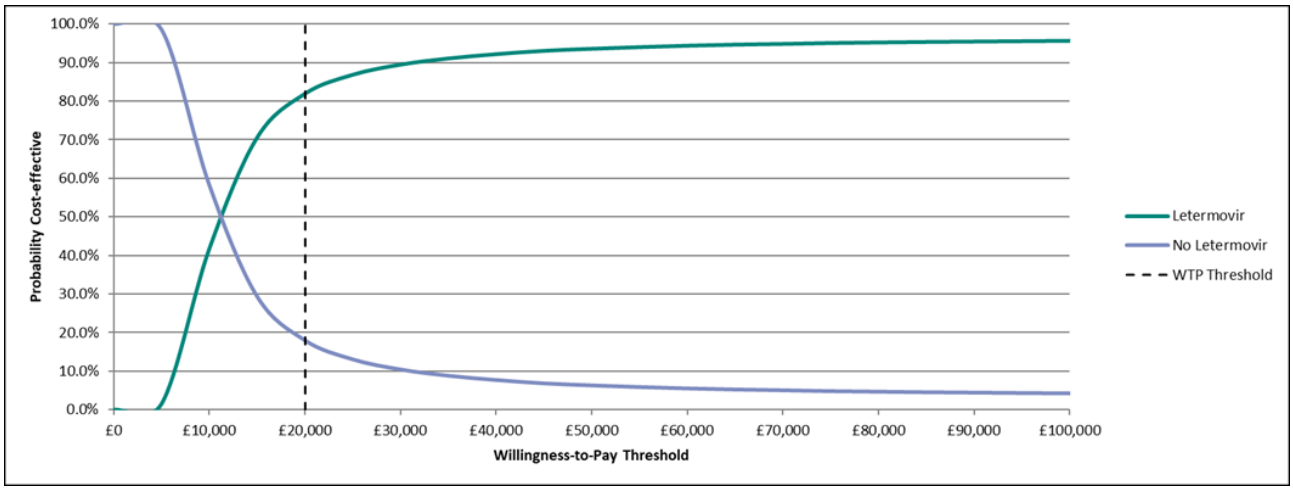
QALY=quality-adjusted life year; P=probability; ICER=incremental cost-effectiveness ratio; SoC=standard of care

Figure 9 : Cost-effectiveness plane: 10,000 iterations from PSA at a WTP threshold of £20,000



QALYs=quality-adjusted life year; WTP=willingness-to-pay

Figure 10: Cost-effectiveness acceptability curve (CEAC)



WTP=willingness-to-pay

3.8.2 Deterministic sensitivity analysis

In addition to the PSA, model inputs were varied in a one-way sensitivity analysis to determine the influence various factors had over the ICER. The one-way sensitivity analysis inputs and bounds are shown in Appendix O. Ranges were inferred from a 95% confidence interval, interquartile ranges or the minimum and maximum value observed in the trial to give absolute extremes (age). In the absence of information, large arbitrary ranges +/- 25% were used to investigate sensitivity.

Results of the one-way sensitivity analysis are summarised in a tornado diagram (**Error! Reference source not found.**) and the ICER and cost-effectiveness quadrant detail for each input are shown in

Table 52**Error! Reference source not found.**. These are presented with the PAS for letermovir. The sensitivity analysis inputs and bounds are shown in the appendices.

The one-way sensitivity analysis results show that the base-case model results (in terms of the ICER) are most sensitive to the age parameter.

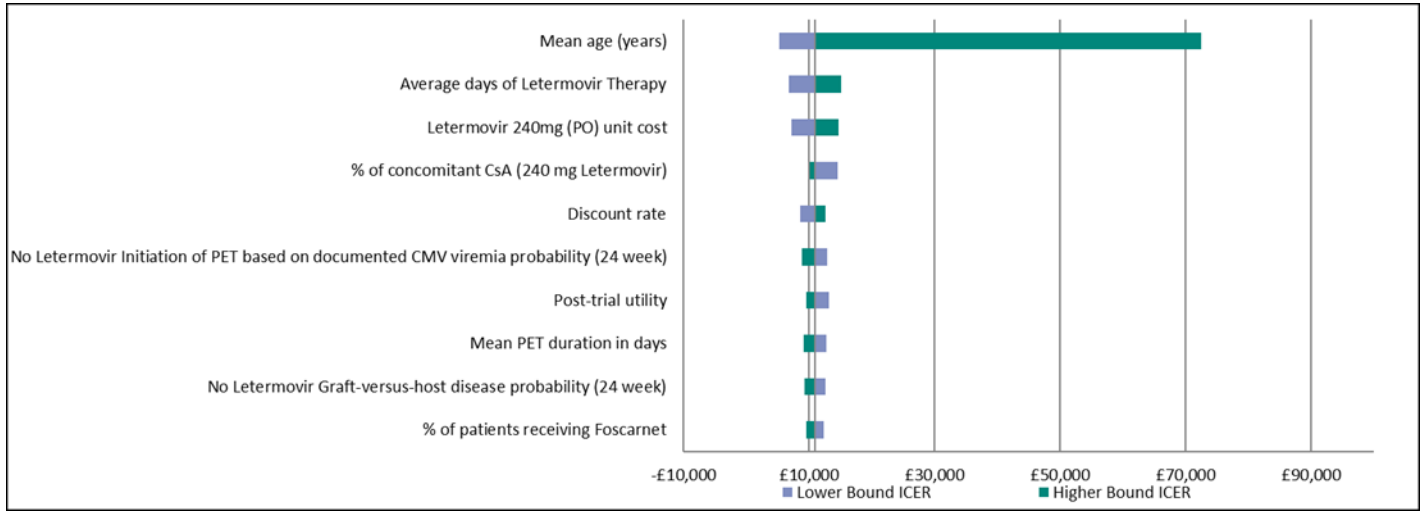
Table 52: One-way sensitivity analysis results

Rank	Model input	Lower bound		Upper bound	
		ICER	Quadrant	ICER	Quadrant
1	Mean age (years)	£5,260	1	£69,560	1
2	Average days of letermovir therapy	£6,752	1	£14,958	1
3	Letermovir 240mg (PO) unit cost	£7,169	1	£14,542	1

Rank	Model input	Lower bound		Upper bound	
		ICER	Quadrant	ICER	Quadrant
4	Percentage of concomitant CsA (240 mg letermovir)	£14,523	1	£72,516	1
5	Discount rate	£8,531	1	£15,055	1
6	No letermovir initiation of pre-emptive therapy based on documented CMV viraemia probability (24 week)	£12,928	1	£14,639	1
7	Mean pre-emptive therapy duration in days	£13,097	1	£10,142	1
8	No letermovir graft-versus-host disease probability (24 week)	£12,682	1	£12,646	1
9	Post-trial utility	£12,527	1	£8,874	1
10	Letermovir initiation of pre-emptive therapy based on documented CMV viraemia probability (24 week)	£12,274	1	£9,506	1

CsA=ciclosporin A; ICER=incremental cost-effectiveness ratio; PO=oral

Figure 11 : Tornado diagram of parameter sensitivity on lifetime ICER



CsA=ciclosporin A; ICER=incremental cost-effectiveness ratio; WTP=willingness-to-pay; PO=Oral

Two-way sensitivity analysis was conducted for mortality parameters to show the robustness of ICER estimates to plausible combinations of these input parameters. Each input parameter was varied across the 95% confidence interval, in increments of 0.5%.

Cells in **Error! Reference source not found.** shaded green display ICERs below £20,000 per QALY, bright yellow between £20,000 and £30,000 per QALY, light yellow above £30,000 per QALY and red when standard of care dominates a letermovir strategy. Over the most plausible combinations, the ICER is below £30,000. Estimated ICERs rise above £30,000 per QALY in some combinations where the mortality benefit is reduced and letermovir is dominated in some extreme combinations where letermovir mortality is higher than SoC.

Figure 12 : Two-way sensitivity analysis - all-cause mortality parameters

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

3.8.3 Scenario analysis

Scenario analyses were conducted considering alternative data sources for certain model parameters to investigate the robustness of model results with different assumptions. The first related to key model parameters used to derive letermovir and pre-emptive therapy costs, the second related to key parameters used to derive the QALY estimates, the third related to the time horizon used to inform the QALY estimates, and the fourth related to the method missing patient data approach used in PN001 to estimate the probability of initiation of pre-emptive therapy and CMV end-organ disease. Further details are provided below:

1) Key model parameters used to derive letermovir and pre-emptive therapy cost
    a. The impact of increasing the average duration of days on letermovir
        - Using the median therapy length seen in the UK cohort of the trial population
        - Increasing the duration as per SmPC guidance
        - Increasing the duration of IV therapy to 28 days while maintaining the overall treatment duration
    b) Align the percentage of patients receiving oral letermovir to reflect the UK cohort of the trial population
    c) Align the percentage of patients receiving oral letermovir to reflect the ASaT population of PN001
    d) The impact of decreasing the percent of patients receiving concomitant CsA to reflect the trial population
    e) Align the duration of pre-emptive therapy exposure to the clinical trial PN001
2) Align medicine dose and duration (percentage of patients receiving IV letermovir, percentage of patients receiving concomitant CsA, average days of pre-emptive therapy) to the clinical trial PN001
3) Key input parameters to drive the QALY estimates
    a. Using the NC=F approach for missing data
    b. Applying a disutility in year 1 and 2 after trial period (for 30% of survivors) to account for the loss in quality of life from contracting GvHD
4) Beyond trial mortality in year 1 and 2 based on the probability of mortality between 24-week and 48-weekUsing the NC=F approach for missing data

Scenarios related to costs can be seen in Table 53**Error! Reference source not found.**, where most scenarios suggest letermovir is cost-effective. Letermovir dominates SoC when using the mean duration pre-emptive therapy as observed in PN001.

Model results based on NC=F data for initiation of pre-emptive therapy and CMV end-organ disease are also shown in Table 53. These data suggest less use of pre-emptive therapy in both arms and relatively more in the placebo arm. This increases the ICER from a base-case estimate of £10,904 to £12,204.

A disutility of 0.09 was applied to 30% of the surviving cohort at year 1 and 2 post trial to account for the loss in quality of life when contracting GvHD (Pidala et al (2011); Ara and Brazier (2008))[51, 52].

Table 53: Scenario analyses

Model input	Parameter value	Reference	ICER
Average days of letermovir therapy	81	Median therapy length of UK trial population (MSD, data on file) [66]	£13,679
Average days of letermovir therapy	100	As per letermovir SmPC [1]	£18,226
% of patients receiving Letermovir Therapy (PO)	73%	As per letermovir ASaT trial population	£12,432
Percentage of patients receiving oral letermovir therapy (PO)	100%	As per letermovir UK trial population (MSD data on file) [66]	£10,556
Average days of letermovir IV therapy	28	>90% of IV therapy in trial was 4 weeks or less (Table 12-1 CSR) [29]	£11,285
Percentage of patients receiving 240mg Letermovir	51.9%	As per trial population - Table 10-13 CSR (20)	£17,471
Average days of pre-emptive therapy	59	Mean duration of pre-emptive therapy treatment as per trial - Table 11-29 CSR [29]	Letermovir dominant
Beyond trial mortality in year 1 and 2 based on probability of mortality between 24-week and 48-week	11.5%	Derived from 24-week and 48-week trial data (Week 48 CSR)	£13,629*
cGvHD disutility	0.090	Pidala J et al. 2011; Ara & Brazier 2008 [52, 53]	£10,871
Medicine dose and duration			
Percentage of concomitant CsA (240 mg letermovir)	51.9%	Table 10-13 CSR [29]	£14,962
Percentage of IV letermovir	27%	Page 21 CSR [29]	
Average days of pre-emptive therapy	59	Table 11-29 CSR [29]	

Model input	Parameter value	Reference	ICER
NC=F approach for missing data			
Letermovir initiation of pre-emptive therapy	16.0%	Table 11-2 week 24 CSR [29]	£12,204
Letermovir CMV disease	1.5%		
SoC initiation of pre-emptive therapy	40.0%		
SoC CMV disease	1.7%		
CMV=cytomegalovirus; CSR=clinical study report; ICER=incremental cost-effectiveness ratio; IV=intravenous; NC=F=non-completer=failure; PO=oral; SoC=standard of care; SmPC=Summary of Product Characteristics *Model run based on week 48 data			

3.8.4 Exploratory Analysis

The base-case model results presented in Section 3.7 are the cost-effectiveness results using the default model input values for a lifetime horizon analysis based on 24-week trial data. Additionally, an exploratory analysis was performed to see how the ICERs of letermovir compared with SoC changed when alternative time horizons to the base case are considered. The results of this analysis are summarised in Table 54. Letermovir is cost-effective compared to SoC at a short time horizon of 5 years and the ICER drops significantly for a time horizon of 10 years and more.

Table 54 : Exploratory analysis results

Model time horizon		Reference	ICER
Lifetime based on week 24 data	At 5 years	Table 11-1 week 24 CSR and calculation	£21,723
	At 10 years	Table 11-1 week 24 CSR and calculation	£14,274
	At 20 years	Table 11-1 week 24 CSR and calculation	£11,132
Lifetime based on week 48 data	At 5 years	Table 11-2 week 48 CSR and calculation	£22,662
	At 10 years	Table 11-2 week 24 CSR and calculation	£15,355
	At 20 years	Table 11-2 week 24 CSR and calculation	£12,135
	Lifetime	Table 11-2 week 24 CSR and calculation	£11,897

3.8.5 Summary of sensitivity analyses results

A simple de novo cost-effectiveness model was developed to explore the expected costs and outcomes for letermovir as CMV prophylaxis in allogeneic HSCT recipients compared with SoC in a variety of different scenarios, populated using clinical data from the pivotal trial. Specific data were utilised where possible to reflect treatment strategies and costs likely to occur in clinical practice in England.

The model results show that patients treated with letermovir are expected to have prolonged life, with improved HRQoL, and are expected to require less pre-emptive therapy due to CMV viraemia, and experience fewer negative treatment outcomes (CMV infection, graft-versus-host disease), than patients treated with SoC. While the prophylaxis cost of letermovir causes the total cost for this strategy to exceed the total cost of SoC, the costs of prophylaxis are partially offset by the decreased costs for pre-emptive therapy and the associated negative outcomes. Even so, the improved outcomes outweigh the total cost for letermovir versus SoC, and result in letermovir being deemed cost-effective at a WTP threshold of £20,000 per QALY gained in the base-case analysis, with an ICER of £10,904.

One-way sensitivity analyses demonstrate that the results are robust to sensitivity in most model inputs, although show that age is an important factor in determining cost-effectiveness. Cost-effectiveness is sensitive to all-cause mortality model inputs, informed by 95% confidence interval from the trial data. However, both two-way and probabilistic sensitivity analysis show that letermovir has a high probability at being the most cost-effective strategy across the plausible combinations of these inputs, or when considering all parameter uncertainty jointly. Scenarios using alternate assumptions reiterate the robustness of model results and show that using a different approach to handling missing trial data does not have a marked impact on cost-effectiveness results.

There are limitations relating to lack of data for some model inputs, as only exploratory analyses were carried out at longer follow-up points in the trial, as well as long-term mortality. As with all modelling, assumptions have been necessary, but this was mitigated by providing justification for these as well as taking a conservative approach that favoured SoC and testing the effect of alternative assumptions in scenario analyses.

B.3.9 Subgroup analysis

N/A

B.3.10 Validation

3.10.1 Validation of cost-effectiveness analysis

Through correspondence with English clinicians[22], modelling assumptions were checked to ensure they reflected English clinical practice. The main recommendations were as below:

- Twice-weekly PCR monitoring for CMV levels of viraemia were included into the cost-effectiveness analysis.
- All patients are treated with 14 days of induction and then for the next few weeks as needed. It was confirmed that 21 days of exposure to pre-emptive therapy was adequate to account for the instances of increased duration of exposure.
- The low use of tacrolimus and sirolimus suggests there would be a high level of use of CsA, which is reflective of the UK cohort of PN001. This accompanied with EBMT data, provides support for the high level of CsA use.

The analysis is considered directly applicable to clinical practice in England based on the following:

- The patient population considered in the model and included in PN001 resembles the population considered for an allogeneic HSCT in England. The inclusion criteria of PN001 align to the clinical treatment pathway for clinical practice in England.
- Where possible, English specific data have been used in order to best estimate the health effects and costs for the English population.
- Extensive sensitivity analyses were conducted to vary data sources and scenarios related to the estimation of clinical outcomes, QALYs, and costs to reflect the clinical practice variability throughout England.

The model inputs and functionalities of the model have been validated by an external Senior Health Economist from PHMR. MSD commissioned PHMR to adapt a global model to align to the English population and NICE requirements. The accuracy of the implementation and programming of the model was then verified by internal quality control processes. In addition, Professor Richard Grieve provided external validation of the modelling techniques involved in replicating the clinical pathway for CMV, and the assumptions used, to ensure close alignment to UK clinical practice.

There are no equity considerations with letermovir, as it can be used by any R+ patient undergoing an allogeneic HSCT in England.

B.3.11 Interpretation and conclusions of economic evidence

3.11.1 Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of letermovir for the prophylaxis of CMV reactivation in allogeneic-HSCT. The economic evaluation reflects patients assessed in PN001 and is relevant to all patients who could potentially benefit from use of the technology, as identified in the decision problem.

No studies assessing the cost-effectiveness of treatment for the target population have been identified, and therefore it is not possible to compare the results of the economic model developed in this submission with any available publication.

3.11.2 Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation was consistent with the CMV seropositive recipients of an allogeneic HSCT population eligible for letermovir as per its marketing authorisation. As mentioned previously (see section 3.2.1), the PN001 trial, which assessed patients in line with the marketing authorisation, was used in the model. Therefore, the economic evaluation is relevant to all patients who could potentially use letermovir as prophylaxis against the reactivation of CMV.

3.11.3 Generalisability of the analysis to the clinical practice in England

The analysis is directly applicable to clinical practice in England since:

- The patient population in PN001 and the de novo economic evaluation are reflective of patients considered for an allogeneic HSCT in England. The inclusion criteria of PN001 align to the clinical treatment pathway for clinical practice in England.
- The resource utilitisation and unit costs reflective of UK clinical practice were mainly derived from the NHS Reference Costs and after consulting with expert English clinicians. These cost inputs are considered most appropriate to model the cost-effectiveness of letermovir for use in England.

- Extensive sensitivity analyses have been conducted in this evidence submission, considering alternative data sources and scenarios related to the estimation of clinical outcomes, QALYs, and costs to reflect the clinical practice variability throughout England; demonstrating that letermovir is a cost-effective intervention in the majority of the analyses conducted.

3.11.4 Strengths and weaknesses of the evaluation

The cost-effectiveness analysis utilised published data from reputable, peer-reviewed journals and was supplemented with English clinician expertise where no published evidence was available.

- Estimation of utilities: Utility values were obtained directly from PN001, where EQ-5D data were collected at significant time points within the trial (Day 0 and Week 14, 24, 48).
- Treatment duration: The model assumes patients are treated for 69.4 days, which is based on the mean duration of days for patients in the letermovir arm of PN001. A scenario analysis was conducted to determine the influence that longer letermovir treatment would have on the ICER.
- Resource utilisation and unit costs used in the analyses are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs, PSSRU or BNF. Where literature was not available to inform healthcare resource utilisation, English clinical expertise was sought.

It is necessary to point out the potential weakness of the evaluation given the lack of robust longer-term survival data available in this patient population. However, the approach of assuming no further survival gains from letermovir and applying one mortality probability to both arms, leading to attenuating survival over time, is a conservative approach taken to best address this.

There is also a paucity of HRQoL data for the post-trial period. In order to account for this, the approach was taken that long term HRQoL is not superior to that of the general population, and a sensitivity analysis was conducted to test the robustness of these results.

In general, sensitivity analyses were conducted to address uncertainty around specified parameters within the model, which helped in understanding the influence that various parameters had over the cost-effectiveness results.

As the approaches taken in the modelling are mainly conservative, the results presented in this submission support the conclusion that letermovir is a cost-effective treatment option as prophylaxis for CMV reactivation and disease in CMV-seropositive recipients (R+) of an allogenic haematopoietic stem cell transplant.

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Single technology appraisal

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

Dear Company,

The Evidence Review Group, Centre for Reviews and Dissemination and Centre for Health Economics – York, and the technical team at NICE have looked at the submission received on 6 March 2018 from Merck Sharp & Dohme. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **13 April 2018**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Aimely Lee, Technical Lead (Aimely.Lee@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Trial PN001 Patient characteristics and analysis populations

A1. **Priority question:** The company submission includes results based mainly on the full analysis set (FAS) and all subjects as treated (ASaT) populations, but patient baseline characteristics are presented only for the ASaT population (Table 9). We have identified the patient characteristics for the FAS population in the clinical study report (CSR) but we found a discrepancy in the number of patients with haploidentical donors. Please confirm the numbers in the letermovir and placebo groups for the FAS and ASaT populations.

A2. **Priority question:** Haematopoietic stem cell transplantation (HSCT) is indicated at different time points in the treatment pathway. In order to better understand the patient' health status, please provide information on the line of therapy the HSCT was part of (consolidation of first line, second line etc., clarifying if patients had had any relapse prior to this line of treatment). If possible please provide this information by underlying indication.

A3. **Priority question:** The 100 days treatment duration with letermovir is dictated by the protocol rather than patient outcome. Can the company provide details of patient status when letermovir was stopped: proportion of patient in whom immunosuppression therapy had been stopped; PCR (polymerase chain reaction) result; proportion with lymphocyte count above 0.2? Can the company provide summary statistics for these clinical characteristics for those patients who later developed/did not develop clinically significant cytomegalovirus (CMV) infection by 24 weeks?

A4. Please provide the number of patients in the PN001 trial by location. If possible please provide this for both the ASaT and FAS populations.

Trial PN001 results

A5. **Priority question:** Full results are not provided for the analysis of all randomised patients who received at least one dose of treatment, i.e. the ASaT population. Please can these be presented as those for the FAS population in Table 11 (CMV infection) and Table 12 (initiation of pre-emptive therapy)?

A6. **Priority question:** Please could full results be provided for the analysis of all randomised patients who received at least one dose of treatment, but were not included in the FAS population because they had detectable CMV DNA on Day 1.

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Please can these be presented as those for the FAS population in Table 11 (CMV infection) and Table 12 (initiation of PET)?

A7. **Priority question:** In Section 2.6.2 the key secondary outcome of clinically significant infection through week 14 is not reported. This outcome is included in the economic model (Table 39 and Table 48. Please present the full results for this outcome (as for week 24 in Table 11).

A8. **Priority question:** In Section 2.6.3.2 the percentages given in the text for initiation of pre-emptive therapy through week 14 seem incorrect as they are higher than those given in Table 12 for through week 24. Please could the results for initiation of pre-emptive therapy by week 14 be tabulated?

A9. **Priority question:** Section 2.6.4 presents Time to onset of clinically significant CMV infection by week 24. The results of the analysis of the Kaplan-Meier has used a non-standard method. Please can the data be reanalysed using a hazard modelling approach and please provide the hazard ratio, with 95% confidence intervals for these.

A10. **Priority question:** Similarly, Section 2.6.5.1 presents 'Time to All-cause mortality' to week 24 (Figure 5) and week 48 (Figure 6). Please can the data be reanalysed using a hazard modelling approach and please provide the hazard ratio, with 95% confidence intervals for these.

A11. The point estimates in Table 15 (page 58) for the letermovir group for graft versus host disease (GvHD) through week 24, re-hospitalisation through week 14 and 24, and documented CMV viraemia through week 14 and 24, fall outside of the confidence intervals. Please provide the correct values for these.

A12. Regarding the incidence of CMV end organ disease the text is unclear (page 49 and Table 11 in the company submission). Through wk 24 there were 5 in the letermovir group and 3 in the placebo group. Through wk 14 the respective numbers were 1 and 2. So between week 14 and week 24 there were 4 in the letermovir group and 1 in the placebo group. Please clarify if this is correct?

A13. Please could you present a subgroup analysis of the primary outcome (i.e. clinically-significant CMV infection by week 24 post-transplant) based on whether or not patients had undergone T-cell depletion

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Adverse events

A14. **Priority question:** Please provide adverse event data between 24 and 48 weeks if recorded.

A15. In the Summary Document A (p34), it states that there is a numerically lower rate of renal adverse events in the letermovir group. Please explain why this is a potentially important benefit of letermovir.

Trial Chemaly 2014

A16. **Priority question:** To help understand how supportive the results of the Chemaly 2014 Phase II are, please answer the following queries :

a. What was treatment duration and follow-up?

b. We note that 18 patients received 240mg letermovir plus ciclosporin A (i.e. the licensed dose), please could you provide the results of this post hoc sub group versus placebo.

c. Table 22 suggests the patients in the Chemaly 2014 trial were at very low risk of CMV reactivation. Please explain how this evidence supports the results of PN001.

<u>Section B: Clarification on cost-effectiveness data</u>

Clinical inputs

B1. **Priority question:** The economic model presented assumes that mortality between year 1 and year 2 is the same as from year 2 and 3, with mortality based on data from the Wingard et al study. This is potentially a strong assumption given that mortality risk falls substantially with time following stem cell transplant. Can the company present further justification for this assumption and present data validating this assumption?

B2. **Priority question:** One approach to extrapolating the available survival data and to fill the gap between the natural history data provided in Wingard et al. and the trial is to use parametric methods to extrapolate the trial survival data. Can the company please implement appropriate parametric extrapolation of the trial data and include this as a scenario analysis in the model. The presentation of this analysis should include the full set of distribution parameters estimates, Akaike information criterion and Bayesian information criterion fit statistics, diagnostics (Q-Q plots for example) and plots. Please do this for all populations listed in question B3 and B4.

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B3. **Priority question:** Clinical inputs used in the model are based on unadjusted "data as observed" (DAO) analysis. The clinical section presents a number of analyses in which alternative approaches to account for missing data are used. Further the model inconsistently uses either data from the ASaT population and the FAS population e.g. age, duration of follow up and underlying disease mix are based on ASaT population, while other clinical inputs are based on the FAS population. Can the company provided a version of the model with the following data used:

1. All clinical inputs using DAO analysis using ASaT population;
2. All clinical inputs using DAO analysis using FAS population;
3. All clinical inputs using missing-not-at-random analysis method to adjust of missing data and using the ASaT population;
4. All clinical inputs using missing-not-at-random analysis method to adjust of missing data and using the FAS population;

B4. **Priority question:** Mortality in the economic model is based on the Kaplan-Meier data for the trial and was subject to significant censoring as a substantial number of participants were lost to follow-up. Additional follow-up presented at the request of the FDA, however, allowed vitality status of patients to be ascertained. Can the company present additional scenario analysis incorporating this mortality data into the economic model? Please do this for both the FAS and ASaT populations.

B5. The estimates of cost-effectiveness are quite sensitive to the age of the cohort and the underlying disease mix. To allow the ERG to explore the impact of these population characteristics appropriately in the model can the company carry out regression analysis in which the impact of age and underlying disease mix on the treatment effect (Initiation of pre-emptive therapy based on documented CMV viraemia, CMV end-organ disease, CMV-related re-hospitalisation, Opportunistic infection, Graft-versus-host disease, All-cause mortality) is explored. Please also include risk stratum as covariate in this analysis. Please conduct this analysis for both the ASaT and FAS populations, and using the FDA mortality data.

B6. **Priority question:** Can the company comment on why there was delay between a patient receiving their stem cell transplant and initiation of treatment with letermovir? Does the company consider that such a delay would occur in clinical practice?

Health related quality of life

B7. **Priority question:** The EQ-5D values used in the model were derived from Table 11-12 of the clinical study report. Please explain the calculation of the mean change from baseline values and justify your choice for using these values.

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B8. **Priority question:** The utility values used to represent the long-term utilities of patients in the post-trial time period of the model appropriately incorporate the increasing co-morbidity of age (i.e. the utility values are age-adjusted). However, these values do not incorporate any long-term utility decrement associated with having undergone a haematopoietic stem cell transplant (HSCT). Studies ((Leunis et al (2014) and Zittoun et al (1997)) suggest that patients who received HSCT had worse health-related quality of life compared with the general population and compared with patients who have receive high-dose chemotherapy. Please present a scenario analysis where a utility decrement from the long-term effects of HSCT has been incorporated.

B9. **Priority question:** The submission discusses a scenario analysis where a disutility value of 0.09 is applied in year 1 and year 2 after the trial period for 30% of survivors, relating to GvHD. It is unclear if this scenario has been undertaken within the model. Please can the company present this additional scenario analysis were a disutility for GvHD disease has been included?

B10. **Priority question:** The model does not include any disutility associated with adverse events or with the CMV reactivation which initiated pre-emptive therapy. Can the company present a scenario with these additional disutilities included?

Costs

B11. **Priority question:** The economic model accounts for differences in re-hospitalisation rates in the year following stem cell transplantation and routine testing, but does not account for any routine ongoing healthcare costs other than those relating GvHD. van Agthoven et al. (2002) suggests substantial ongoing care costs in the 2 years following stem cell transplantation and recent NICE Technology appraisal in acute myeloid leukaemia and acute lymphocytic leukaemia have included ongoing care costs for several years after stem cell transplantation. Can the company please justify the modelled assumptions relating to ongoing costs and include additional scenario analysis in which ongoing health care costs are included in the model?

B12. **Priority question:** A significant proportion of people with haematological cancers will experience relapse in their underlying disease following a SCT. These people will incur additional resource use and experience lower quality of life. The current model does not account for these additional costs and disutilities. Can the company present additional scenario analysis in which the possibility of relapse is accounted for?

B13. **Priority question:** The model accounts for the use of intravenous methylprednisolone for treatment of GvHD. This is based on the recommendations from Dignan et al. (2012). However, this paper recommends corticosteroid as a first line treatment and has several second line treatment options recommended,

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depending on the symptoms of GvHD that present in the patient. These second-line treatments are quite expensive compared with methylprednisolone and therefore, the costs included in the model are likely to be underestimated. Can the company include a scenario where second-line treatments for GvHD are included?

Other

B14. **Priority Question:** There appears to be a minor calculation error relating to costs as changing the cohort impacts on the ICER reported. Can the company please correct this error?

Section C: Textual clarifications and additional points

C1. **Searches for HRQoL and costs/resource use.**

In the description of the cost effectiveness searches it is stated that the company searched these databases:
Embase (OvidSP)
Medline
Medline Epub Ahead of Print
In-process & Other Non-Indexed Citations
Medline Daily
Medline<1946 to Present
Medline In-Process Citations & Daily Update (OvidSP)
The Cochrane Library
Cochrane Database of Systematic Reviews (CDSR)
Database of Abstracts of Reviews of Effects (DARE)
Health Technology Assessment Database (HTAD)
NHS Economic Evaluations Database (NHS EED)

There is also a PRISMA diagram that shows records identified and the 2 (or no?) records meeting the inclusion criteria.

For the HRQoL and resource use sections the main company submissionstates that the same databases were used as for the cost-effectiveness searches but the only search strategies that are presented are for MEDLINE and Embase. Please either provide search strategies for the NHS EED and HTA databases, or a statement confirming that results from the cost effectiveness searches were also reviewed for relevance to the HRQoL and resource use sections. Please could you also provide a PRISMA diagram for these two sections?

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References

Dignan FL, Clark A, Amrolia P, Cornish J, Jackson G, Mahendra P, Scarisbrick JJ, Taylor PC, Hadzic N, *et al.* Diagnosis and management of acute graft-versus-host disease. *British Journal of Haematology.* 2012 Jul;158(1): 30-45.

Leunis, A, Redekop WK, Uyl-de Groot CA, Löwenberg B. Impaired health-related quality of life in acute myeloid leukemia survivors: a single-center study. *European Journal of Haematology*. 2014 Sep;93(3):198-206

van Agthoven M, Groot MT, Verdonck LF, Lowenberg B, Schattenberg AVMB, Oudshoorn M, *et al*. Cost analysis of HLA-identical sibling and voluntary unrelated allogeneic bone marrow and peripheral blood stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic leukaemia. *Bone Marrow Transplant*. 2002 Aug;30(4):243-51.

Wingard JR, Majhail NS, Brazauskas R, Wang Z, Sobocinski KA, Jacobsohn D, *et al*. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *Journal of Clinical Oncology*. 2011;29(16):2230-9.

R Zittoun, S Suciu, M Watson, *et al*. Quality of life in patients with acute myelogenous leukemia in prolonged first complete remission after bone marrow transplantation (allogeneic or autologous) or chemotherapy: a cross-sectional study of the EORTC-GIMEMA AML 8A trial, *Bone Marrow Transplant*. 1997 Aug;20(4): 307-315

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Single technology appraisal

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

Dear Company,

The Evidence Review Group, Centre for Reviews and Dissemination and Centre for Health Economics – York, and the technical team at NICE have looked at the submission received on 6 March 2018 from Merck Sharp & Dohme. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **13 April 2018**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Aimely Lee, Technical Lead (Aimely.Lee@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Trial PN001 Patient characteristics and analysis populations

A1. **Priority question:** The company submission includes results based mainly on the full analysis set (FAS) and all subjects as treated (ASaT) populations, but patient baseline characteristics are presented only for the ASaT population (Table 9). We have identified the patient characteristics for the FAS population in the clinical study report (CSR) but we found a discrepancy in the number of patients with haploidentical donors. Please confirm the numbers in the letermovir and placebo groups for the FAS and ASaT populations.

MSD can confirm that for the ASaT population, the correct number of patients with haploidentical donors is 60 in the letermovir group and 21 in the placebo group respectively, as reported in Table 9 of the main submission (Document B). The respective figures for the FAS population are presented in the table below.

Table 1: Subcategories of Patients at High Risk (FAS population)

	Letermovir n	Letermovir (%)	Placebo n	Placebo (%)	Total n	Total (%)
Patients in population	[redacted]		[redacted]		[redacted]	
High Risk						
Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or -DR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haploidentical Donor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use of umbilical cord blood as stem cell source	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use of ex vivo T-cell-depleted grafts(including ex vivo use of alemtuzumab [Campath™])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2 or greater graft-versus-host disease (GvHD), requiring the use of systemic corticosteroids (defined as the use of e 1 mg/kg/day of prednisone or equivalent dose of another corticosteroid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n (%) = Number (percent) of patients in each sub-category.
Note: patients may have more than one high risk factor.

Information in the week 48 CSR represents the most current and accurate description of patient baseline characteristics. Discrepancies between the week 24 and week 48 baseline

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tables were due to data cleaning performed between database lock (DBL) at week 24 and DBL at week 48.

A2. **Priority question:** Haematopoietic stem cell transplantation (HSCT) is indicated at different time points in the treatment pathway. In order to better understand the patient' health status, please provide information on the line of therapy the HSCT was part of (consolidation of first line, second line etc., clarifying if patients had had any relapse prior to this line of treatment). If possible please provide this information by underlying indication.

The inclusion criteria for PN001 required that all patients were undergoing their first allogeneic HSCT. Consequently, no additional data on line of therapy was collected.

A3. **Priority question:** The 100 days treatment duration with letermovir is dictated by the protocol rather than patient outcome. Can the company provide details of patient status when letermovir was stopped: proportion of patient in whom immunosuppression therapy had been stopped; PCR (polymerase chain reaction) result; proportion with lymphocyte count above 0.2? Can the company provide summary statistics for these clinical characteristics for those patients who later developed/did not develop clinically significant cytomegalovirus (CMV) infection by 24 weeks?

Table 2: Patients who stopped immunosuppressant therapy prior to stopping treatment with letermovir

Population	Letermovir		Placebo	
	N With data	n (%)	N with data	n (%)
ASaT (all)	[redacted]	[redacted]	[redacted]	[redacted]
ASaT (with clinically-significant CMV infection	[redacted]	[redacted]	[redacted]	[redacted]
ASaT (without clinically-significant CMV infection	[redacted]	[redacted]	[redacted]	[redacted]
FAS (all)	[redacted]	[redacted]	[redacted]	[redacted]
FAS (with clinically-significant CMV infection)	[redacted]	[redacted]	[redacted]	[redacted]
FAS (without clinically-significant CMV infection)	[redacted]	[redacted]	[redacted]	[redacted]

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Table 3: Distribution of CMV DNA Levels at the Time of End of Treatment Through Week 24 Post-Transplant (FAS Population)

	Letermovir (N=325)		Placebo (N=170)	
	n	% (95% CI)	n	% (95% CI)
All Patients (N=495)				
Patients with data	325		170	
Mean (SD)	[redacted]		[redacted]	
Median	[redacted]		[redacted]	
Range	[redacted]		[redacted]	
(Q1, Q3)	[redacted]		[redacted]	
not detected	[redacted]	[redacted]	[redacted]	[redacted]
detected but not quantifiable	[redacted]	[redacted]	[redacted]	[redacted]
quantifiable and <1000	[redacted]	[redacted]	[redacted]	[redacted]
≥1000 and <10000	[redacted]	[redacted]	[redacted]	[redacted]
≥10000	[redacted]	[redacted]	[redacted]	[redacted]
Patients with clinically significant CMV infection (N=128)				
Patients with data	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Median	[redacted]		[redacted]	
Range	[redacted]		[redacted]	
(Q1, Q3)	[redacted]		[redacted]	
not detected	[redacted]	[redacted]	[redacted]	[redacted]
detected but not quantifiable	[redacted]	[redacted]	[redacted]	[redacted]
quantifiable and <1000	[redacted]	[redacted]	[redacted]	[redacted]
≥1000 and <10000	[redacted]	[redacted]	[redacted]	[redacted]
≥10000	[redacted]	[redacted]	[redacted]	[redacted]
Patients without clinically significant CMV infection (N=367)				
Patients with data	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Median	[redacted]		[redacted]	
Range	[redacted]		[redacted]	
(Q1, Q3)	[redacted]		[redacted]	
not detected	[redacted]	[redacted]	[redacted]	[redacted]
detected but not quantifiable	[redacted]	[redacted]	[redacted]	[redacted]
quantifiable and <1000	[redacted]	[redacted]	[redacted]	[redacted]
≥1000 and <10000	[redacted]	[redacted]	[redacted]	[redacted]
≥10000	[redacted]	[redacted]	[redacted]	[redacted]

Note: CMV DNA data were restricted to samples obtained and sent to the central laboratory within 14 days prior to, and 7 days after treatment end date.

CMV DNA not detected was imputed as 1 copy/mL. CMV DNA detected but not quantifiable was imputed as150 copies/mL.

N = number of evaluable patients in in each treatment group.

n = Number of patients in each sub-category.

% = Percent of patients in each sub-category.

Q1=25th percentile; Q3=75th percentile; CI=Confidence Interval; SD=Standard Deviation

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Table 4: Distribution of CMV DNA Levels at the Time of End of Treatment Through Week 24 Post-Transplant (ASaT Population)

	Letermovir (N=373)		Placebo (N=192)	
	n	% (95% CI)	n	% (95% CI)
All Patients (N=565)				
Patients with data	373		192	
Mean (SD)	[redacted]		[redacted]	
Median	[redacted]		[redacted]	
Range	[redacted]		[redacted]	
(Q1, Q3)	[redacted]		[redacted]	
not detected	[redacted]	[redacted]	[redacted]	[redacted]
detected but not quantifiable	[redacted]	[redacted]	[redacted]	[redacted]
quantifiable and <1000	[redacted]	[redacted]	[redacted]	[redacted]
≥1000 and <10000	[redacted]	[redacted]	[redacted]	[redacted]
≥10000	[redacted]	[redacted]	[redacted]	[redacted]
Patients with clinically significant CMV infection (N=167)				
Patients with data	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Median	[redacted]		[redacted]	
Range	[redacted]		[redacted]	
(Q1, Q3)	[redacted]		[redacted]	
not detected	[redacted]	[redacted]	[redacted]	[redacted]
detected but not quantifiable	[redacted]	[redacted]	[redacted]	[redacted]
quantifiable and <1000	[redacted]	[redacted]	[redacted]	[redacted]
≥1000 and <10000	[redacted]	[redacted]	[redacted]	[redacted]
≥10000	[redacted]	[redacted]	[redacted]	[redacted]
Patients without clinically significant CMV infection (N=398)				
Patients with data	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Median	[redacted]		[redacted]	
Range	[redacted]		[redacted]	
(Q1, Q3)	[redacted]		[redacted]	
not detected	[redacted]	[redacted]	[redacted]	[redacted]
detected but not quantifiable	[redacted]	[redacted]	[redacted]	[redacted]
quantifiable and <1000	[redacted]	[redacted]	[redacted]	[redacted]
≥1000 and <10000	[redacted]	[redacted]	[redacted]	[redacted]
≥10000	[redacted]	[redacted]	[redacted]	[redacted]

Note: CMV DNA data were restricted to samples obtained and sent to the central laboratory within 14 days prior to, and 7 days after treatment end date.

CMV DNA not detected was imputed as 1 copy/mL. CMV DNA detected but not quantifiable was imputed as150 copies/mL.

N = number of evaluable patients in in each treatment group.

n = Number of patients in each sub-category.

% = Percent of patients in each sub-category.

Q1=25th percentile; Q3=75th percentile; CI=Confidence Interval; SD=Standard Deviation

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Table 5: Patients with lymphocyte counts >0.2 at the time of stopping treatment with letermovir

Population	Letermovir		Placebo	
	N With data	n (%)	N with data	n (%)
ASaT (all)	[redacted]	[redacted]	[redacted]	[redacted]
ASaT (with clinically-significant CMV infection	[redacted]	[redacted]	[redacted]	[redacted]
ASaT (without clinically-significant CMV infection	[redacted]	[redacted]	[redacted]	[redacted]
FAS (all)	[redacted]	[redacted]	[redacted]	[redacted]
FAS (with clinically-significant CMV infection)	[redacted]	[redacted]	[redacted]	[redacted]
FAS (without clinically-significant CMV infection)	[redacted]	[redacted]	[redacted]	[redacted]

A4. Please provide the number of patients in the PN001 trial by location. If possible please provide this for both the ASaT and FAS populations.

Table 6: PN001 - Patients Randomised by Investigator and Treatment Group (All Randomised Patients and FAS populations

Country	Number (All Randomised Patients)			Number (FAS population)		
	LET (N=376)	PBO (N=194)	Total (N=570)	LET (N=325)	PBO (N=170)	Total (N=495)
Austria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Belgium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brazil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Canada	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Finland	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Italy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Korea, Republic of	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lithuania	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New Zealand	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peru	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Poland	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Romania	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Spain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sweden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Turkey	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
United Kingdom	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
United States	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trial PN001 results

A5. **Priority question:** Full results are not provided for the analysis of all randomised patients who received at least one dose of treatment, i.e. the ASaT population. Please can these be presented as those for the FAS population in Table 11 (CMV infection) and Table 12 (initiation of pre-emptive therapy)?

Table 7: PN001- Analysis of Proportion of Patients with Clinically Significant CMV Infection through Week 24 Post-Transplant (NC=F Approach, All Randomised and Treated Patients

Parameter	Letermovir (N=373) n (%)	Placebo (N=192) n (%)
Failures[†]	[redacted]	[redacted]
Clinically significant CMV infection by Week 24[‡]	[redacted]	[redacted]
Initiation of PET based on documented CMV viraemia	[redacted]	[redacted]
CMV end-organ disease	[redacted]	[redacted]
Discontinued from study before Week 24	[redacted]	[redacted]
Missing outcome in Week 24 visit window	[redacted]	[redacted]
Stratum-adjusted treatment difference (Letermovir-Placebo)[§]		
Difference (95% CI)	[redacted]	
p-value	[redacted]	

[†] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

[‡] Clinically significant CMV infection was defined as CMV end organ disease or initiation of PET based on documented CMV viraemia and the clinical condition of the patient. In one instance in both the letermovir and placebo arm, 1 patient is counted as both a case of initiation of PET and as a case of CMV end-organ disease.

[§] 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A nominal one-sided p-value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all patients who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

N = number of patients in each treatment group.

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

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Table 8: PN001- Proportion of Patients with Initiation of Pre-emptive Therapy (PET) for Documented CMV Viraemia through Week 24 Post-Transplant (NC=F Approach, ASaT Population)

Parameter	Letermovir (N=373) n (%)	Placebo (N=192) n (%)
Failures[†]	[redacted]	[redacted]
Initiation of PET based on documented CMV viraemia	[redacted]	[redacted]
Discontinued from study before Week 24	[redacted]	[redacted]
Missing outcome in Week 24 visit window	[redacted]	[redacted]
Stratum-adjusted treatment difference (Letermovir-Placebo)[‡]		
Difference (95% CI)	[redacted]	
p-value	[redacted]	

[†] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

[‡] 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A nominal one-sided p-value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all patients who initiated pre-emptive therapy (PET) or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

N = number of patients in each treatment group.

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

A6. **Priority question:** Please could full results be provided for the analysis of all randomised patients who received at least one dose of treatment, but were not included in the FAS population because they had detectable CMV DNA on Day 1. Please can these be presented as those for the FAS population in Table 11 (CMV infection) and Table 12 (initiation of PET)?

Table 9: PN001- Proportion of Patients with Clinically-Significant CMV Infection through Week 24 Post-Transplant (NC=F Approach, Patients with Detected CMV DNA on Day 1, All Randomised and Treated Patients)

Parameter	Letermovir (N=48) n (%)	Placebo (N=22) n (%)
Failures[†]	**31 (64.6)**	**20 (90.9)**
Clinically significant CMV infection by Week 24[‡]	22 (45.8)	17 (77.3)
Initiation of PET based on documented CMV viraemia	21 (43.8)	17 (77.3)
CMV end-organ disease	2 (4.2)	1 (4.5)
Discontinued from study before Week 24	8 (16.7)	3 (13.6)
Missing outcome in Week 24 visit window	1 (2.1)	0 (0.0)
Stratum-adjusted treatment difference (Letermovir-Placebo)[§]		
Difference (95% CI)	-26.1 (-45.9, -6.3)	
p-value	0.0048	

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† The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.
‡ Clinically significant CMV infection was defined as CMV end organ disease or initiation of PET based on documented CMV viraemia and the clinical condition of the patient. In one instance in both the letermovir and placebo arm, 1 patient is counted as both a case of initiation of PET and as a case of CMV end-organ disease.
§ 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A nominal one-sided p-value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.
Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all patients who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.
N = number of patients in each treatment group.
n (%) = Number (percent) of patients in each sub-category.

Table 10: PN001- Proportion of Patients with Initiation of Pre-emptive Therapy for documented CMV Viraemia through Week 24 Post-Transplant (NC=F Approach, Patients with Detected CMV DNA on Day 1)

Parameter	Letermovir (N=48) n (%)	Placebo (N=22) n (%)
Failures†	[redacted]	[redacted]
Initiation of PET based on documented CMV viraemia	[redacted]	[redacted]
Discontinued from study before Week 24	[redacted]	[redacted]
Missing outcome in Week 24 visit window	[redacted]	[redacted]
Stratum-adjusted treatment difference (Letermovir-Placebo)‡		
Difference (95% CI)	[redacted]	
p-value	[redacted]	

† The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.
‡ 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A nominal one-sided p-value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.
Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all patients who initiated pre-emptive therapy (PET) or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.
N = number of patients in each treatment group.
n (%) = Number (percent) of patients in each sub-category.

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A7. **Priority question:** In Section 2.6.2 the key secondary outcome of clinically significant infection through week 14 is not reported. This outcome is included in the economic model (Table 39 and Table 48. Please present the full results for this outcome (as for week 24 in Table 11).

Table 11: PN001- Analysis of Proportion of Patients with Clinically Significant CMV Infection by week 14 Post-Transplant (NC=F Approach, FAS Population)

Parameter	Letermovir (n = 325) n (%)	Placebo (n = 170) n (%)
Failures [a]	**62 (19.1)**	**85 (50.0)**
Clinically significant CMV infection by week 14[b]	25 (7.7)	67 (39.4)
Initiation of pre-emptive therapy based on documented CMV viraemia	24 (7.4)	65 (38.2)
CMV end-organ disease	1 (0.3)	2 (1.2)
Discontinued from study before week 14	33 (10.2)	16 (9.4)
Missing outcome in week 14 visit window	4 (1.2)	2 (1.2)
Stratum-adjusted treatment difference (letermovir-placebo)[c]		
Difference (95% CI)	–31.3 (–39.9 to –22.6)	
P value	<0.0001	

CI = confidence interval; CMV = cytomegalovirus; FAS = full analysis set; NC = F = non-completer = failure.
[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.
[b] Clinically significant CMV infection was defined as CMV end-organ disease or initiation of pre-emptive therapy based on documented CMV viraemia and the clinical condition of the patient.
[c] 95% CIs and *P* value for the treatment differences in percentage of response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A 1-sided *P* value ≤ 0.0249 was used for declaring statistical significance.
Note: Approach to handling missing values: With NC = F approach, failure was defined as all patients who developed clinically-significant CMV infection or prematurely discontinued from the study or had a missing outcome through week 24 post-transplant visit window.
N = number of patients in each treatment group
n (%) = Number (percent) of patients in each sub-category.

Table 12: PN001- Analysis of Proportion of Patients with Clinically Significant CMV Infection by week 14 Post-Transplant (DAO Approach, FAS Population)

Parameter	Letermovir (n = 288) n (%)	Placebo (n = 152) n (%)
[redacted]	[redacted]	[redacted]

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Parameter	Letermovir (n = 288) n (%)	Placebo (n = 152) n (%)

CI = confidence interval; CMV = cytomegalovirus; FAS = full analysis set; NC = F = non-completer = failure.
[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.
[b] Clinically significant CMV infection was defined as CMV end-organ disease or initiation of pre-emptive therapy based on documented CMV viraemia and the clinical condition of the patient.
[c] 95% CIs and *P* value for the treatment differences in percentage of response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A nominal 1-sided *P* value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.
Note: Approach to handling missing values: Data-as-Observed (DAO) approach. With DAO approach, any patient with missing value for a particular endpoint was excluded from the analysis.
N = number of patients in each treatment group
n (%) = Number (percent) of patients in each sub-category.

A8. **Priority question:** In Section 2.6.3.2 the percentages given in the text for initiation of pre-emptive therapy through week 14 seem incorrect as they are higher than those given in Table 12 for through week 24. Please could the results for initiation of pre-emptive therapy by week 14 be tabulated?

Table 13: PN001- Proportion of Patients with Initiation of Pre-emptive therapy for Documented CMV Viraemia through Week 14 Post-Transplant (NC=F Approach, FAS Population)

Parameter	Letermovir (n=325) N (%)	Placebo (n=170) N (%)
Failures	**61 (18.8)**	**84 (49.4)**
Initiation of pre-emptive therapy based on documented CMV viraemia	24 (7.4)	65 (38.2)
Discontinued from study before week 14	33 (10.2)	17 (10.0)
Missing outcome in week 14 visit window	4 (1.2)	2 (1.2)
Stratum-adjusted treatment difference (Letermovir-Placebo)		
Difference (95% CI)	-31.0 (-39.6, -22.4)	
p-value	<0.0001	

† The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.
‡ 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A nominal one-sided p-value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.
Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all patients who initiated pre-emptive therapy or prematurely discontinued from the study or had a missing outcome through week 24 post-transplant visit window.
N = number of patients in each treatment group. n (%) = Number (percent) of patients in each sub-category.

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A9. **Priority question:** Section 2.6.4 presents Time to onset of clinically significant CMV infection by week 24. The results of the analysis of the Kaplan-Meier has used a non-standard method. Please can the data be reanalysed using a hazard modelling approach and please provide the hazard ratio, with 95% confidence intervals for these.

Table 14: PN001- Time to onset of clinically-significant CMV infection by Week 24 Post-Transplant (FAS Population, Hazard Modelling Approach)

Study: PN001[a]	Letermovir			Placebo			Letermovir vs. Placebo	
	N[b]	Patients with Event n (%)	Median Time[c] in Weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in Weeks [95 %-CI]	Hazard Ratio[d] [95 %-CI]	p-Value[d,e]
Time to Clinically significant CMV infection at week 24	325	[redacted]	[redacted]	170	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: 24JAN2017
b: Number of patients: Full Analysis Set (FAS)
c: Kaplan-Meier method
d: Cox proportional hazard model, stratified by risk factor group (high vs low)
e: Two-sided p-value based on Wald test
CI: confidence interval.

A10. **Priority question:** Similarly, Section 2.6.5.1 presents 'Time to All-cause mortality' to week 24 (Figure 5) and week 48 (Figure 6). Please can the data be reanalysed using a hazard modelling approach and please provide the hazard ratio, with 95% confidence intervals for these.

Table 15: PN001- Time to all-cause mortality by Week 24 Post-Transplant (FAS Population, Hazard Modelling Approach)

Study: 8228-001	Letermovir			Placebo			Letermovir vs. Placebo	
	N[a]	Patients with Event n (%)	Median Time[b] in Weeks [95 %-CI]	N[a]	Patients with Event n (%)	Median Time[b] in Weeks [95 %-CI]	Hazard Ratio[c] [95 %-CI]	p-Value[c,d]
Time to All-Cause Mortality at week 24	325	[redacted]	[redacted]	170	[redacted]	[redacted]	[redacted]	[redacted]

a: Number of patients: Full Analysis Set (FAS)
b: Kaplan-Meier method

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c: Cox proportional hazard model, stratified by risk factor group (high vs low)
d: Two-sided p-value based on Wald test
Database Cutoff Date: 24Jan2017
CI: confidence interval.

Table 16: PN001- Time to all-cause mortality by Week 48 Post-Transplant (FAS Population, Hazard Modelling Approach)

Study: 8228-001	Letermovir			Placebo			Letermovir vs. Placebo	
	N[a]	Patients with Event n (%)	Median Time[b] in Weeks [95 %-CI]	N[a]	Patients with Event n (%)	Median Time[b] in Weeks [95 %-CI]	Hazard Ratio[c] [95 %-CI]	p-Value[c,d]
Time to All-Cause Mortality	325	[redacted]	[redacted]	170	[redacted]	[redacted]	[redacted]	[redacted]

a: Number of patients: Full Analysis Set (FAS)
b: Kaplan-Meier method
c: Cox proportional hazard model, stratified by risk factor group (high vs low)
d: Two-sided p-value based on Wald test
Database Cutoff Date: 24Jan2017
CI: confidence interval.

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A11. The point estimates in Table 15 (page 58) for the letermovir group for graft versus host disease (GvHD) through week 24, re-hospitalisation through week 14 and 24, and documented CMV viraemia through week 14 and 24, fall outside of the confidence intervals. Please provide the correct values for these.

Table 17: PN001- Exploratory Endpoints for letermovir (FAS population)

Exploratory Endpoints	Letermovir (N=325)	
	n	% (95% CI)
GvHD through Week 24 post-transplant	159	48.9 (43.4, 54.5)
Re-hospitalisation through Week 14 post-transplant	118	36.3 (31.1, 41.8)
Re-hospitalisation through Week 24 post-transplant	158	48.6 (43.1, 54.2)
Documented CMV viraemia through Week 14 post-transplant	103	31.7 (26.7, 37.1)
Documented CMV viraemia through Week 24 post-transplant	186	57.2 (51.7, 62.7)

A12. Regarding the incidence of CMV end organ disease the text is unclear (page 49 and Table 11 in the company submission). Through wk 24 there were 5 in the letermovir group and 3 in the placebo group. Through wk 14 the respective numbers were 1 and 2. So between week 14 and week 24 there were 4 in the letermovir group and 1 in the placebo group. Please clarify if this is correct?

MSD can confirm that these figures are correct. Clinically-significant CMV infection (either due to initiation of pre-emptive therapy or onset of CMV end-organ disease) was observed in the letermovir group between weeks 14 and 24 post-transplant, following discontinuation of prophylaxis. Further exploration of baseline and post-randomisation variables determined that the increased rate in this subset ('late failures') reflected graft-versus-host disease (GvHD) and corticosteroid use post-randomisation, and baseline high risk for CMV reactivation.

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A13. Please could you present a subgroup analysis of the primary outcome (i.e. clinically-significant CMV infection by week 24 post-transplant) based on whether or not patients had undergone T-cell depletion

Table 18: PN001- Proportion of Patients with Clinically-Significant CMV Infection through Week 24 Post-transplant by Ex-Vivo T-cell Depletion (NC=F Approach, FAS population)

Risk category	Letermovir		Placebo		Letermovir vs. Placebo Difference in % (95% CI)†
	n/N	% (95% CI)	n/N	% (95% CI)	
Total	[redacted]		[redacted]		[redacted]
Ex-vivo T-cell depletion					
Yes	[redacted]		[redacted]		[redacted]
No	[redacted]		[redacted]		[redacted]

† Treatment difference and 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk).
Note: Approach to handling missing values: Non-Completer=Failure approach. With NC=F approach, failures was defined as all patients who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.
N = number of patients in each treatment group.
N (%) = Number (percent) of patients in each sub-category.
N/A = Not Applicable.

Table 19: PN001- Proportion of Patients with Clinically-Significant CMV Infection through Week 24 Post-transplant by Ex-Vivo T-cell Depletion (DAO Approach, FAS population)

Risk category	Letermovir		Placebo		Letermovir vs. Placebo Difference in % (95% CI)†
	n/N	% (95% CI)	n/N	% (95% CI)	
Total	[redacted]		[redacted]		[redacted]
Ex-vivo T-cell depletion					
Yes	[redacted]		[redacted]		[redacted]
No	[redacted]		[redacted]		[redacted]

† Treatment difference and 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk).
Note: Approach to handling missing values: Data-as-Observed (DAO) approach. With DAO approach, any patient with missing value for a particular endpoint was excluded for the analysis.
N = number of patients in each treatment group.
N (%) = Number (percent) of patients in each sub-category.
N/A = Not Applicable.

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Adverse events

A14. **Priority question:** Please provide adverse event data between 24 and 48 weeks if recorded.

Overall, the AE profile through to Week 48 post-transplant was similar for the letermovir and placebo groups, and is consistent with the profile through Week 24 post-transplant. The majority of patients experienced one or more AEs through Week 48 post-transplant ([redacted] in the letermovir group vs. [redacted] in the placebo group). Through Week 48 post-transplant, the proportion of patients with at least one SAE reported was [redacted] in the letermovir group vs. [redacted] in the placebo group.

A total of [redacted] patients in the letermovir group vs. [redacted] of patients in the placebo group discontinued due to a SAE. There were [redacted] patients with drug-related SAEs ([redacted] in the letermovir group vs. [redacted] in the placebo group) through Week 48 post-transplant; there were no additional drug-related SAEs reported after Week 24 post-transplant. The incidence of AEs associated with fatal outcome was [redacted] in the letermovir group vs. [redacted] in the placebo group.

Table 20: PN001- Analysis of Adverse Event Summary through Week 48 Post-Transplant (ASaT Population)

	Letermovir n (%)	Placebo n (%)	Difference in % vs Placebo Estimate (95% CI)†
Patients in population	[redacted]	[redacted]	[redacted]
with one or more adverse events			
with no adverse events			
with drug-related‡ adverse events			
with serious adverse events			
with serious drug-related adverse events			
who died			
discontinued§ due to an adverse event			
discontinued due to a drug-related adverse event			
discontinued due to a serious adverse event			
discontinued due to a serious drug-related adverse event			

† Based on Miettinen & Nurminen method.
‡ Determined by the investigator to be related to the drug.
§ Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with ciclosporin A.
NA = Not Applicable.

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Table 21: PN001- Analysis of Patients With Adverse Events (Incidence ≥4 Patients in One or More Treatment Groups) Through Week 48 Post-Transplant (ASaT Population)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Patients in population	373		192		
with one or more adverse events					
with no adverse events					
Blood and lymphatic system disorders					
Anaemia					
Eosinophilia					
Febrile neutropaenia					
Leukopaenia					
Neutropaenia					
Pancytopaenia					
Thrombocytopaenia					
Cardiac disorders					
Atrial fibrillation					
Atrial flutter					
Cardiac failure					
Pericardial effusion					
Sinus tachycardia					
Tachycardia					
Ear and labyrinth disorders					
Ear pain					
Vertigo					
Endocrine disorders					
Eye disorders					
Blepharitis					
Conjunctival haemorrhage					
Dry eye					
Eye pain					
Lacrimation increased					
Retinal haemorrhage					
Vision blurred					
Gastrointestinal disorders					
Abdominal discomfort					
Abdominal distension					
Abdominal pain					
Abdominal pain upper					
Angina bullosa haemorrhagica					
Aphthous ulcer					

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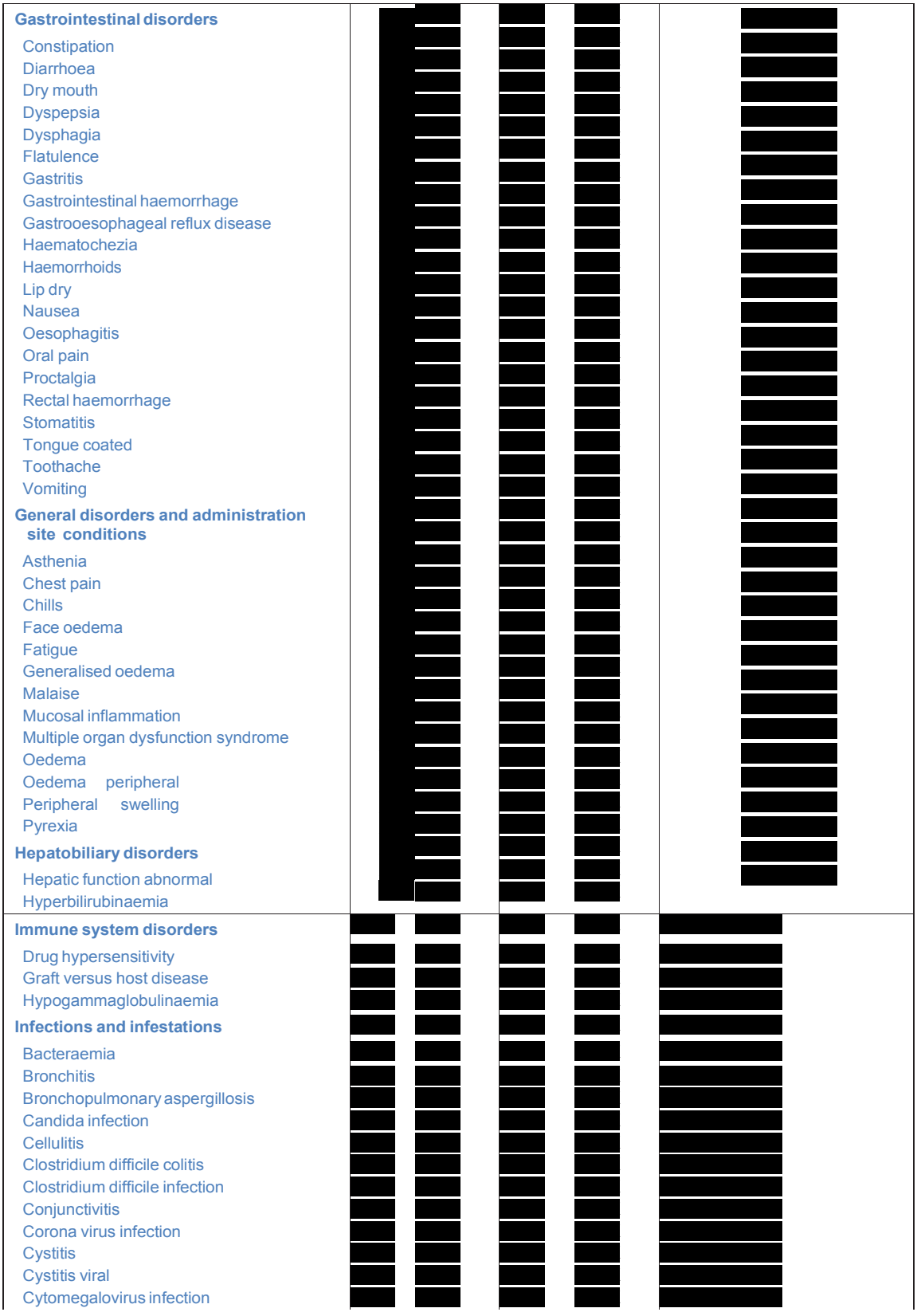

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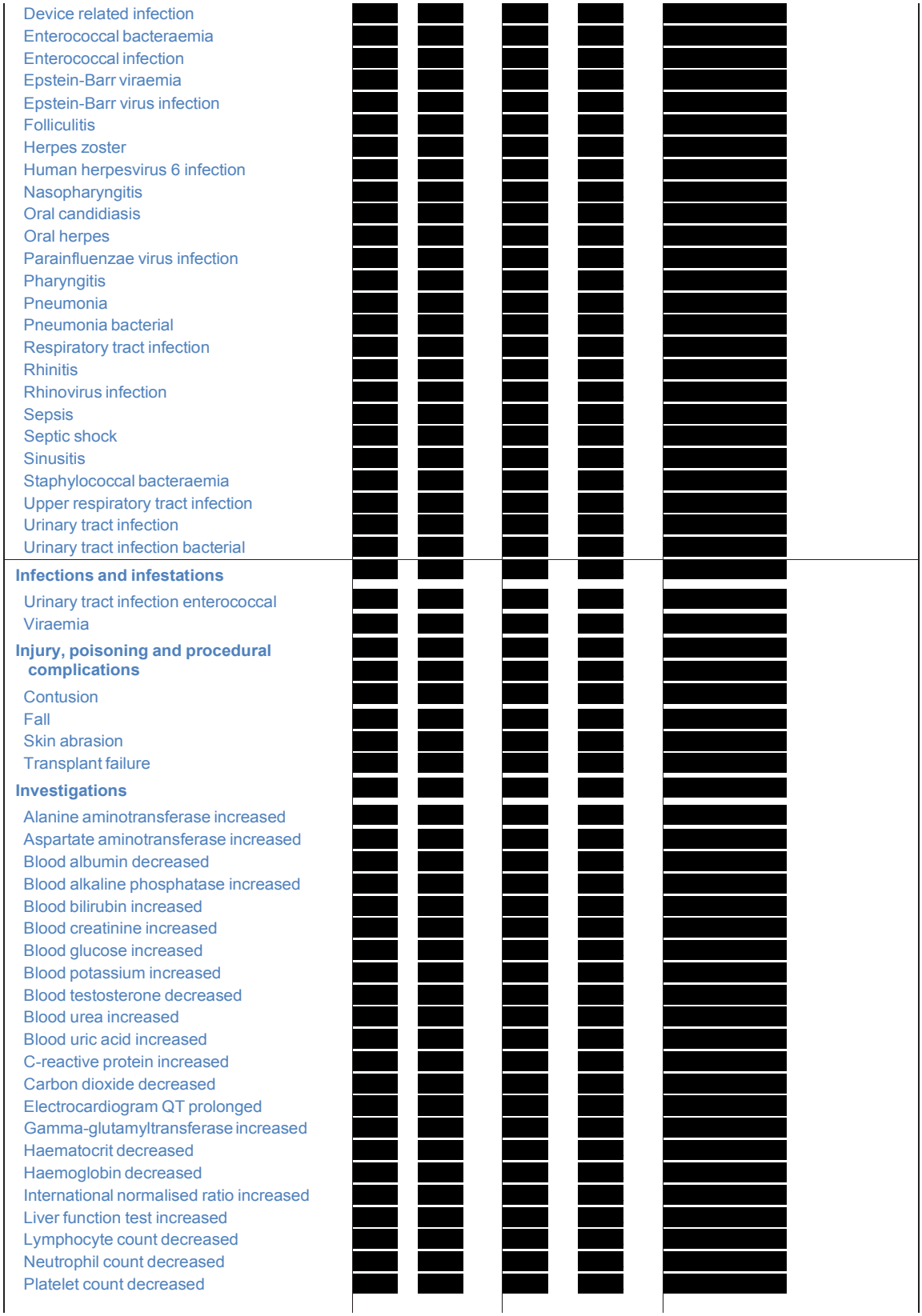

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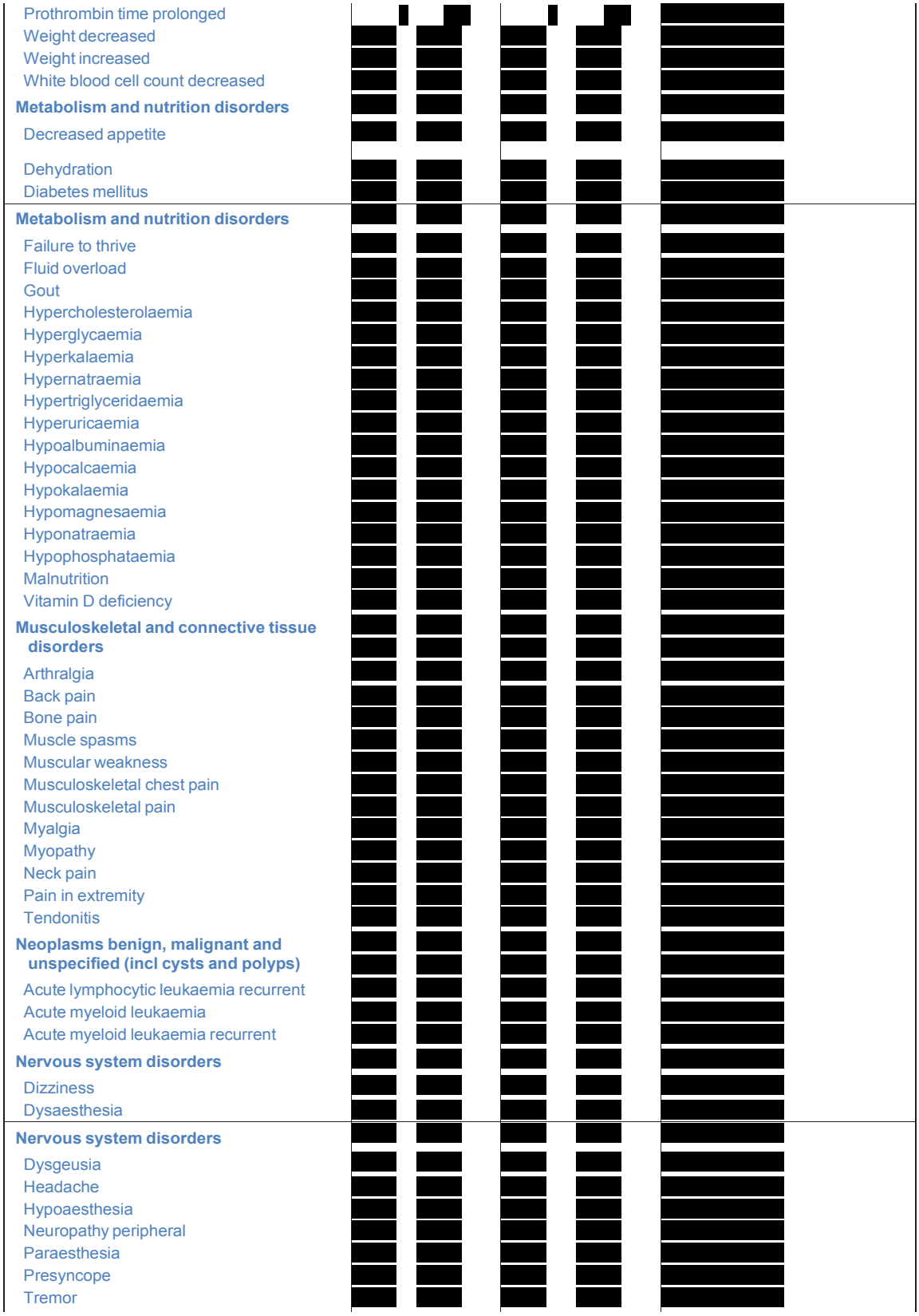

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Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Delirium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mental status changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cystitis haemorrhagic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysuria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nocturia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pollakiuria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vaginal discharge	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vaginal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea exertional	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemoptysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Respiratory, thoracic and mediastinal disorders					
Pleural effusion					
Productive cough					
Pulmonary oedema					
Respiratory failure					
Rhinorrhoea					
Upper-airway cough syndrome					
Skin and subcutaneous tissue disorders					
Dermatitis contact					
Dry skin					
Erythema					
Night sweats					
Palmar erythema					
Petechiae					
Pruritus					
Rash					
Rash erythematous					
Rash macular					
Rash maculo-papular					
Rash pruritic					
Skin exfoliation					
Skin hyperpigmentation					
Skin lesion					
Swelling face					
Vascular disorders					
Deep vein thrombosis					
Haematoma					
Hypertension					
Hypotension					
Orthostatic hypotension					
Venoocclusive disease					

† Based on Miettinen & Nurminen method.

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

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with ciclosporin A.

Serious Adverse Events

There was a slight increase in the number of patients with SAEs between Week 24 and Week 48 post-transplant (additional patients in the letermovir group, and additional patients in the placebo group through Week 48 post-transplant when compared to Week 24 post-transplant).

A total of patients experienced a drug-related SAE through Week 48 post-transplant, with) in the letermovir group and in the placebo group. No specific drug-related SAE was experienced by more than a single patient.

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Table 22: PN001- Analysis of Patients With Serious Adverse Events (Incidence ≥4 Patients in One or More Treatment Groups) Through Week 48 Post-transplant (ASaT Population)

	Letermovir	Placebo	Difference in % vs Placebo
	n	n (%)	Estimate (95% CI)[†]
Patients in population	373	192	
with one or more serious adverse events			
with no serious adverse events			
Blood and lymphatic system disorders			
Febrile neutropenia			
Thrombocytopenia			
Cardiac disorders			
Gastrointestinal disorders			
Diarrhoea			
General disorders and administration conditions			
Multiple organ dysfunction syndrome			
Pyrexia			
Hepatobiliary disorders			
Immune system disorders			
Graft versus host disease			
Infections and infestations			
Bronchopulmonary aspergillosis			
Cytomegalovirus infection			
Pneumonia			
Sepsis			
Septic shock			
Sinusitis			
Staphylococcal bacteraemia			
Urinary tract infection			
Injury, poisoning and procedural complications			
Metabolism and nutrition disorders			
Musculoskeletal and connective tissue disorders			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia recurrent			
Acute myeloid leukaemia			
Acute myeloid leukaemia recurrent			
Nervous system disorders			
Renal & urinary disorders			
Acute kidney injury			
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
Vascular disorders			

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† Based on Miettinen & Nurminen method.
Every patient is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with ciclosporin A.

Drug-Related Serious Adverse Events

There were no additional drug-related SAEs (incidence >0% in one or more treatment groups) reported between Week 24 and Week 48 post-transplant.

[redacted] patients ([redacted]) experienced a drug-related SAE through Week 48 post-transplant, with [redacted] ([redacted]) in the letermovir group and [redacted] ([redacted]) in the placebo group. No specific drug-related SAE was experienced by more than a single patient.

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Table 23: PN001- Patients With Serious Drug-Related Adverse Events (Incidence > 0% in One or More Treatment Groups) Through Week 48 Post-Transplant (ASaT Population)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	373		192		565	
with one or more serious drug-related adverse events			3	(1.6)	6	(1.1)
with no serious drug-related adverse events						
Blood and lymphatic system disorders						
Pancytopenia						
Thrombocytopenia						
Injury, poisoning and procedural complications						
Delayed engraftment						
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Bowen's disease						
Psychiatric disorders						
Mental status changes						
Renal and urinary disorders						
Acute kidney injury						

Every patient is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

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Deaths

The proportion of patients with AEs associated with fatal outcomes was [redacted] in the letermovir group compared to [redacted] in the placebo group through Week 24 post-transplant. There were an additional [redacted] with AEs associated with fatal outcomes in the letermovir group compared to [redacted] additional patients [redacted] in the placebo group between Week 24 post-transplant and Week 48 post-transplant. The incidence of AEs associated with fatal outcomes experienced by patients in the letermovir and placebo groups was [redacted] vs. [redacted], respectively through Week 48 post-transplant.

The most frequently reported specific AEs associated with fatal outcomes through Week 48 post-transplant (letermovir vs. placebo) were recurrent AML ([redacted] vs. [redacted], GvHD [redacted] vs. [redacted]), pneumonia ([redacted] vs. [redacted]), sepsis ([redacted]), septic shock ([redacted] vs. [redacted]), and AML ([redacted] vs. [redacted]), which are consistent with the Week 24 profile for AEs associated with fatal outcomes.

None of the AEs associated with fatal outcomes was considered to be related to study medication by the investigator.

A15. In the Summary Document A (p34), it states that there is a numerically lower rate of renal adverse events in the letermovir group. Please explain why this is a potentially important benefit of letermovir.

Other than letermovir, all other anti-CMV agents are nephrotoxic, especially foscarnet and cidofovir. In PN001 the statistically significant benefit observed with letermovir over placebo in the primary endpoint led to fewer patients in this study arm being exposed to these agents. A numerically lower rate of renal System Organ Class (SOC) AEs was also observed in the letermovir group compared with the placebo group, indicating that letermovir use is not associated with nephrotoxicity. This would represent a benefit for letermovir use over all other available anti-CMV agents.

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Trial Chemaly 2014

A16. **Priority question:** To help understand how supportive the results of the Chemaly 2014 Phase II are, please answer the following queries :

a. What was treatment duration and follow-up?

In the Chemaly et al., 2014 study (PN020), patients were treated for 12 weeks (84 days) post-engraftment. An additional follow-up visit was conducted at Day 92 (+/- 2 days) for safety assessment.

b. We note that 18 patients received 240mg letermovir plus ciclosporin A (i.e. the licensed dose), please could you provide the results of this post hoc sub group versus placebo.

Table 24: Analysis of Incidence of HCMV Prophylaxis Failure within the 84-day treatment period (non-completers considered as failure) among patients with concomitant ciclosporin A (Full Analysis Set)

	AIC090027 240 mg/day N=18	Placebo N=19
Failed Yes HCMV prophylaxis failed Other discontinuation No	[redacted]	[redacted]
Odds ratio and 95% CI for active dose vs placebo	[redacted]	
Fisher's exact test of active dose vs. placebo p-value	[redacted]	

Note: Failed is defined as all patients who developed systemic detectable HCMV replication, developed HCMV End-Organ disease or discontinued treatment prior to day 84 due to other reasons (Adverse Event, Death, Protocol non-compliance, Patient withdrew consent or other).
Patient 105006 in the 240mg/day group has reason for discontinuation from trial medication of Adverse Event (GI-GvHD); however, this patient met the criteria for systemic detectable HCMV replication prior to discontinuation and is therefore counted as a true failure.
Patient 110001 in the 240mg/day group discontinued from trial medication due to initiation of alternative anti-HCMV medication, however they do not meet the criteria for systemic detectable HCMV replication and are therefore counted as other discontinuations.

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c. Table 22 suggests the patients in the Chemaly 2014 trial were at very low risk of CMV reactivation. Please explain how this evidence supports the results of PN001.

PN020 was a dose-finding study in which patients were not stratified by risk categories, and no such risk categories were pre-defined. It should also be noted that the rates of CMV infection for the placebo group in this study (36% virologic failure at Week 12, or Day 84) were similar to those observed in PN001 (39.4% of placebo-arm patients experiencing clinically-significant CMV infection by Week 14 post-transplant).

In PN001, subgroup analysis by risk category (high vs low) showed letermovir was efficacious *regardless* of risk category i.e. it was efficacious in both high AND low risk (which was anyone who wasn't high risk) categories. Therefore, the results of the Chemaly 2014 trial are consistent with the results seen in PN001.

Section B: Clarification on cost-effectiveness data

Clinical inputs

B1. **Priority question:** The economic model presented assumes that mortality between year 1 and year 2 is the same as from year 2 and 3, with mortality based on data from the Wingard et al study. This is potentially a strong assumption given that mortality risk falls substantially with time following stem cell transplant. Can the company present further justification for this assumption and present data validating this assumption?

MSD explored several methods for extrapolating the mortality benefit seen in the trial. Due to the lack of available data on numerous key inputs certain assumptions and limitations were unavoidable. MSD arrived at two potential approaches when extrapolating the mortality benefit; directly approximating a survival curve similar to those seen in national registries or via using relative risks from published literature and applying them to population specific life tables.

MSD adopted the later approach as survival curves available from registries like the European Society for Blood and Marrow Transplantation (EBMT) were not able to adjust for the underlying disease mix of indications, and did not have sufficient follow-up data to project mortality to the end of life.
Please find the key differences between the two extrapolation methods below.

- The mortality data from the registry did not align with the data collected from the trial. Figure 1 and Figure 2 display a survival rate between 0.6 and 0.7 for related transplant, and between 0.4 and 0.8 for unrelated transplant at 12 months in European allogeneic-HSCT recipients. In contrast, survival for the placebo group in

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PN001 was 0.75 at 48 weeks with the difference potentially due to numerous factors such as the time of the study, the advances seen in administering allogeneic-HSCT, and population demographics. Aligning the two estimates would require strong and unverifiable assumptions.

Figure 1: Kaplan-Meier estimates of overall survival in patients undergoing HLA-identical sibling stem-cell transplant with CMV-seropositive or -seronegative donors

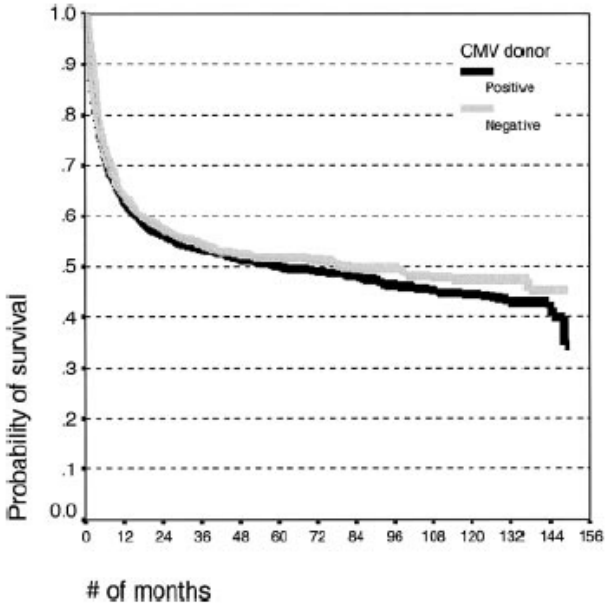

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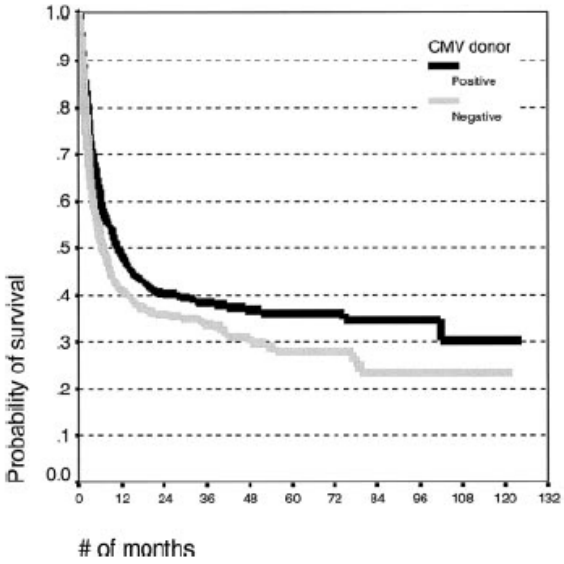
Figure 2: Kaplan-Meier estimates of overall survival in patients undergoing unrelated donor stem-cell transplant with CMV-seropositive or -seronegative donors



- One potential contributor to the differences between the registry and trial data may be the underlying indication for the transplant. These indications were strongly associated with the risk of mortality post-transplant, and only one source of data was found that illustrated the relative risks of each indication with a sufficient follow-up period. Controlling for the underlying mix of indications in our trial and the ability to adjust the indications to be generalisable to each market was deemed an important component of an accurate cost-effective model.

B2. **Priority question:** One approach to extrapolating the available survival data and to fill the gap between the natural history data provided in Wingard et al. and the trial is to use parametric methods to extrapolate the trial survival data. Can the company please implement appropriate parametric extrapolation of the trial data and include this as a scenario analysis in the model. The presentation of this analysis should include the full set of distribution parameters estimates, Akaike information criterion and Bayesian information criterion fit statistics, diagnostics (Q-Q plots for example) and plots. Please do this for all populations listed in question B3 and B4.

Parametric extrapolation of the trial survival data has been conducted and results have been used in the model to run scenarios. All results are presented below for both ASaT and FAS population. The model outputs are for a lifetime time horizon based on 24-weeks.

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Table 25: Distribution parameter estimates - ASaT population

EXP	Weibull	Lognormal	Loglogistic	Gompertz
constant	constant	constant	constant	constant
0.000708	0.0002706	7.066542	6.850712	0.00064
HR	p	sigma	Gamma	gamma
1.276933	1.168105	1.57919	0.7994615	0.0006297
	HR	time ratio	time ratio	HR
	1.28181	-0.2475711	-0.2313914	1.278573
AIC	AIC	AIC	AIC	AIC
774.7658	773.7048	770.0549	772.1445	776.3115
BIC	BIC	BIC	BIC	BIC
783.4394	786.7152	783.0653	785.155	789.322

Table 26: Distribution parameter estimates - FAS population

EXP	Weibull	Lognormal	Loglogistic	Gompertz
constant	constant	constant	Constant	constant
0.0006792	0.0002908	7.132777	6.908704	0.000652
HR	p	sigma	Gamma	gamma
1.308779	1.148219	1.599566	0.8132452	0.000262
	HR	time ratio	time ratio	HR
	1.312517	-0.294693	-0.2615714	1.309297
AIC	AIC	AIC	AIC	AIC
677.6737	677.5897	673.0835	675.8683	679.6061
BIC	BIC	BIC	BIC	BIC
686.0828	685.6972	688.482	688.482	692.2198

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Table 27: Exponential distribution – AsaT population

Arm	Life years	QALYs	Costs
Letermovir	3.09	2.82	£31,329
SoC	2.36	2.17	£25,742
Difference	0.74	0.65	£5,587
ICER	£7,587	£8,598	-

Table 28: Weibull distribution - ASaT population

Arm	Life years	QALYs	Costs
Letermovir	2.45	2.30	£31,315
SoC	1.91	1.81	£25,717
Difference	0.54	0.49	£5,599
ICER	£10,395	£11,453	-

Table 29: Lognormal distribution - ASaT population

Arm	Life years	QALYs	Costs
Letermovir	5.22	4.49	£31,313
SoC	4.19	3.61	£25,742
Difference	1.04	0.87	£5,571
ICER	£5,377	£6,379	-

Table 30: Loglogistic distribution - ASaT population

Arm	Life years	QALYs	Costs
Letermovir	4.10	3.60	£31,310
SoC	3.28	2.90	£25,691
Difference	0.82	0.71	£5,620
ICER	£6,829	£7,920	-

Table 31: Gompertz distribution - ASaT population

Arm	Life years	QALYs	Costs
Letermovir	2.19	2.08	£31,320
SoC	1.77	1.69	£25,729
Difference	0.42	0.39	£5,591
ICER	£13,362	£14,309	-

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Table 32: Exponential distribution - FAS population

Arm	Life years	QALYs	Costs
Letermovir	3.21	2.39	£31,448
SoC	2.91	2.20	£25,797
Difference	0.81	0.71	£5,651
ICER	£6,937	£7,910	-

Table 33: Weibull distribution - FAS population

Arm	Life years	QALYs	Costs
Letermovir	2.59	2.42	£31,437
SoC	1.98	1.86	£25,778
Difference	0.61	0.55	£5,660
ICER	£9,231	£10,279	-

Table 34: Lognormal distribution - FAS population

Arm	Life years	QALYs	Costs
Letermovir	5.49	4.70	£31,452
SoC	4.28	3.69	£25,757
Difference	1.21	1.01	£5,695
ICER	£4,772	£5,645	-

Table 35: Loglogistic distribution - FAS population

Arm	Life years	QALYs	Costs
Letermovir	4.32	3.78	£31,433
SoC	3.39	2.98	£25,735
Difference	0.93	0.80	£5,698
ICER	£6,124	£7,158	-

Table 36: Gompertz distribution - FAS population

Arm	Life years	QALYs	Costs
Letermovir	2.65	2.05	£31,444
SoC	2.46	1.92	£25,792
Difference	0.60	0.54	£5,652
ICER	£9,492	£10,531	-

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B3. **Priority question:** Clinical inputs used in the model are based on unadjusted "data as observed" (DAO) analysis. The clinical section presents a number of analyses in which alternative approaches to account for missing data are used. Further the model inconsistently uses either data from the ASaT population and the FAS population e.g. age, duration of follow up and underlying disease mix are based on ASaT population, while other clinical inputs are based on the FAS population. Can the company provided a version of the model with the following data used:

1. All clinical inputs using DAO analysis using ASaT population;
2. All clinical inputs using DAO analysis using FAS population;
3. All clinical inputs using missing-not-at-random analysis method to adjust of missing data and using the ASaT population;
4. All clinical inputs using missing-not-at-random analysis method to adjust of missing data and using the FAS population;

Please find attached to the clarification responses a model with the drop-down option of selecting the data approach 1, 2, 3 and 4. For the data approaches of 3 and 4 we have not provided models based on the missing-not-at-random (MNAR) analysis method. The only true way to distinguish between MNAR and missing-at-random (MAR) is to measure some of the missing data. However in most missing data situations, such as this, there is no mechanism of getting a hold of the missing data.

As a comparable solution we have provided the model populations of 3 and 4 using time-to-event analysis methods.

Please find the ICER results for each analysis approach presented below in tabular format using the base case time horizon (lifetime based on 24 weeks).

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Table 37: Clinical input analysis

Model input	ICER (Lifetime based on 24-week)
All clinical inputs using DAO analysis using ASaT population	£11,905
All clinical inputs using DAO analysis using FAS population	£11,322
All clinical inputs using time-to-event analysis method to adjust of missing data and using the ASaT population	£13,347
All clinical inputs using time-to-event analysis method to adjust of missing data and using the FAS population	£12,003

B4. **Priority question:** Mortality in the economic model is based on the Kaplan-Meier data for the trial and was subject to significant censoring as a substantial number of participants were lost to follow-up. Additional follow-up presented at the request of the FDA, however, allowed vitality status of patients to be ascertained. Can the company present additional scenario analysis incorporating this mortality data into the economic model? Please do this for both the FAS and ASaT populations.

The model has been run over a lifetime horizon using mortality data at 48-week from a post hoc analysis on those who withdrew from the study. The absolute mortality risk in each arm reflects a relative risk of [redacted] for the ASaT population and [redacted] for the FAS population.

Table 38: Post-hoc analysis all-cause mortality scenario - ASaT population

Model input	Parameter value	Reference	ICER (Lifetime based on 48-week)
All-cause mortality at week 48	[redacted]% vs. [redacted]% no letermovir)	Post-hoc analysis	£11,034
Arm	**Life years**	**QALYS**	**Costs**
Letermovir	7.81	6.28	£29,223
SoC	7.30	5.84	£24,390
Difference	0.50	0.44	£4,832
ICER	£9,615	£11,034	-

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Table 39: Post-hoc analysis all-cause mortality scenario - FAS population

Model input	Parameter value	Reference	ICER (Lifetime based on 48-week)
All-cause mortality at week 48	[redacted]% vs. [redacted]% (Letermovir vs. no letermovir)	Post-hoc analysis	£13,710
Arm	**Life years**	**QALYS**	**Costs**
Letermovir	7.84	6.30	£29,267
SoC	7.45	5.96	£24,626
Difference	0.38	0.34	£4,641
ICER	£12,187	£13,710	-

B5. The estimates of cost-effectiveness are quite sensitive to the age of the cohort and the underlying disease mix. To allow the ERG to explore the impact of these population characteristics appropriately in the model can the company carry out regression analysis in which the impact of age and underlying disease mix on the treatment effect (Initiation of pre-emptive therapy based on documented CMV viraemia, CMV end-organ disease, CMV-related re-hospitalisation, Opportunistic infection, Graft-versus-host disease, All-cause mortality) is explored. Please also include risk stratum as covariate in this analysis. Please conduct this analysis for both the ASaT and FAS populations, and using the FDA mortality data.

As discussed on the clarification teleconference with NICE and the ERG (3rd April 2018), it was agreed that this question was not a priority. Due to the extensive analyses required to answer the priority questions, we have not conducted these additional analyses.

B6. **Priority question:** Can the company comment on why there was delay between a patient receiving their stem cell transplant and initiation of treatment with letermovir? Does the company consider that such a delay would occur in clinical practice?

As letermovir is available as an IV formulation, it would be preferable to start letermovir treatment on, or soon after, the day of transplant. However, other previously conducted studies for the prevention of CMV reactivation (including PN020) encouraged patient initiation after engraftment had occurred. The reluctance to initiate an investigational agent prior to the important milestone of engraftment is mainly due to the commonly seen toxicities involved with previous generation CMV antivirals. As such, without data to unequivocally demonstrate that letermovir would not have a deleterious effect on engraftment, investigators in the trial required the flexibility to start letermovir between Day 0 and Day 28 post-allogeneic HSCT.

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Even with this flexibility, approximately 66% of patients in PN001 initiated letermovir treatment prior to engraftment. It can be expected that with increasing confidence in the use of letermovir, coupled with the observation that letermovir initiation is not associated with myelotoxicity and does not affect engraftment, the trend will be for clinicians to initiate letermovir use earlier than in the pivotal clinical trial. However, until further data on real world utilisation is collected, these assumptions cannot be further ratified.

Health related quality of life

B7. **Priority question:** The EQ-5D values used in the model were derived from Table 11-12 of the clinical study report. Please explain the calculation of the mean change from baseline values and justify your choice for using these values.

There were three ways we considered calculating the change from baseline. The first would be to take the difference in each patient's QoL instruments and average this across all patients [sum(t2-t1)/n)]. The second method would be to average the instruments at each time point and then subtract [sum(t2)/n – sum(t1)/n]. These two approaches would yield the same answer unless there were missing responses. We expected this to be the case and decided it would be better to use the first method to keep consistency within each patient when measuring change from baseline. It might be expected that baseline values would vary greatly based on the underlying indication and treatment regimen; however, it was felt there was not enough data published on QoL in HSCT to fully understand the impact of these missing data points on the results. This was specified prior to database lock (DBL).

Given the lack of data around how CMV or HSCT affects QoL we were unable to perform imputation on the missing data. Additionally, there were also some queries about how to handle differences in baseline values between groups. Due to the uncertainty in the method suited for this analysis, our statistical team approached the analysis in a variety of ways. We have attached the report outlining these scenarios [attachment - [redacted]].

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B8. **Priority question:** The utility values used to represent the long-term utilities of patients in the post-trial time period of the model appropriately incorporate the increasing co-morbidity of age (i.e. the utility values are age-adjusted). However, these values do not incorporate any long-term utility decrement associated with having undergone a haematopoietic stem cell transplant (HSCT). Studies ((Leunis et al (2014) and Zittoun et al (1997)) suggest that patients who received HSCT had worse health-related quality of life compared with the general population and compared with patients who have receive high-dose chemotherapy. Please present a scenario analysis where a utility decrement from the long-term effects of HSCT has been incorporated.

In Leunis et al. (2014), the mean age of patients with AML is 52.7 years [1]. This patient population has a post-trial utility of 0.82, while the utility value for the general population aged between 50 to ≤55 is 0.8344 [2]. Therefore, the patient population suffers a utility decrement of 0.0144. To incorporate long-term utility decrement associated with having undergone a HSCT, we applied a constant utility decrement to the general population age-adjusted utility values using the value above.

Table 40: Long-term utility decrement from allogeneic HSCT scenario analysis

Model input	Parameter value	ICER (Lifetime based on 24-week)
Long term utility decrement applied to the general population utilities	0.0144	£10,959

B9. **Priority question:** The submission discusses a scenario analysis where a disutility value of 0.09 is applied in year 1 and year 2 after the trial period for 30% of survivors, relating to GvHD. It is unclear if this scenario has been undertaken within the model. Please can the company present this additional scenario analysis were a disutility for GvHD disease has been included?

Please find the requested analysis presented in Table 53 on Page 141 of the submission. The analysis provides an ICER of £10,871.

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B10. **Priority question:** The model does not include any disutility associated with adverse events or with the CMV reactivation which initiated pre-emptive therapy. Can the company present a scenario with these additional disutilities included?

Due to the dearth of literature in the patient population relevant to the submission, there has not been any disutility associated with CMV-reactivation included in the analysis.

As the utility figures applied to all patients (including those who have experienced AEs), it is assumed that the utility decrement has already been included in the AE calculation and to include any further decrement would double count the impact of AEs on utility values.

Costs

B11. **Priority question:** The economic model accounts for differences in re-hospitalisation rates in the year following stem cell transplantation and routine testing, but does not account for any routine ongoing healthcare costs other than those relating GvHD. van Agthoven et al. (2002) suggests substantial ongoing care costs in the 2 years following stem cell transplantation and recent NICE Technology appraisal in acute myeloid leukaemia and acute lymphocytic leukaemia have included ongoing care costs for several years after stem cell transplantation. Can the company please justify the modelled assumptions relating to ongoing costs and include additional scenario analysis in which ongoing health care costs are included in the model?

The model approach was to try and incorporate all important costs and outcomes that are likely to differ between arms. Most differences in costs between prophylaxis with letermovir and standard of care are likely to be captured during the trial follow-up. Graft versus host disease was identified as a large event cost in the trial that should be incorporated beyond the trial period, because of the nature of this event. Other routine costs could be included, but in designing the model, the perimeter of related costs did not encompass these additional considerations.

A scenario has been run to include follow-up costs in the two years following stem-cell transplant (SCT). Given the limited data available, data was sourced from TA451 (ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia) [3]. As stated in the company's submission, costs were estimated based on a study undertaken by the NHS Blood and Transplant Service (UK Stem Cell Strategy Oversight Committee), which obtained resource use information from a Dutch cost study [4]. Resource use was combined with UK specific costs, which were obtained from the PSSRU [5]. In the absence of UK costs, costs were obtained from the Dutch costing study [4] and converted using the Health and Social Care Pay and Price index [5].

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The Dutch study captured the cost of hospital days, outpatient visits, medications, day care, radiotherapy, blood components, diagnostics, donor lymphocytes infusion and other procedures.

The UK Stem Cell Strategy Oversight Committee report could not be found online and therefore data from TA451, inflated to 2015/2016 costs using published indices, have been used to perform the scenario analysis [3, 5]. The follow-up cost in year one and two post SCT was £12,215 and £3,518 respectively. The inflated costs, given in net present value terms are £12,378 and £3,565.

Table 41: Long-term follow-up costs from allogeneic-HSCT scenario analysis

Parameter	Unit cost	ICER (lifetime based on 24-week)
Follow-up cost year 1 post SCT	£12,378	£12,322
Follow-up cost year 2 post SCT	£3,565	

B12. **Priority question:** A significant proportion of people with haematological cancers will experience relapse in their underlying disease following a SCT. These people will incur additional resource use and experience lower quality of life. The current model does not account for these additional costs and disutilities. Can the company present additional scenario analysis in which the possibility of relapse is accounted for?

A scenario analysis has been conducted to incorporate the additional cost and utility decrement from relapse after a HSCT.

The probability of relapse was sourced from Wingard et al. (2011) for consistency [6]. The study reports a probability of relapse of 10% for patients with AML, which was used in the model as it is the main patient population.

Given no reputable source was identified regarding the disutility from disease relapse it was decided to apply the utility decrement from undergoing a HSCT. Given that this was applied to the whole population, it was felt this was a conservative approach in light of the difficulties in sourcing another value to be applied to the 10% who experienced disease relapse. As the probability of disease relapse is small, applying a disutility to the 10% of patients impacted would not be expected to have a considerable influence over the ICER. As such, the same utility decrement associated with having undergone a HSCT as in question B8 was applied.

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Given the limited data available, cost of relapse was sourced from TA451 (ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia) [3] and inflated to 2015/2016 prices using published indices [5]. The per-cycle cost of £6,460 (£6,375.39 original value) covers medication as well as follow-up and monitoring costs. Patients with relapse have a poor prognosis. Indeed, according to Wingard et al. (2011), most deaths after HSCT happen in the following two years due to relapse [6]. Two studies, investigating the long-term survival of AML patients in relapse, were identified and reported a 29% survival at 1-year and 11% at 5-years from relapse [7] and 9% to 21% at 2-year from relapse [8]. Based on this data, we have conducted three scenario analyses, assuming an average survival of 6-month, 1-year and 2-year following relapse. The overall cost of relapse is therefore the per-cycle cost multiple by the appropriate number of cycles (3-month cycle).

Table 42: Relapse after stem-cell transplant scenario – 6 month survival

Parameter	Parameter value	ICER (lifetime based on 24-week)
Proportion of patients relapsing	10%	£11,074
Disutility from SCT	0.0114	
Cost of relapse	£12,920	

Table 43: Relapse after stem-cell transplant scenario - 1 year survival

Parameter	Parameter value	ICER (lifetime based on 24-week)
Proportion of patients relapsing	10%	£11,190
Disutility from SCT	0.0114	
Cost of relapse	£25,840	

Table 44: Relapse after stem-cell transplant - 2 year survival

Parameter	Parameter value	ICER (lifetime based on 24-week)
Proportion of patients relapsing	10%	£11,421
Disutility from SCT	0.0114	
Cost of relapse	£51,680	

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B13. **Priority question:** The model accounts for the use of intravenous methylprednisolone for treatment of GvHD. This is based on the recommendations from Dignan et al. (2012). However, this paper recommends corticosteroid as a first line treatment and has several second line treatment options recommended, depending on the symptoms of GvHD that present in the patient. These second-line treatments are quite expensive compared with methylprednisolone and therefore, the costs included in the model are likely to be underestimated. Can the company include a scenario where second-line treatments for GvHD are included?

Second line costs of GvHD were not considered in the cost-effectiveness analysis because it applies to only a small proportion of patients. Based on the recommended second line treatment in the clinical commissioning policy (CCP) [9], a scenario was run including additional costs of extracorporeal photopheresis (ECP):

"We have concluded that there is enough evidence to consider making the following treatments available:

- patients with acute GvHD - extracorporeal photopheresis (ECP)
- patients with chronic GvHD - ECP, pentostatin, rituximab and imatinib."

Based on the CCP 10% were assumed to require second line treatment for acute GvHD and 6% for chronic GVHD.

Contemporary England specific costs of ECP were difficult to identify, but a 2010 study published by NHS Scotland did report estimates, which had been derived for the National Specialist Commissioning Advisory Group [10]. These costs were in chronic GvHD, but in the absence of any data were assumed to be the same for both acute and chronic GvHD.

The 3-year cost of ECP (discounted at 3.5%) was £50,606. This was inflated to 2015/16 prices using published indices [5]. This inflated cost, given in net present value terms is £54,319.

In acute GvHD this was used to reflect the cost of second line treatment for 10% of patients who received first-line treatment for cGvHD with steroids up to week 24. This equates to 7% of survivors receiving second line treatment.

In the chronic setting this was used to reflect the cost of second line treatment for 6% of patients who received first-line treatment for cGvHD with steroids after the trial follow-up. This equates to 1.8% of survivors receiving second line treatment.

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Table 45: Chronic GvHD second-line treatment scenario

Parameter	Unit cost	Percentage of GvHD requiring second line treatment	ICER (lifetime based on 24-week)
aGvHD (second line ECP)	£54,319	10%	£11,187
cGvHD (second line ECP)		6%	

Other

B14. **Priority Question:** There appears to be a minor calculation error relating to costs as changing the cohort impacts on the ICER reported. Can the company please correct this error?

Please accept our apologies; the total costs for SoC are presented in document B incorrectly for the base case. Table 50 of Document B (page 131) should read a total cost for SoC of £28,805. The incremental cost and ICER remain unchanged.

Section C: Textual clarifications and additional points

C1. **Searches for HRQoL and costs/resource use.**

In the description of the cost effectiveness searches it is stated that the company searched these databases:
Embase (OvidSP)
Medline
Medline Epub Ahead of Print
In-process & Other Non-Indexed Citations
Medline Daily
Medline<1946 to Present
Medline In-Process Citations & Daily Update (OvidSP)
The Cochrane Library
Cochrane Database of Systematic Reviews (CDSR)
Database of Abstracts of Reviews of Effects (DARE)
Health Technology Assessment Database (HTAD)
NHS Economic Evaluations Database (NHS EED)

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There is also a PRISMA diagram that shows records identified and the 2 (or no?) records meeting the inclusion criteria.

For the HRQoL and resource use sections the main company submissionstates that the same databases were used as for the cost-effectiveness searches but the only search strategies that are presented are for MEDLINE and Embase. Please either provide search strategies for the NHS EED and HTA databases, or a **statement confirming that results from the cost effectiveness searches were also reviewed for relevance** to the HRQoL and resource use sections. Please **could you also provide a PRISMA diagram for these two sections**?

Specific HRQoL searches were only performed in MEDLINE and Embase however the search results from all databases were screened at the same time, and all results were reviewed for relevance to HRQoL and resource use.

No results were identified for HRQoL as outlined in Section 3.4.3 of Document B, and three studies were identified for cost and resources utilisation as outlined in Appendix I of Document B.

Please find a PRISMA diagram relating to the literature searches for cost and resource utilisation in Figure 7.

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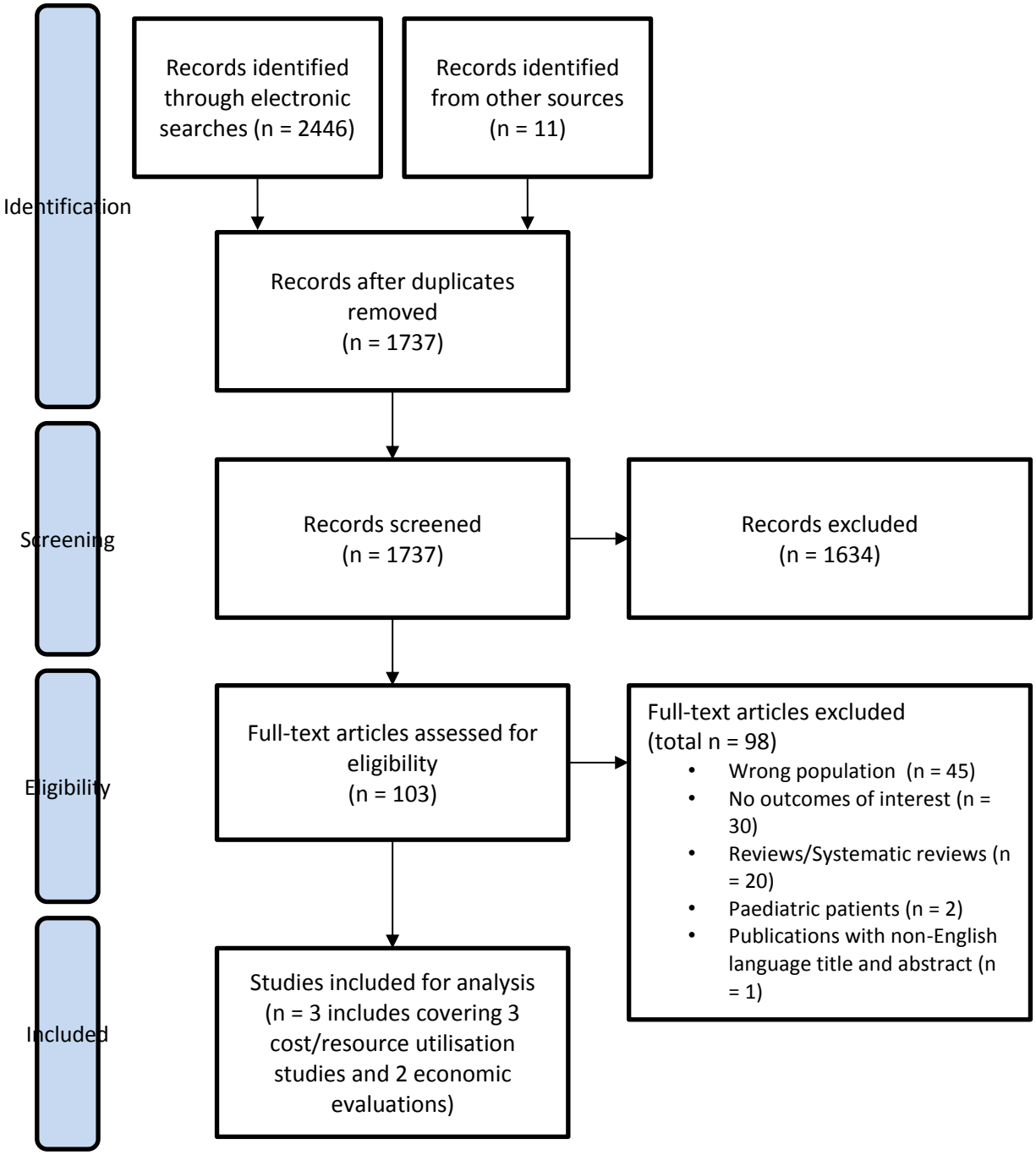
Figure 7: PRISMA diagram for cost and resource utilisation



As no results were found relating to HRQoL a PRISMA diagram has not been provided.

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Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	Anthony Nolan
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	• Anthony Nolan saves and improves the lives of people with blood cancers and blood disorders in need of a potentially curative stem cell transplant. We provide patients with matching donors from our stem cell donor register and facilitate their transplants, support them and their families throughout their transplant journey, and advocate on their behalf. We have over 660,000 potential donors on the Anthony Nolan Stem Cell Register. • Our vision: To save and improve the lives of everyone who needs a stem cell transplant. • Our aims:

	○ To improve outcomes and quality of life for our patients. ○ To lead and influence the global transplant community in improving outcomes. ○ To deliver excellence, efficiency and transparency in our work. • We support patients and their families at all points on their journey through and beyond stem cell transplantation. To interact with patients, we host a forum on our website, publish a blog, convene a panel of patients and families, provide a telephone helpline, and run support and information events. • Anthony Nolan receives income from NHS providers to cover the costs of providing stem cell donations. This is supplemented by charitable fundraising activities, research grants and income from service provision.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	• Anthony Nolan created a survey for patients and carers on cytomegalovirus (CMV) reactivation. This was shared with our Patients and Families Panel; via the Anthony Nolan Patients and Families Facebook page; on a blog on our website; and discussed with patients via Anthony Nolan Clinical Nurse Specialists at transplant centres. • At the time of submission, there were 21 responses to the consultation; 13 respondents had experienced CMV reactivation themselves, while 8 were carers of people experiencing CMV reactivation. • We also conducted five telephone interviews and one face-to-face interview on experiences of CMV reactivation or caring for those experiencing CMV reactivation. • We interviewed patients and carers with a wide range of experiences, from those who had very few symptoms or side effects, to those who are still regularly reactivating more than two years after transplant. • We also discussed the use of CMV medicines with medical professionals to support this submission.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Living with CMV reactivation** • CMV reactivation itself is unusual in that it can have no symptoms. Prophylaxis is used to prevent the reactivation worsening and escalating to CMV disease, which can cause issues such as CMV retinitis, CMV pneumonitis and CMV colitis. • Of the 13 patients who responded to the Anthony Nolan CMV Survey, 6 (46%) found that living with CMV reactivation was difficult or very difficult. • The main physical difficulties experienced due to CMV reactivation are due to the side-effects of the treatment (especially ganciclovir, valganciclovir, foscarnet, and cidofovir). See question 7 below. **Mental health and well-being** • Patients and carers told us that being diagnosed as having CMV reactivation - or caring for someone who had been diagnosed with CMV reactivation - had a significantly negative effect on their mental health and well-being. 8 of 13 (62%) patients surveyed said that CMV reactivation had a 'negative' or 'very negative' effect on their mental health and well-being, with a majority of those (6 of 8) being in the latter category. • Returning to hospital or extending their stay in hospital due to CMV reactivation had a significant effect on the mental health and well-being of patients and their carers. o *"I had very little quality of life, no social life, unable to work and lost the bit of independence I had built up after leaving hospital after the transplant. I was very depressed and anxious."* o *"Because my CMV reactivated so soon after transplant, my immunity was still extremely compromised. The need to return to hospital, without the special isolation arrangement in the transplant unit, was therefore a very stressful turn of events for me."* • A common theme was that many patients described this as feeling like they were taking a *"massive step backwards"* in their recoveries. They saw the stem cell transplant as a potentially lifesaving treatment, which was hindered by the CMV reactivation. o *"To get to this point, nine months in, to be told that the lifesaving chance has failed because of something which is dormant in your body and that there was no treatment, nothing they could do about it, and that was kind of it, was just the most horrific time. All the way through you're living on this knife-edge and you're dealing with it day by day, then you found a match, you've gone through transplant, it's started to engraft, you've been through isolation for six weeks."*

- *"I think you want to put all your effort into getting better after the transplant, so it [CMV reactivation] felt like a massive backwards step and I was very concerned that I didn't have much of an immune system, and it was trying to fight this virus. Alongside having absolutely no energy from the transplant, this knocked me for six."*
- *"It's more that it was stopping the transplant working [rather than the symptoms of CMV reactivation], and that's the thing, you go so far, and then this thing stops what it's trying to do."*

Effect on daily life

- Patients told us that living with CMV reactivation had a significant effect of their day-to-day life, including their ability to look after themselves, to have a social life, travel, and live independently.
  - *"Having this reactivation occur for the last 2 years has been very depressing and due to weekly CMV check-ups has stopped me having holidays and any quality of life as well as disrupting my working life".*
  - *"If it were not for the constant reactivation I would be free of weekly hospital visits and my mental state would improve greatly as I could at last take some "me" time and resume a normal life".*
  - *"It just seems never-ending. I want a normal life, not tied to a hospital."*
  - *"She went from being so fiercely independent - and had been her whole life – and then relied on everyone else".*
  - *"My mum never went back to work. She never worked, she never drove again as she couldn't drive."*
- Patients told us that they had to spend more time off work than anticipated due to CMV reactivation, with one even losing their job as a consequence.
  - One patient told us that their original sick note from their consultant was six months. However, they needed a donor lymphocyte infusion, a procedure which could not happen until the CMV reactivation was under control, which took longer than this period: *"In the end it was so long that I hadn't been at work that they couldn't give any end date for my treatment so they [work] just asked me to leave. They told me I had to come to a disciplinary or agree to resign… The CMV meant the difference between having a job and not having a job."*

Carers

	• Carers highlighted the challenges of looking after someone experiencing CMV reactivation. Indeed, all of the 8 respondents who cared for someone experiencing CMV reactivation said it was 'difficult' or 'very difficult'. • Carers and families showed that caring for someone experiencing CMV reactivation could be incredibly challenging for their mental health. They recognised the link the between CMV reactivation and increased mortality, which caused significant mental stress. o *"Emotionally, it was one of the hardest things sitting in that room, and we were all just in tears and trying to accept... I can remember coming home and not sleeping for about two days... It's trying to process so much information...It was one of the worst things ever to just walk out of that and go 'Dad's dead, we've done all of this and it hasn't worked and it won't work'."* • Carers found it challenging to be the information gatherer and diffuser, especially caring for a parent. o *"For me personally, it has taken about three or four years to get over the whole thing, because you are the lynchpin of the family. Trying to communicate it also, because everyone wants to know the detail. When you're the one who has to explain what everything is, what CMV is, what reactivation is, how it affects the transplant, it is really difficult."* • Some carers found it difficult to continue with their career when caring for someone with CMV reactivation. Some found being away for work incredibly stressful, while it caused others to give up work altogether. o *"It was so upsetting [to see the patient they cared for return to hospital]. Every time I was away on a trip and my phone went off, I just thought oh my god, this is it now, this is the phone call."* o *"My mum retired to look after Dad. They didn't have a lot of time. I stopped working."* o *"[CMV reactivation] involved my spouse going back into hospital for 7 days. Which meant I had to take another week's unpaid leave. I had already taken 6 months unpaid leave for chemo and transplant."*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments	**Side effects** • Although we appreciate that not all of these treatments will be used in the same way as letermovir (primary versus secondary prophylaxis), it is hoped that letermovir would prevent the need for patients to have to progress onto the later, more aggressive treatments such as foscarnet and cidofovir.

and care available on the NHS?	• Either of the first- or second-line treatments are seen as generally being successful in fighting the virus (at least in the short term). However, they come with a range of serious side-effects which make the patient experience more challenging. o Valganciclovir ▪ Patients reported that valganciclovir had a positive effect in that it was mentally beneficial to have a treatment which can be taken orally at home, rather than via a drip at the hospital. ▪ However, patients also told us that valganciclovir has a negative impact on blood counts, with neutrophils shown to be virtually zero as a consequence of this treatment. The patient then had "*small cut on my hand, and it got an infection, and it tracked up the vein in my arm – it made it like a red railway track – so that had me admitted for another week, as it was turning to sepsis*." ▪ Another patient, whose son was just 18 months old when they had their transplant, told us that valganciclovir *"used to just make me really ill, really sick. An example was that... we were potty training [the patient's son], and he thought the toilet was just for being sick into, because all he had seen was me being sick into it."* o Ganciclovir ▪ A carer told us that they perceived ganciclovir as being a key factor in the first stem cell transplant not grafting properly, having a huge effect on their mental health. o Foscarnet ▪ Patients who had experienced foscarnet told us that it is *"the real problem"* with their CMV reactivation. ▪ Patients highlighted the difficulty surrounding the length of the intravenous treatment which takes five hours a day for nine days. Following this, there is a one-to-two hour 'flush' during which fluid is given to the patient. In the words of a patient: *"It's a really long procedure; you say goodbye to a day every time you go in."* ▪ On the more extreme level, a patient described the feel as *"Burning all the way up my arms and into my heart… I thought my veins were going to disintegrate to be honest."* ▪ *Another said that they "would initially be sick for a couple of hours, and it would last a couple of hours after that, but you'd feel ill and you'd know you had the next dose coming the next day."* ▪ One patient described that treatment with foscarnet meant they *"felt as though I was buzzing like an electric shock, like one of those handshake buzzers. My body felt as though*

	it was vibrating at 50Hz. They realised afterwards that that was a sign of my kidneys failing. They had to stop treatment on that particular occasion. It made me feel really poorly for some time afterwards". o Cidofovir ▪ Cidofovir has also been shown to cause significant side-effects in patients, with patients claiming that experiencing cidofovir was worse than foscarnet, despite only being a one-day treatment compared to the nine days required for foscarnet. ▪ The cidofovir caused such eye inflammation in one patient that when healthcare professionals tried to give them a second dose, the patient told the HCPs 'you're not taking my vision away as well, it's not happening'. **Quality of life** • All of the intravenous treatments (ganciclovir, foscarnet, and cidofovir) mean that patients are required to spend time in hospital, either on a day basis or as an in-patient. This had a significant effect on patients' ability to have a normal life, including working and having a social life. • A patient with an 18-month-old son at the time of their transplant had never been away from him until this point. *"I went from never being away from him to him not recognising me. When I finally did home, I thought we would be able to build our relationship back up, and then I was told that I had to go back to hospital and I was absolutely crushed."* • Many patients described how problems with their well-being were exacerbated by the treatments for CMV reactivation and their side effects. • In order to treat viral infections, the immune system has to be improved. However, the immune system may improve to the point where graft versus host disease (GvHD) starts to occur. In order to manage GvHD, the immune system is heavily suppressed, leaving patients susceptible to viruses, including CMV. This balancing act can leave patients on a 'see-saw', rebounding from one problem to the other, having a significant effect on a patient's mental health and positive outlook. o *"It's cycle that I want to get off. It makes me feel like I'm a stack of dominos. You touch one thing and it takes something else down. It's a roundabout now I've been on for at least a year and a half longer than anticipated."*

8. Is there an unmet need for patients with this condition?	• Prophylactic treatments and pre-emptive therapy are the two key strategies used for prevention of CMV disease in transplant recipients. Pre-emptive therapy - treatment of patients with evidence of CMV replication in the blood - is the strategy of choice for HSCT recipients due prevent progression to CMV disease. • There are no medicines licensed in the UK for prevention of CMV reactivation or disease in patients who have received an allogeneic HSCT. • The use of currently available CMV antiviral medicines for recipients of HSCTs are linked to higher incidence of infection due to their myelosuppressive effect. • There is an unmet need for an effective and safe CMV prophylactic medical technology for prophylaxis in HSCT recipients.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**How it is taken** • Patients consistently told us that being able to manage their condition at home had a significant effect on their daily life and their mental health. This could also be discerned as all patients who were prescribed intravenous treatments found it frustrating to have to return to hospital for treatment or extend their stay as a consequence of CMV reactivation. • Therefore, patients would welcome the fact that letermovir has the option to be taken orally, and therefore managed by the patient in conjunction with a blood test schedule at their blood clinic. o *"I would rather be at home or at work than stuck in a hospital bed, or in a day case chair with a cannula stuck in me and dripped for 5 hours at a time."* o *"**...**when I'm on valganciclovir which is annoying, when you you're sleeping and in the middle of the night you get incredibly painful leg cramps. I can deal with it because you can walk around and go back to bed, it's not like a hospital thing."* o *"The oral tablets which could be taken at home were so much better for the patient and family."* o *"A medicine that would reduce instances of reactivation would be a massive win-win for hospital staff run off their feet and patients as vulnerable as I was, and also free up scarce hospital beds".* **Toxicity** • Patients told us that if this drug has a smaller toxicity and side-effect profile, then it would be a significant improvement from other drugs used to treat CMV.

	○ *"A kinder treatment is definitely needed; after going through chemo and total body irradiation the treatment for CMV was by far the worst part."* ○ *"If there is any kinder medication that would help in the long recovery it should be available without delay".* ○ *"Any drug that would improve the life of a transplant patient living with the effect or threat of CMV reactivation would improve their quality of life significantly and aid their recovery from the transplant enormously."*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	• Patients told us that having to make regular trips to the blood clinic when taking oral medication at home had a significant effect on their quality of life. For some, being at risk of CMV meant that they had to visit the blood clinic three times each week, and would have to arrive before 9:00am and be required to wait then entire day to get the results before being cleared to go home. However, this was still deemed preferable to intravenous treatments which require regular attendance at hospital as a day patient.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	• In western countries infection rates increase with age, such that approximately 70% of individuals over the age of 60 years are CMV-seropositive.
Equality	
12. Are there any potential equality issues that should be	• We have not identified any equality issues

taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	• The costs of treating someone after having discovered CMV reactivation is significant. Often, this requires extended in-patient stays in hospital (some patients told us that they had more than 30 days in hospital over several reactivations of CMV), several rounds of expensive medicines as well as follow up care and support. Use of prophylaxis for CMV reactivation could therefore reduce the overall cost of treating a stem cell transplant patient.
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission: • There is currently no authorised medical technology for CMV prophylaxis directly following allogeneic stem cell transplant. • Current treatments for CMV reactivation have serious side effects which cause severe problems for patients. • CMV reactivation affects quality of life and causes patients to return to hospital (as an outpatient or an in-patient), and can delay or prevent their return to an active life. • The experience of CMV reactivation, and its associated effects, can have a significant psychological impact for both patients and their families. • • Patients and their families would therefore benefit significantly from a treatment which could prevent CMV reactivation.	

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists/British Society for Haematology**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**British Society of Haematology, Royal College of Pathologists**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Prophylaxis against viral reactivation in CMV seropositive patients following allogeneic stem cell transplantation

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in detectable viraemia requiring pre-emptive intervention with currently available antiviral drugs
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Viral reactivation is frequent (60-80%) in CMV seropositive patients, rates dependent on transplant conditioning platform (higher end of this range with T cell depletion as widely practiced in the UK). Drugs used to manage reactivation have significant toxicities (myelosuppression, renal impairment), and CMV disease (end organ damage), though rare, has a significant associated mortality.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	There are no effective, non-toxic prophylactics. Therefore, current management is surveillance monitoring for viral reactivation (generally by PCR on blood), with pre-emptive intervention when viral DNA is detected using either ganciclovir, valganciclovir, or foscarnet (cidofovir is active but generally reserved for second line therapy).

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BCSH guidelines: Emery V, Zuckermann M, Jackson G, Aitken C, Osman H, Pagliuca A, Potter M, **Peggs** Clark A. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. ***Br J Haemato*** 2013 Jul; 162(1):25-39
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway of care is pretty standard in terms of surveillance, though frequency of monitoring varies. Intervention thresholds also vary slightly according to viral load measures, reflecting prior lack of standardisation of quantification assays. Similar use of foscarnet and either ganciclovir or valganciclovir (some centres prefer the oral formulation, others have concerns re bio-availability).
• What impact would the technology have on the current pathway of care?	Presumed prophylaxis of all seropositive cases. Monitoring would remain the same, as would intervention strategies if virus were detected, but likely significant reduction in detectable reactivation rates as per the phase III trial
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Currently available drugs cannot be used as prophylactics because of toxicity. It is not currently available for use in the NHS.
• How does healthcare resource use differ	There is no current prophylaxis versus CMV, so this is an additional resource. However, this is offset by predicted reduction in requirement for pre-emptive intervention

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	CMV seropositive patients undergoing allogeneic stem cell tarnsplants
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, I expect at least a 30% reduction in viral reactivation rates (probably greater in the UK because of widespread use of T cell depletion which results in much higher reactivation rates than documented in the control arm of the Phase III trial performed mainly in the US)
• Do you expect the technology to increase length of life more than current care?	Very difficult to judge. The Phase III study indicated a possible survival advantage. This is plausible given the link of CMV seropositivity with inferior outcomes post allograft, but is not definitively proven in the trial.
• Do you expect the technology to increase health-related quality of	Yes. The drug has a very good toxicity profile and is well tolerated by virtually all patients. Given the high reactivation rates in the UK, most CMV seropositive patients receive pre-emptive therapy, which

life more than current care?	significantly impacts QoL, and a reduction in the requirement for this would give an overall benefit to the technology
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	n/a
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Oral medication. No current standard in this indication. So very easy to introduce, and no practical issues re increased testing or monitoring. It may even be possible to curtail surveillance monitoring, though this is currently unclear.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing. I would advocate using in all CMV seropositive allograft recipients, stopping either at day 100 as per the trial, or on failure and emergence of viral DNAemia (switch to pre-emptive therapy).
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No – assuming these calculations incorporate a measure of reduced need for pre-emptive intervention.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Yes. It will likely reduce exposure to the more toxic antivirals we use pre-emptively, improving QoL, and reducing the need for hospital readmission.

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, there are no other prophylactic agents currently
• Does the use of the technology address any particular unmet need of the patient population?	Yes, as above – a universal effective, non-toxic prophylactic would be a major change to current practice addressing an otherwise unmet need
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Remarkably good toxicity profile. Unlikely to be any significant adverse impact.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, in terms of CMV management. As the trial included only small numbers of T deplete transplants where reactivation rates are higher, it is plausible/likely that clinical benefit in the UK will be even greater than demonstrated in the trial

• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	Reduced need for pre-emptive therapy. If the survival advantage is real then this is also a major outcome improval
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. How do data on real-world experience compare with the trial data?	There is no real world data, as the drug has not been available to us on NP programmes.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	n/a
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Letermovir represents the first viable oral prophylactic for the prevention of CMV reactivation following allogeneic haematopoietic stem cell transplantation
- The phase III data confirms it is well tolerated and reduces CMV reactivation rates significantly
- This reduces the need for exposure to pre-emptive treatment, which has significant toxicities, and can be difficult to administer/require re-hospitalisation
- A survival benefit in the phase III trial is plausible, though not definitively proven
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Robert Danby**
2. Name of organisation	**Anthony Nolan and Oxford University Hospitals NHS Foundation Trust**

3. Job title or position	**Consultant Haematologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent Cytomegalovirus (CMV) reactivation/infection following allogeneic haematopoietic cell transplantation in recipients (adults) who are CMV seropositive at transplant.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction of CMV viraemia requiring pre-emptive treatment (>= 20% reduction) Prevention of CMV disease (symptoms or signs of compatible with end organ damage in the presence of detectable CMV)

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes because: a. Current CMV prophylaxis strategies in allogeneic HSCT are - Poorly effective (e.g. Aciclovir 800mg qds) - Associated with significant toxicity including myelosuppression and renal toxicity (Ganciclovir). b. CMV reactivation/viraemia and CMV disease are associated with increased morbidity and non-relapse mortality. c. Pre-emptive therapy following CMV reactivation/viraemia AND/OR therapy for CMV disease (i.e. Ganciclovir, Valganciclovir, Foscarnet or Cidofovir) are associated with significant adverse effects (e.g. myelosuppression/renal dysfunction) and morbidity. d. (Pre-emptive) therapy for CMV is associated with considerable reduction in patient quality of life due to increased visits to hospital (out-patient and in-patient), more regular blood tests and monitoring,
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	CMV Prophylaxis: - High dose Aciclovir (Valaciclovir) e.g. 800mg qds - Some UK centres/regimens may use Ganciclovir/Valganciclovir in high risk cases - Early detection/monitoring of CMV viraemia and pre-emptive therapy

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	**2008 European Conference on Infections in Leukemia (ECIL) guideline** [Ljungman P, de la Camara R, Cordonnier C, Einsele H, Engelhard D, Reusser P, et al. Management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT. Bone Marrow Transplant. 2008;42(4):227–40] **2009 international consensus guidelines [**Zaia J, Baden L, Boeckh MJ, Chakrabarti S, Einsele H, Ljungman P, et al. Viral disease prevention after hematopoietic cell transplantation. Bone Marrow Transplant. 2009;44(8):471–82.] **2013 BSH/BSBMT Guidelines:** [Emery V, Zuckerman M, Jackson G et al. Management of cytomegalovirus infection in haematopoietic stem cell transplantation. Br J Haematol. 2013 Jul;162 (1):25-39.]
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes although individual transplant centres/clinicians may vary their prophylaxis regimen depending on the patient's individual risk of CMV reactivation/disease. For example, the risk of CMV reactivation depends on the patient and donor CMV serostatus, donor type (increased with mismatched donors/cord blood/haploidentical); transplant conditioning regimen and use of T-cell depletion (increased with T-cell depletion), GvHD prophylaxis/treatment (increased with high dose steroids).
• What impact would the technology have on the current pathway of care?	Letermovir would replace current CMV prophylaxis therapy (Aciclovir/Valaciclovir/Ganciclovir) for those patients who are CMV seropositive at transplant. Early detection/monitoring of CMV viraemia and pre-emptive therapy would continue as per current pathway of care. Some transplant centres may still use low dose Aciclovir (200mg tds) for HSV/VZV prophylaxis.

	Reduced incidence of CMV reactivation/disease with Letermovir would reduce the number of patients requiring (pre-emptive) therapy for CMV.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes for CMV seropositive patients (Letermovir to replace current prophylaxis e.g. Aciclovir). Monitoring for CMV viraemia using PCR will continue as per current practice However, as I understand the license does cover CMV seronegative patients receiving an allogeneic stem cell transplant from CMV seropositive donors, who also have a risk of CMV viraemia/infection. Therefore, these patients will continue on current CMV prophylaxis pathways.
• How does healthcare resource use differ between the technology and current care?	Increased direct costs for Letermovir compared to current care (What is the price of Letermovir?) The same healthcare resources are needed for Letermovir prescribing and CMV monitoring as per current pathway. With a lower rate of CMV reactivation/infection, however, there will be a reduction on healthcare resources required for the treatment of CMV reactivation/infection i.e. lower treatment costs, fewer blood tests, reduced outpatient and inpatient visits.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary/tertiary care (allogeneic transplant centres) and specialist transplant clinic; in-patient and out-patient
• What investment is needed to introduce the technology? (For	No significant investment required other than funding cost of Letermovir. Will require limited training for current staff (transplant teams).

example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, reduction in CMV reactivation, leading to fewer patients requiring (pre-emptive) treatment for CMV viraemia and/or CMV disease. (Possible) reduction in non-relapse mortality.
• Do you expect the technology to increase length of life more than current care?	Yes as CMV reactivation is associated with increased non-relapse mortality. (For certain diseases, e.g. AML, CMV reactivation *may* be associated with a small reduction in relapse risk, although this remains uncertain. Therefore, the benefit in non-relapse mortality is likely to offset any increased risk of relapse. Of note, an increased risk of relapse was not demonstrated in the clinical trials of Letermovir)
• Do you expect the technology to increase health-related quality of life more than current care?	Yes: reducing incidence of CMV reactivation will reduce the need for CMV treatment which is associated with increased patient morbidity, non-relapse mortality and reduced quality of life.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective for those patients (as a group) with high risk of CMV reactivation i.e. CMV seropositive patients receiving a T-cell depleted allogeneic stem cell transplant, haploidentical or cord blood transplant.

The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No major difference for patients of health care workers. Will need to monitor for side effects as limited use/data so far. Possible higher rate of cardiac events (tachycardia) compared to placaebo. Will need to monitor for potential drug interactions. Letermovir is moderate inhibitor of CYP3A and an inhibitor of OATP1B1/3 transporters. Letermovir will need dose reduction for those patients on Ciclosporin (commonly used post-allogeneic HSCT)
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting: CMV seropositive patients receiving an allogeneic stem cell transplant, between day 0 and day 28 of transplant, Stopping: Day 100 (Unclear if can be continued beyond 100 days in those patients that remain at high risk of CMV reactivation beyond that time point e.g. poor T cell reconstitution).

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Reduction in hospital visits/admissions due to lower requirement for CMV treatment (Ganciclovir/Foscarnet/Cidofovir)
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, clinical data shows a significant reduction in CMV reactivation/infection without high risk of adverse events, in particular myelotoxicity, graft failure and renal toxicity
• Is the technology a 'step-change' in the management of the condition?	Yes

• Does the use of the technology address any particular unmet need of the patient population?	Yes, how to effectively reduce CMV reactivation/viraemia without using therapies that have major adverse effects.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	From the published data so far, it would appear that Letermovir is reasonably safe with no increased major adverse events compared to placebo. Possibly higher risk of nausea/vomiting/oedema. Possibly higher risk of cardiac events (tachycardia, atrial fibrillation) which may need further monitoring/investigation.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	In general, Yes, However, the use of Alemtuzumab in the study patients (Marty et al 2017) was only 3.2% in the Letermovir group and 5.7% in the placaebo group (approx. 30% of patients had ATG). In the UK, although transplant conditioning regimens vary from centre to centre, the use of Alemtuzumab is generally much higher. The use of T-cell depletion (including Alemtuzumab) is associated with a higher risk of CMV reactivation and, therefore, the baseline rate of CV reactivation in the UK may be higher than in the published clinical trials.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction in CMV infection (defined as CMV disease or CMV viraemia leading to pre-emptive treatment) at week 24. Reduction in all-cause mortality at week 24 (lower non-relapse mortality) Similar adverse event profile to placaebo, with no significant negative effect of engraftment
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No long term data as patients only followed to week 48.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Adverse effects - not to my knowledge. Possible iCYP2C9/19-mediated drug-drug interactions (Posaconazole, Voriconazole)
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	Similar data. In our transplant centre, approx. 50%of our patients had CMV reactivation (>10e3 copies/ml) with current CMV prophylaxis (Aciclovir) i.e. similar to the placebo group in published data.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not to my knowledge
22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23. Are comparators aciclovir and valaciclovir considered to be established clinical practice	Yes for the prophylaxis of CMV reactivation/infection in allogeneic HSCT

in the NHS for treating adults with sero-positive cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Letermovir is a novel therapy to reduce risk CMV infection (CMV viraemia and/or disease) following allogeneic HSCT.
- Letermovir should reduce to need for (pre-emptive) CMV therapy which is associated with significant toxicity, morbidity, reduced quality of life and increased treatment costs.
- Letermovir could improve non-relapse mortality
- Letermovir appears safe with no increased major adverse events compared to placebo.
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Steve Rothberg**
2. Are you (please tick all that apply):	✓ a patient with the condition? ☐ a carer of a patient with the condition?

	☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Anthony Nolan
4. Did your nominating organisation submit a submission?	✓ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	✓ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	I will add to the statement made by Anthony Nolan
7. How did you gather the information included in your statement? (please tick all that apply)	✓ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was diagnosed with AML on 12 March 2009. I competed four cycles of chemotherapy over the next 5 months and was discharged In August 2009. In March 2010, my relapse was diagnosed and I was advised that a transplant was needed to save my life. I had my transplant (matched unrelated donor) on 17 September 2010. I was discharged on 6 October 2010, by which time I had spent 150 nights in hospital since my original diagnosis 17 months earlier. A week later I was advised that my CMV had reactivated. My CMV reactivated 25 days after my transplant. Unlike many who suffer CMV reactivation, I did not experience any additional physical symptoms from CMV (or side-effects of the medicines) beyond those symptoms associated with being just 4 weeks since transplant. In terms of mental wellbeing, the CMV reactivation was a terrible setback for me, my wife (my carer) and my daughters (at that point aged 13 and

	11). I had been progressing well since transplant but after so much treatment over such a long period, any negative news comes as a bitter blow. Ten days later (35 days after transplant) my CMV level was back under control but 5 days after that (40 days after transplant) the levels were really high again, even higher than during the initial reactivation. Practically, this meant readmission to hospital for IV treatment. Emotionally, my family and I started to feel as though my CMV might prove to be an insurmountable problem. After the failure of my first round of treatment, the fear that the transplant would also not succeed was inescapable.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	For my first reactivation, I took a course of Valganciclovir tablets at home. When this treatment failed to control my CMV, I was prescribed a one-week course of IV Ganciclovir, which also meant readmission to hospital. I was also extremely distressed about the prospect of a return to hospital. With my immunity so compromised by transplant, I had decided to isolate myself from everybody except my wife and daughters. I lived this way for 6 months because the risk of catching an infection was something that terrified me but this risk was also something that I felt I could mitigate by self-imposed isolation. Clinic trips terrified me. I wore a mask and avoided touching any surfaces. Because my CMV reactivated so soon after transplant, my immunity was still extremely compromised, even more so by my initial course of valganciclovir. The need to return to hospital, without the special isolation arrangement in the transplant unit, was therefore a very stressful turn of events for me. The reality was even worse than I feared. The familiar pressure on beds meant that there was no haematology bed for me and I was an ‘outlier’ on a ward that was not specialist in my condition. I went all day without my regular medicines. Ironically, the full set of medicines that I brought in from home (about 20 doses a day at the time) had to be locked in my cupboard while the same medicines were re-prescribed by the hospital. Staff are so busy and the consequence for me was this chaotic readmission. To make matters worse, I initially had to share toilet facilities. It’s hard to convey just how frightening this was for a vulnerable immuno-suppressed patient.

	After a couple of days, I was moved to a side-room which was an immense relief for me but it meant that a precious side room was now occupied by an immuno-compromised patient whose active treatment was for just 3 hours a day. In the end, my CMV levels dropped and, though the harm to my mental wellbeing (and that of my carer and daughters) was significant, I was lucky enough not to contract the infection that could have severely complicated my recovery or even cost me my life.
10. Is there an unmet need for patients with this condition?	Current CMV treatments are administered only after reactivation and, though I was lucky and did not experience side-effects of the drugs, patients report unpleasant side-effects of all the medicines available with increasing severity if the medicines generally used first (valganciclovir and ganciclovir) are not successful. These drugs are, I understand, followed by foscarnet and cidofovir and these can have very severe side-effects. After the first line treatment (valganciclovir), all other medicines are delivered IV and require readmission to hospital. A high proportion of CMV positive transplant recipients will have their CMV reactivate. The unmet need is for a low toxicity prophylactic that is taken by all at-risk patients to reduce the chance of reactivation in the first place.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	A new low toxicity prophylactic that is taken by all at-risk patients to reduce the chance of reactivation would eliminate the consequences for physical and mental (for patients and their families) wellbeing described above. Potentially, there would also be benefit through reduced hospital admissions to costs and bed (side-room) availability.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	From my perspective as a patient (not a clinician) and, in particular, as a patient whose CMV reactivated, I am not aware of disadvantages

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	CMV positive stem cell transplant patients such as myself will benefit the most
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	

Key messages
16. In up to 5 bullet points, please summarise the key messages of your statement: • There is currently no authorised medical technology for CMV prophylaxis directly following allogeneic stem cell transplant. • Current treatments for CMV reactivation have serious side effects which cause severe problems for patients. • CMV reactivation affects quality of life and causes patients to return to hospital without the protections against infection associated with a transplant unit • The experience of CMV reactivation, and its associated effects, can have a significant psychological impact for both patients and their families. • Patients and their families would therefore benefit significantly from a treatment which could prevent CMV reactivation..

Thank you for your time.

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

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- Your response should not be longer than 10 pages.

About you	
1. Your name	**Malcolm Qualie**
2. Name of organisation	**NHS England**

3. Job title or position	**Pharmacy Lead, Specialised Commissioning**
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are two main potential strategies for managing CMV infection: 1) Prophylaxis with antivirals drugs and 2) Pre-emptive therapy (PET), the practice of active surveillance for viral replication and initiating treatment with anti- CMV agents when CMV viremia is detected. In general, Trusts follow their own internal guidelines with respect to the above. However, toxicities associated with currently available therapies limit the effectiveness of prophylaxis. Ganciclovir/ valganciclovir are myelosuppressive. Early studies of prophylaxis showed reduced rates of CMV disease, but no improvement in mortality due to increased incidences of both bacterial and fungal infection, presumably secondary to induced cytopenias. Foscarnet and cidofovir are nephrotoxic, and no prospective prophylaxis studies have been reported. Therefore, the current standard approach in Europe is to reduce CMV-related morbidity and mortality post-HSCT transplant by early initiation of PET against CMV. Ganciclovir or foscarnet are both recommended dependent on bone marrow reserve and renal function. Valganciclovir is an oral alternative if there are no

	issues with absorption. The pre-emptive strategy limits unnecessary exposure to these agents, helping to limit their toxicities.
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Unknown but given local Trusts tend to use their own internal guidelines the choice of treatment is likely to differ within Trusts.
7. What impact would the technology have on the current pathway of care?	Letermovir is a novel inhibitor of CMV viral terminase. It specifically acts on this target and there is no known cross-resistance between letermovir and currently licensed medicinal products for treatment of CMV. Letermovir is available in two formulations, oral and IV. It is administered as an oral formulation unless the patient cannot tolerate oral medications. Letermovir has demonstrated superior efficacy over placebo in prevention of clinically significant CMV infection through Week 24 post-transplant, during both the 100 day treatment period and the washout period thereafter. In addition, the safety profile (unlike current options) of letermovir is comparable to placebo. It would therefore become the 1st line option for prophylaxis if approved given the issues with current products used for prophylaxis. It would potentially reduce the need for PET.

The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	It is currently not used within the NHS in England
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes it will be delivered in secondary care units who undertake allogenic stem cell transplants
• How does healthcare resource use differ between the technology and current care?	The introduction of letermovir will change the current pathway of care and therefore the NHS may incur an additional upfront cost compared to the current treatment pathway particularly as a number of the current treatments are generic. However, due to its safety and efficacy benefits over current treatment practice there will be a potential reduction in costs associated with CMV disease including pre-emptive therapy treatment and administrative costs, G-CSF treatment costs, GvHD treatment costs, and hospitalisations.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In Trusts undertaking allogenic stem cell transplants
• What investment is needed to introduce the technology? (For	There should be no additional infrastructure costs required. However, it is anticipated that the drug costs may increase

example, for facilities, equipment, or training.)	
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Unknown
10. What is the outcome of any evaluations or audits of the use of the technology?	No audits have been undertaken
Equality	
11a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
11b. Consider whether these issues are different from issues with current care and why.	n/a

Topic-specific questions	
12. Are comparators aciclovir and valaciclovir considered to be established clinical practice in the NHS for treating adults with sero-positive cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant?	See 5.

Thank you for your time.

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Evidence Review Group's Report

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

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

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Declared competing interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

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List of abbreviations

AE	Adverse event
ALL	Acute Lymphocytic Leukaemia
AML	Acute Myeloblastic Leukaemia
ASaT	All subjects as treated
AUC	Area under the curve
BID	Bis in die (twice daily)
BNF	British national formulary
BSBMT	British Society of Blood and Marrow Transplantation
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CML	Chronic myeloid leukaemia
CMV	Cytomegalovirus
CS	Company submission
CsA	Ciclosporin A
CSR	Clinical study report
D+	CMV Seropositive Donor
DAO	Data as observed
DFS	Disease-free survival
EMA	European Medicines Agency
EQ-5D	EuroQol-5 dimensions
ERG	Evidence Review Group
FACT-BMT	Functional Assessment of Cancer Therapy and Bone Marrow Transplantation
FAS	Full analysis set
FDA	US Food and Drug Administration
GvHD	Graft versus Host Disease
HLA	Human leukocyte antigen

HMRN	Haematological Malignancy Research Network
HRQoL	Health related quality of Life
Allo-HSCT	Allogeneic haematopoietic stem cell transplant
HSV	Herpes simplex virus
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IV	Intravenous
K-M	Kaplan-Meier
MAR	Missing-at-random
MDS	Myelodysplastic syndromes
MNAR	Missing-not-at-random
NC=F	Non-completion = failure
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PAS	Patient access scheme
PET	Pre-emptive therapy
PFCs	Points for Clarification
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
qPCR	Quantitative polymerase chain reaction
R+	CMV seropositive transplant recipient
SAE	Serious adverse event
SLR	Systematic literature review
SmPC	EMA Summary of Product Characteristics
SMR	Standardised mortality ratio
SoC	Standard of care
WTP	Willingness-to-pay

1 Summary

1.1 Critique of the decision problem in the company's submission

The company's submission (CS) considered the population specified in the final NICE scope, i.e. adults with seropositive cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant. The licensed therapeutic indication is as follows; 'PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT)'. There is some lack of clarity regarding whether patients with detectable CMV DNA but a low viral load would be initiated on letermovir in clinical practice.

The intervention specified in the final NICE scope and the CS is letermovir. The licence for letermovir states that prophylaxis should be started after HSCT, between the day of transplant and no later than 28 days post-transplant. It states that prophylaxis with letermovir should continue through 100 days post-transplant. Letermovir can be started before or after engraftment occurs.

The recommended dosage of letermovir is one 480 mg tablet once daily. The dosage of letermovir should be reduced to 240 mg once daily when co-administered with ciclosporin A (CsA). Letermovir is also available as concentrate for solution for intravenous (IV) infusion (240 mg and 480 mg), and the oral and IV formulations may be used interchangeably at the discretion of the physician, with no dose adjustment necessary.

The NICE final scope listed aciclovir and valaciclovir as well as 'no preventative treatment' as comparators; however, it noted that neither active drug had current marketing authorisation for the relevant indication. The CS therefore included only 'no prophylaxis against CMV reactivation', i.e. no active comparators were included. The ERG and the clinical advisors to the ERG agreed that aciclovir and valaciclovir are not relevant comparators for letermovir in this appraisal.

The outcomes listed in the company's decision problem are based on the outcomes reported in the pivotal Phase III trial (PN001). They adequately reflect those listed in NICE's final scope. The ERG noted that criteria for initiation of PET, and therefore the definition of 'clinically significant CMV infection' differed between the trial and NHS clinical practice.

The NICE final scope specified that people at high risk of CMV reactivation should be considered as a subgroup (should the evidence allow). This subgroup was included in the CS together with analyses based on risk categories for CMV reactivation, patient characteristics, and conditioning and concomitant immunosuppressive regimen as per study protocol.

1.2 Other relevant factors

A Patient Access Scheme was included in the submission – [redacted].

1.3 Summary of clinical effectiveness evidence submitted by the company

PN001 was a phase III randomised, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of letermovir compared to placebo for the prevention of clinically-significant human CMV infection in adult, R+ recipients of an allogeneic HSCT. Adult patients with documented seropositivity for CMV but no detectable CMV DNA at baseline, within 28 days of a first HSCT were randomised in a 2:1 ratio to receive either letermovir at a dose of 480 mg once daily (adjusted to 240 mg when co-administered with CsA), or placebo. Study medication was continued through to week 14 (~100 days). Randomization was stratified by study centre and high or low risk for CMV reactivation

Patients were monitored through to week 24 post-transplant for the primary efficacy endpoint. Patients who completed the trial subsequently entered a follow-up phase from week 24 to week 48 post-transplant to collect data related to CMV disease, health outcomes, and quality of life (QoL) measures.

The primary outcome of trial PN001 was the proportion of patients with clinically-significant CMV infection through Week 24 (~ 6 months) post-transplant, defined as the occurrence of either one of the following outcomes:

- Initiation of anti-CMV pre-emptive therapy based on documented CMV viraemia (as measured by the central laboratory) and the clinical condition of the patient. Initiation of pre-emptive therapy in this study referred to the practice of initiating therapy with ganciclovir, valganciclovir, foscarnet and/or cidofovir

OR

- Onset of CMV end-organ disease.

The majority of patients were male (327/565 [58%]), white (462/565 [82%]), and with a mean age of around 51 years old. At baseline 31% of patients were at high risk for reactivation and 52% were receiving concomitant CsA. The most common primary reasons for transplant were acute myeloid leukaemia (AML) (38%), myelodysplastic syndrome (MDS) (17%), and lymphoma (13%). No information was available regarding the line of therapy. The majority of patients had received

transplants using peripheral blood stem cells (73%). The median time to initiation of the study drug was 9 days after transplant.

The results of the primary and sensitivity analyses demonstrate that letermovir significantly reduces the rate of clinically significant CMV infection through 24 weeks. The proportion of patients who failed prophylaxis by Week 24 i.e. had clinically significant CMV infection (NC=F; FAS population) was 122/325 (37.5%) in the letermovir group vs 103/170 (60.6%) in those receiving placebo, with a stratum-adjusted treatment difference of (letermovir-placebo, 95% CI) -23.5 (-32.5 to -14.6) and one sided p-value of <0.0001. Most prophylaxis failures initiated PET based on documented CMV viraemia (52/325 [16.0%] versus 103/170 [60.6%]); very few patients developed CMV end-organ disease (5/325 [1.5%] vs 3/170 [1.8%]).

The ERG noted that patients who tested positive for CMV DNA on Day 1 (who were protocol violators and therefore not included in the primary analysis) also benefited from letermovir treatment (Clinically significant CMV infection by Week 24 with NC=F: 26.1% (-45.9%, -6.3%), one sided p-value <0.0048).

Subgroup analyses of the primary outcome showed that the treatment effect consistently favoured letermovir across subgroups based on patient baseline, epidemiological, and clinical characteristics. The ERG notes that in some subgroups the effect size is numerically different from that of the whole trial population: higher in high-risk patients; donor mismatch subgroups; haploidentical donors; female subgroups; and with use of non-myeloablative conditioning regimens; and was lower in Asian race; Hispanic or Latino ethnicity; US patients; and use of tacrolimus as immunosuppressant. No tests for interaction were conducted to evaluate the statistical significance of these subgroup differences.

The time to onset of clinically-significant CMV infection through Week 24 post-transplant and time to initiation of PET through Week 24 post-transplant were summarised using Kaplan-Meier (K-M) plots. Given the very small number of CMV end-organ disease events it is not surprising that the time to clinically-significant CMV infection curve and the time to initiation of PET curves are very similar.

At Week 24 post-transplant, the event rate (95% CI) for clinically-significant CMV infection was 18.9% (14.4%, 23.5%) in the letermovir group versus 44.3% (36.4%, 52.1%) in the placebo group groups (nominal two-sided p<0.001), after controlling for stratification of high and low risk of CMV end-organ disease at baseline) (hazard ratio (95% CI) of 0.29 (0.21, 0.42) for letermovir vs placebo).

There was a large separation between the curves from Day 0 to Week 14 while patients were on study drug. Once medication was discontinued at Week 14, there was a small rebound effect in the

letermovir group. Factors associated with CMV DNAemia after cessation of letermovir prophylaxis up to Week 24 post-transplant included high baseline risk for CMV reactivation, GvHD, and corticosteroid use.

All-cause mortality was lower in the letermovir group than in the placebo group at Week 24 (using most complete data letermovir 12.1% (95% CI 8.6, 15.7) compared with placebo 17.2% (95% CI 11.5, 22.9) (Stratified 2-sided p-value for difference= 0.0401). However, at Week 48 the difference was not statistically significant (letermovir 23.8%; 95% CI 19.1, 28.5 vs placebo 27.6%; 20.8, 34.4, p= 0.2117).

When stratified by prior CMV infection in an additional ad hoc analysis there was a lower mortality rate through Week 48 in the letermovir group (9/57 [15.8%]) versus the placebo group (22/71 [31.0%]) among patients with clinically-significant CMV infection through Week 24; and similar mortality rates between the letermovir (52/268 [19.4%]) and placebo (18/99 [18.2%]) groups in patients without clinically-significant CMV infection through Week 24. The ERG suggests that the results indicate that letermovir may have some impact on additional CMV-related mortality, despite not completely preventing CMV reactivation.

[redacted].

Health related quality of life was assessed using two validated tools of patient-reported outcomes (PROs) - the EQ-5D (Version 3L) and the FACT-BMT (Version 4) - at the time of randomisation, Week 14, Week 24, and Week 48 post-transplant. An assessment was also conducted upon CMV infection onset or at the early discontinuation visit, if applicable. [redacted].

The results for other exploratory endpoints (GvHD, re-hospitalisation and opportunistic infections) indicate that bacterial/fungal infections through Week 14 and through Week 24 were numerically slightly higher in letermovir group compared with placebo group. GvHD, re-hospitalisation, re-

hospitalisation for CMV infection, and documented CMV viraemia through Week 14 and through Week 24 were all numerically lower in letermovir group compared with placebo group. The result for documented CMV viraemia favoured letermovir by a large margin.

The results of the Phase II trial (Chemaly 2014[1] whilst not directly comparable with the results from PN001, are generally supportive.

Evidence for the adverse effects of letermovir presented in the CS was derived solely from the ASaT population (n=565) of trial PN001. The AEs reported during the treatment phase of trial PN001 are the most directly relevant, though those reported after the withdrawal of letermovir or placebo may be contaminated by toxic pre-emptive therapies. Not surprisingly given the underlying indications, almost all patients experienced at least one AE, but overall, the AE profile was similar in the letermovir and placebo groups, with the exception of AEs leading to discontinuation of study medication (19.3% letermovir; 51.0% placebo), reflecting the higher proportion of patients discontinuing due to CMV infection in the placebo group (6.2% in letermovir group compared to 39.1% in the placebo group).

The incidences of the following treatment phase AEs were significantly higher in the letermovir group compared to the placebo group: Cardiac Disorders (12.6% letermovir vs.6.3% placebo; 6.4% difference [95% CI: 1.1, 11.0]) and Ear and Labyrinth Disorders SOC (4.6% letermovir vs. 1.0% placebo; 3.5% difference [95% CI: 0.5, 6.3]), and AEs of myalgia (5.1% letermovir vs. 1.6% placebo; 3.5% difference (95% CI: 0.2%, 6.5%), hyperkalaemia (7.2% letermovir vs. 2.1% placebo; 5.2% difference (95% CI: 1.4%, 8.6%), and dyspnoea (8.0% letermovir vs. 3.1% placebo; 4.9% difference (95% CI: 0.8%, 8.6%).

Overall, the proportions of patients with SAEs reported during the Treatment Phase were similar across treatment groups (44.2% letermovir vs. 46.9% placebo; difference -2.6 [95% CI -11.3%, 6.0%]).

The results of the comparison between letermovir and placebo for adverse events through Week 24 through Week 48 were similar to those in the treatment phase. There were no additional reports of drug-related AEs or SAEs, indicating that there were no delayed AEs associated with letermovir. However, these results are difficult to interpret due to the toxicities associated with various PET regimens.

[redacted]

[redacted].

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Trial design and patient characteristics

The PN001 trial was of good quality (low risk of bias) but had some deficiencies in the trial design which make it sub-optimal for addressing the research question and understanding the implications for clinical practice.

- The main limitation is the fixed treatment duration of 100 days, which did not allow prophylaxis to continue until each individual patient was considered at low risk of CMV reactivation. Therefore the trial will not have collected the best data to evaluate the efficacy of letermovir to prevent infection and reduce mortality.
- The lack of follow-up of the occurrence of clinically significant CMV infection beyond Week 24 also limits the information collected on the effect of letermovir.
- While the population is appropriate, the requirement for no detectable CMV DNA at baseline is of uncertain relevance to clinical practice.

In addition, there were some additional issues of generalisability of the trial to NHS practice which may impact the expected treatment efficacy.

- The clinical advisors to the ERG believed that whilst the population in PN001 was not a perfect match to patients in the NHS, it could be considered to be essentially generalisable, despite only 12 patients (AsAT population – 6 in letermovir arm and 6 in placebo) recruited to the trial from UK centres. The UK patient population might be younger, more white, more male, and include more matched unrelated patients than that in the trial.
- The prevalence and intensity of T-cell depletion differed markedly between the trial and UK practice, with only 4% of trial patients receiving the profoundly T-cell depleting agent alemtuzumab versus ~85% in some UK centres. As the incidence of CMV reactivation is substantially higher in T-cell depleted patients, the trial likely underestimates CMV reactivation rates, and overestimates incidence of GvHD, which is suppressed by T-cell depletion.
- The prevalence of CsA use also differed significantly between the trial and NHS clinical practice. While the ERG's clinical advisors suggested 90% of patients would receive CsA-based immunosuppressive therapy, only 51.7% of letermovir patients (ASaT population) in the trial received CsA, with the remainder given tacrolimus-based or other immunosuppressive regimens.

- The start of prophylaxis in the trial was delayed, which is unlikely to occur in practice. Thus the duration of treatment in the trial and model (69.4 days, ASaT population) is probably shorter than expected in clinical practice, and may have led to an underestimate of the cost and potential efficacy of letermovir prophylaxis.
- The level of CMV-DNA at which PET was initiated in the trial (and prophylactic treatment withdrawn) was considerably lower than is seen in clinical practice in the UK. The ERG's clinical advisors agreed that a patient with a viral load of ~200 copies/ml would not be started on pre-emptive therapy in the absence of CMV disease symptoms (as recommended in the trial protocol), and would instead only initiate PET if the virus copy number reaches a centre specific threshold (between >1000 and >10,000 copies/ml), or the patient shows evidence of CMV disease. However, the clinical advisors stressed that there are no fixed rules; clinical experience and the condition of each individual patient has to be considered. On the whole, the trial population likely initiated letermovir later (median delay of 9 days), and started pre-emptive therapy (and therefore stopped taking letermovir) sooner than they would in clinical practice, and those patients whose infections would have been cleared naturally may have been treated with PET unnecessarily. However, as discussed above, in UK practice the trial's potential overestimation of the infection rate may be compensated for by the higher risk of CMV infection due to higher rates of T-cell depletion.

Patient characteristics were generally balanced between the letermovir and placebo groups with no apparent bias in favour of letermovir. There are some difference between the ASaT and FAS populations and their relevance to NHS practice, such that it is important to differentiate between these when interpreting the results of the analyses.

Efficacy data analysis

The statistical analyses used for the trial were generally appropriate. The primary efficacy analysis in the study was the "non-completer = failure" (NC = F) approach. 'Non-completers' included patients who withdrew from the study and those missing data points. The ERG considers this a conservative assumption that should not bias the relative treatment effect. The main effect of this assumption is to increase the apparent incidence of CMV reactivation in both treatment arms. It should be noted that this primary outcome is not used in the economic model. A number of other approaches were tested in sensitivity analyses.

Various numbers and analyses were presented for all-cause mortality. Separate plots were provided for all-cause mortality through weeks 24 and 48, incidences were provided for the letermovir and placebo groups at 14, 24 and 48 weeks, and nominal log rank p-values (not controlled for multiplicity)

were presented for the curves through Week 24 and separately for the curves through Week 48. The ERG deemed the data through Week 48 elicited by the US FDA, which represents the longest follow-up and includes those patients who withdrew early from the trial but whose post-trial vital status was later ascertained to be the most robust and complete.

Across the various time-points the results are essentially the same: the reduction in mortality with letermovir at Week 48 is not statistically significant.

HRQoL results

[redacted]. Furthermore, the HRQoL results are difficult to interpret, given the timing of assessments in relation to letermovir dosing and administration of other treatments.

Adverse effects

Evidence for the adverse effects of letermovir presented in the CS was derived solely from trial PN001. There are no data for letermovir use longer than 100 days. Overall the AE results are difficult to interpret due to the underlying disease and associated treatment and in the longer term follow-up, the toxicities associated with various PET regimens.

The company's economic submission included a systematic review of published evidence on the cost-effectiveness, health-related quality of life, resource use and costs associated with letermovir prophylaxis. These reviews identified a number of economic evaluations of other therapies, including UK based economic evaluations which were used to inform model parameters in the analysis, but did not identify any relevant economic assessments of letermovir.

The cost effectiveness of letermovir prophylaxis compared with standard care (no prophylaxis) was informed by an economic evaluation conducted by the company. The primary sources of data used to inform the cost-effectiveness model were the PN001 trial, and as such the modelled population reflected the age, weight and primary condition primary condition (e.g. AML, ALL, CLL, etc.) of the patients recruited to the PN001 trial. The model structure consists of a decision tree phase covering the first 24 week post HSCT (48 weeks in scenario analysis) and Markov model phase covering the remaining time horizon of the model.

The decision tree phase of the model utilised six different clinical outcomes with each outcome indicating the occurrence of a clinical event: (i) initiation of PET based on documented CMV viremia, (ii) all-cause mortality, (iii) CMV end-organ disease, (iv) CMV-related re-hospitalization (v)

opportunistic infection, and (vi) graft-versus-host disease. The cumulative probability of each of the six events listed above was drawn from the PN001 trial data with events permitted to occur at 14 weeks, 24 weeks and 48 weeks (scenario analysis only). Each of the six events, with the exceptions of all –cause mortality is associated with specific costs and therefore collectively these clinical events determine the costs-accrued over the decision tree phase of the model. All-cause mortality alone, which is not associated with any costs, determines the accrual of life years and QALYs. Differences in the HRQoL of patients due to, for example, differences in the rates of CMV infections, are not explicitly modelled and instead differences in the HRQoL of the two groups are captured using trial-based utilities, sourced from the PN001 trial.

The Markov phase of the model is primarily used to determine the life-expectancy in patients who survive until the end of the decision tree phase. The mortality rate applied in this phase of the model is assumed to be the same in both treatment groups and therefore no survival gains are assumed beyond the trial follow-up. The mortality rate applied is based on data drawn from general population mortality data sourced from the ONS, with a standardised mortality rate (SMR) applied to account for the reduce life expectancy of patients who receive HSCT. HRQoL in the Markov phase of the model was based on age-adjusted values for the general population.

In the base-case analysis of patients, the company found letermovir prophylaxis to be more costly (cost difference of £5,014) and more effective (0.46 QALY gain) compared with standard care. The deterministic base-case incremental cost-effectiveness ratio (ICER) was £10,904 per QALY, and the mean probabilistic ICER was £10,913 per quality-adjusted life year (QALY). The predicted probability that letermovir prophylaxis was cost-effective compared with standard care was 81.92% at a cost-effectiveness threshold of £20,000 per QALY and 89.49% at a cost-effectiveness threshold of £30,000 per QALY. The company reported that the most influential parameters in the one-way sensitivity analysis included the mean age of the cohort, duration of letermovir prophylaxis therapy, and the proportion of patients receiving concomitant CsA. The company also presented two-way sensitivity analysis of mortality parameters probability, which shows that letermovir is cost-effective at £20,000 per QALY, as long as the difference in mortality rates at 24 weeks exceeds 2.5% and is cost-effective at £30,000 per QALY as long as the mortality difference at 24 weeks exceeds 1.5%.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The economic analysis presented by the company was considered to meet the decision problem specified in NICE's scope. However, the ERG identified a number of key uncertainties.

The ERG considers that the modelling approach taken by company, although transparent and relatively flexible, is potentially too simplistic. The ERG is particularly concerned that the model makes a number of structural assumptions such that there no link between the rate of CMV events (the principal benefit of letermovir) and mortality which is the key driver of cost-effectiveness. This means that uncertainty relating to difference between the CMV events in the two groups cannot be fully explored. Furthermore, the model made no account for the potential for underlying disease relapse and the care and quality of life effects entailed. This is problematic as the costs and QALY decrements associated with relapse will not impact evenly on the two group due differences in the number of patients at risk in the two groups (different mortality rates).

The ERG considers that there is significant uncertainty around the difference in mortality between the two treatment groups and that the values use in the company's base-case model, which are based on outcomes at 24 week data, are an overly optimistic interpretation of the available evidence. The ERG in particular notes that 48 week outcomes were available and that a post-hoc analysis of vitality status requested by the FDA includes more complete mortality data, with fewer patients lost to follow up. The ERG also notes that the mortality benefits observed in the PN001 trial were not statistically significant and are subject to significant uncertainty. This is important because almost all of the QALY benefits associated with letermovir prophylaxis derive from improved survival and sensitivity analysis implemented by the company demonstrates that there is wide range of plausible values for which letermovir would not be considered cost-effective based on threshold of £30,000 per QALY.

The ERG also notes that there is considerable uncertainty regarding the duration over which letermovir prophylaxis will be administered. Specifically, the ERG notes that, in the clinical trial, there was significant delay following HSCT before letermovir prophylaxis (mean [redacted] days) was initiated, likely due to concerns that it may effect graft response. The ERG, however, thinks it is likely that clinicians will be more confident to administer letermovir prophylaxis immediately post HSCT as PN001 demonstrated that letermovir does not impact on graft response. Further, the ERG notes the lack of any futility rules in the SmPC and considers that in clinical practice it is plausible that patients requiring longer periods of prophylaxis (as is allowed under the product licence) would receive prophylaxis beyond 100 days.

The ERG also has a significant number of concerns regarding a wide range of inputs used in the model and notes a number of inconstancies as a result of mixing FAS and ASaT data as well as the use of potentially overly optimistic parameters for a number of resource inputs. Individually these issues have only a small impact on the ICER, but cumulatively act to increase the ICER significantly.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Clinical effectiveness

The PN001 trial, as the main source of evidence, was a good quality, adequately powered placebo controlled RCT at low risk of bias. The results of the trial demonstrate a clinically and statistically significant benefit of letermovir in the prophylaxis of CMV infection in post-HSCT patients and in reducing the need for the initiation of PET.

Cost effectiveness

The ERG considers the submission to meet the requirements of the NICE reference case. The model structure chosen was transparent, included the appropriate comparators and was flexible enough to allow the ERG to incorporate a range of scenario analyses. The short-term data was appropriately derived from the PN001 trial. The long-term utilities used were appropriate adjusted for the age of patients as they move through the model.

1.6.2 Weaknesses and areas of uncertainty

Clinical effectiveness

As outlined in Section 1.4 above, there are some questions over the generalisability of the trial and its results to NHS practice. Most importantly, patients in the trial may have stopped letermovir and initiated PET earlier than in clinical practice. This means the trial may have overestimated the rate of CMV infection on letermovir and also underestimated the potential for prophylaxis with letermovir. This, together with the limited follow-up for all-cause mortality, means that the trial did not demonstrate a significant mortality benefit for letermovir and the estimate of the mortality effect seen is uncertain

Cost effectiveness

There are significant areas of uncertainty in the cost-effectiveness analysis. Foremost is the magnitude of any mortality benefit associated with letermovir prophylaxis which is key driver of cost-effectiveness. A second area relates to the uncertainty regarding the long-term morbidity and survival of patients who have received HSCT. There were also uncertainties surrounding the costing assumptions for PET and duration over which letermovir prophylaxis will be administered.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG did not conduct any further sensitivity analyses relating to clinical effectiveness.

The ERG conducted a series of exploratory analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. These scenarios were for the most part not associated with substantial differences to the ICER. The scenarios associated with the greatest impact on cost-effectiveness outcomes related to changes made by the ERG to duration of letermovir prophylaxis and administration costs for letermovir and PET. The ERG also presented an alternative base-case based on a combination of a number of scenarios generated by the ERG together with a number of scenarios implement by the company as part of their points for clarification response. The ERG's base-case makes the following amendments to the company's base-case model.

1. FAS population used for all clinical parameters;
2. 48 Week trial data used together with post-hoc analysis of mortality;
3. Mean duration of therapy assumed to be 83 days;
4. Inclusion of medium-term care costs for survivors of HSCT and survivor disutility;
5. Revisions to assumptions regarding GvHD costs and QALYs
6. Inclusion of relapse disease based on HMRN rate of relapse;
7. Revisions to administration cost for letermovir and PET;
8. Foscarnet use assumed to be 15%;
9. Mortality data in the Markov phase of the model based on date from HNRM and relative risk from Martin et al.

The results of these scenario analyses including the ERG's base-case are summarised in Table 1. Due to time constraints, deterministic ICERs are presented throughout.

The ERG base-case analysis estimated letermovir prophylaxis to be more costly (cost difference £8,433) and more effective (0.31 QALY gain) compared with standard of care and suggests that the ICER for letermovir prophylaxis compared with SOC is around £27,536 per QALY.

The ERG also carried out a further series of exploratory analyses to explore the impact of alternative assumptions regarding the duration of therapy, the approach used to model missing data, and mortality at 48 weeks. These indicate that small changes to key assumption have disproportionately large impact on the ICER. In particular, even a small change to the mortality benefit associated with

letermovir prophylaxis, results in very significant changes to the ICER. As such the ERG base-case is subject to considerable uncertainty with the true ICER likely to lie within a broad range of £23,124 to £34,471 per QALY, assuming the ERG's base case assumptions.

Table 1: Summary of the relevant amendments to the company's base case model and impact of those amendments on the ICER (PAS included)

Scenario	Treatment	Costs	QALYs	Inc. Cost	Inc. QALY	ICER	Change in ICER
Company's base-case analysis	SoC	28,805	6.73	-	-	-	-
	Letermovir	33,819	7.19	5,014	0.46	10,904	-
#1	SoC	28,765	6.48	-	-	-	-
	Letermovir	34,071	6.93	5,306	0.44	11,966	9.74%
#2	SoC	24,626	5.96	-	-	-	-
	Letermovir	29,267	6.30	4,641	0.338486243	13,710	25.73%
#3	SoC	28,805	6.73	-	-	-	-
	Letermovir	35,315	7.19	6,510	0.46	14,158	29.84%
#4	SoC	38,430	6.61	-	-	-	-
	Letermovir	44,096	7.06	5,666	0.452037366	12,535	14.96%
#5	SoC	30,178	6.68	-	-	-	-
	Letermovir	35,141	7.14	4,963	0.456764171	10,866	-0.35%
#6	SoC	32,471	6.72	-	-	-	-
	Letermovir	37,733	7.18	5,262	0.46	11,449	5%
#7	SoC	27,599	6.73	-	-	-	-
	Letermovir	34,188	7.19	6,588	0.459842171	14,328	31.40%
#8	SoC	27,707	6.73	-	-	-	-
	Letermovir	33,351	7.19	5,644	0.46	12,274	12.56%
#9	SoC	27,108	6.37	-	-	-	-
	Letermovir	32,007	6.81	4,899	0.44	11,242	3.1%
ERG preferred base case analysis (scenarios #1 to #9 combined)	SoC	29,250	5.35	-	-	-	-
	Letermovir	37,683	5.65	8,433	0.31	27,536	152.53%

2 Background

2.1 Critique of company's description of underlying health problem.

The company's description of the underlying health problem, i.e. cytomegalovirus reactivation and infection, was largely appropriate and relevant to the decision problem under consideration. However, this did not necessarily provide a comprehensive picture of the clinical situation, as the ERG considered the underlying health problem in this appraisal to also include the indication for receipt of a haematopoietic stem cell transplant.

Human cytomegalovirus (CMV) is a very common viral pathogen belonging to the *Herpesviridae* family, and is characterised by generally mild or asymptomatic primary infection followed by life-long latency. The company's submission (CS) estimates that between 50 and 60% of the UK population are seropositive (R^+) for CMV, i.e. have previously been infected. In patients with intact immune systems, the virus is maintained in a latent state within the host. In states of immunodeficiency, however, such as following an allogeneic stem cell transplant, reactivation of latent CMV infection can occur and result in significant morbidity and mortality.

While the company did not include a description of the conditions underpinning the need for an allogeneic haematopoietic stem cell transplant (allo-HSCT), the ERG considered this key to understanding the morbidity and treatment response in these patients, and distinctions between the various sub-populations. The indications for allo-HSCT depend on each patient's medical condition, the therapeutic objectives, and the availability of an appropriate donor. While haematological malignancies are the most common indications, with lymphoma, acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS), and acute lymphoblastic leukaemia (ALL) patients comprising the majority of recipients, other non-malignant disorders such as aplastic anaemia represent a small but significant minority. Patients with haematological malignancies which have not responded to chemotherapy may be eligible for allo-HSCT as the only chance of curative treatment. HSCT allows the use of very high doses of chemo- and/or radiotherapy to eradicate the patient's haematopoiesis, including the cells of the immune system and the malignant/aberrant haematopoietic cells (myeloablative therapy). This is known as a conditioning regimen. The patient's immune system is replaced through an infusion of progenitor cells, from which all blood cells are derived. These progenitor cells (also called stem cells) are harvested from a human leukocyte antigen-compatible related or unrelated donor. These stem cells can be directly harvested from the bone marrow, or collected from the blood. The stem cells are infused into the bloodstream, and spontaneously move to the patient's bone marrow, engrafting typically from 14-28 days following infusion.

Recipients of allo-HSCT are immunocompromised, which can lead to CMV reactivation and potentially life-threatening infection. Indeed, CMV is the most common clinically-significant viral infection in this population, and can occur in as many as 80% of patients. The company cites data from the British Society for Bone and Marrow Transplantation (BSBMT), which shows that in 2016, 1,152 adults received an allo-HSCT for the first time in England, in whom CMV seroprevalence was approximately 54%. The CS does not discuss the underlying disease of the patients receiving an allograft, which is indicated for a range of conditions in different lines of therapy.

A number of factors further increase the risk of CMV infection after HSCT. These include the use of T-cell depleting agents such as alemtuzumab (Campath ™) or antithymocyte globulin, prolonged immunosuppression for treatment of graft versus host disease (GvHD), particularly requiring the use of high-dose corticosteroids, transplants from unrelated or human leucocyte antigen (HLA)-mismatched donors, and transplants from donors who have not previously been exposed to CMV. The ERG noted that patients at the highest risk of CMV reactivation were R^+/D^-, i.e. seropositive recipients of a transplant from a seronegative donor, as the donor cells would have to mount a primary immune response against the virus, which takes substantially longer to build and resolve than the secondary response generated from a seropositive graft.

The CS appropriately groups the clinical effects of CMV reactivation into 'direct' and 'indirect' effects; direct effects comprise the spectrum of CMV disease manifestations, including pneumonitis, colitis, hepatitis, retinitis, and encephalitis, while indirect effects include increased rates of GvHD, opportunistic bacterial and fungal infection, and overall non-relapse related mortality. The direct effects of CMV infection are now largely controlled by pre-emptive therapy (PET) regimens (usually ganciclovir/valganciclovir, or foscarnet); however, the toxicity of these drugs is a major contributing factor to post-transplant morbidity and mortality. Despite their successful use against CMV infection, all currently available anti-CMV agents are nucleoside analogues with target-related toxicities such as myelosuppression with ganciclovir/valganciclovir, and nephrotoxicity with foscarnet, each incurring additional management and hospitalisation costs. The CS specifically mentions that ganciclovir associated neutropaenia can incur the cost of granulocyte colony stimulating factor therapy and also that myelotoxicity caused by PET may result in compromised engraftment, incurring high post-transplant resource costs.

2.2 Critique of company's overview of current service provision

The company's overview of current service provision was generally accurate and relevant to the decision problem. It correctly stated that there are no licensed treatment options or NICE recommendations for the prophylaxis of CMV reactivation in R^+ allo-HSCT recipients, and that there

is little evidence informing current management. The CS stated that while in the BSH guideline aciclovir is recommended as an option for CMV prophylaxis, it is generally not used for this purpose due to weak activity against CMV and associated toxicities. The ERG's clinical advisers agreed this was the case.

The CS correctly summarises the current pathway of CMV management in the UK as follows. Upon the emergence of 'CMV viraemia' (i.e. clinically significant blood serum levels of CMV DNA), pre-emptive therapy (PET) with intravenous (IV) ganciclovir is initiated, or valganciclovir (an oral preparation of ganciclovir) as an oral alternative in patients with normal or minimally impaired gastrointestinal absorption. In patients who are ineligible or intolerant to (val)ganciclovir because of pre-existing low blood counts, or the development of this during treatment, foscarnet is used, with cidofovir used as a potential rescue option despite the withdrawal of its marketing authorisation. First-line PET is continued until the patient tests negative for the presence of CMV in the blood, or until the level is below a locally defined threshold (typically taking 21-28 days).I If the patient has a neutrophil count of $<0.5x10^9$ or the CMV DNA load fails to respond sufficiently, foscarnet is administered, requiring hospitalisation for the duration of treatment. The clinical advisors to the ERG indicated that there is no clear definition of the CMV DNA viral load at which treatment with PET is deemed necessary. This varies to a modest extent by centre and patient, as discussed further below.

It is anticipated that letermovir would be initiated in all seropositive allo-HSCT recipients from the day of transplant; supplanting current practice for the first 100 days post-transplant, and thereby minimising the use of PET and its associated sequelae and costs.

The ERG notes some regional differences within England with regards to the monitoring and management of CMV infection in clinical practice. The peripheral blood of seropositive patients is generally tested using quantitative polymerase chain reaction (qPCR) once a week, though some centres test in-patients twice weekly. The threshold for treatment of CMV reactivation, varies by centre, a 'positive' test depending upon the sensitivity of the PCR assay, which can typically detect levels of 150-200 copies of viral DNA per millilitre of blood. As some low level reactivation will clear naturally, most centres use a strategy requiring two consecutive positive results with a rising copy number above that unit's threshold, unless the first result is already above this pre-defined threshold, which varies between >1000 and >10000 copies/ml but is typically at the lower end of this range. However, if a patient is considered to be at particularly high risk of CMV disease, or has evidence of CMV disease, PET may be initiated immediately. The presence of CMV end-organ disease is an indication to start treatment, but would not be expected to occur in the absence of preceding viremia permitting the commencement of PET. The ERG's clinical adviser considered

valganciclovir as the preferred treatment option in current practice under normal circumstances to keep patients out of hospital, or to prevent the additional visits necessary to administer IV ganciclovir as an outpatient, though out-patient ganciclovir pumps are available if there is any concern about gastrointestinal absorption, compliance or response to valganciclovir.

3 Critique of company's definition of decision problem

3.1 Population

The population specified in the final NICE scope was adults who are sero-positive for cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant and this is reflected exactly in the CS. The licensed therapeutic indication is as follows; 'PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT)'. There is some lack of clarity regarding whether patients with detectable CMV DNA but a low viral load who would not yet be considered eligible for pre-emptive therapy would be initiated on letermovir in clinical practice. However, given that patients would be commenced on the day of infusion, the ERG consider it unlikely that patients would have detectable viraemia at that time. This has implications for which analysis and results from the key trial are most relevant to the decision problem; an issue discussed further in Section 4.2.8.

3.2 Intervention

The intervention specified in the CS is letermovir and this matches the final NICE scope. The SmPC for letermovir states that prophylaxis should be started after HSCT, from the day of transplant and no later than 28 days post-transplant. It states that prophylaxis with letermovir should continue through 100 days post-transplant. Letermovir can be started before or after engraftment.

The recommended dosage of letermovir is one 480 mg tablet once daily. A 240 mg tablet is also available. Letermovir is also available as concentrate for solution for intravenous (IV) infusion (240 mg and 480 mg), and the oral and IV formulations may be used interchangeably at the discretion of the physician, with no dose adjustment necessary. However, the dosage of letermovir should be reduced to 240 mg once daily when co-administered with ciclosporin A (CsA), which significantly increases the bioavailability of letermovir. This is an important drug interaction as CsA is used in approximately 90% of patients in clinical practice in England and Wales.

3.3 Comparators

The NICE final scope listed aciclovir and valaciclovir as well as 'no preventative treatment' as comparators; however, the NICE scope noted that neither active drug had current marketing authorisation for the relevant indication. The CS included only 'no prophylaxis against CMV reactivation, i.e. no active comparators were included. The reasons given for this in the CS were: neither drug currently has a marketing authorisation in the UK for this indication; there is no relevant UK evidence supporting use of either treatment for CMV prophylaxis in this patient population (based on a systematic literature review (SLR)), and the overall evidence base is not considered to be robust by professional bodies.[2] Aciclovir is primarily initiated in this patient population as broad coverage against herpes simplex viruses (HSV) (in the letermovir phase III study (PN001) concomitant aciclovir was permitted for this purpose, and was used by 82% of all randomised patients); and UK clinician feedback indicates a lack of observed efficacy with aciclovir as CMV prophylaxis in clinical practice, and neurotoxicity associated with both aciclovir and valaciclovir. The ERG and the clinical advisors to the ERG concur with this reasoning, and agree that aciclovir and valaciclovir are not relevant comparators for letermovir in this appraisal.

3.4 Outcomes

The outcomes listed in the company's decision problem reflect, but do not match exactly those listed in NICE's final scope. Those in the CS are based on the outcomes reported in the pivotal Phase III trial (PN001).

'CMV infection rate' is replaced with 'Clinically-significant CMV infection', the latter defined as the occurrence of either initiation of anti-CMV PET based on documented CMV viraemia (detectable presence of CMV DNA, as measured by the central laboratory) and the clinical condition of the patient, or onset of CMV end-organ disease. Initiation of PET in this study referred to the practice of initiating therapy with ganciclovir, valganciclovir, foscarnet and/or cidofovir.

In the company's decision problem, 'time to all-cause mortality' and 'overall survival' are replaced with 'all-cause mortality', i.e. in the CS all-cause mortality was not analysed using hazard models, but instead incidence rates at set time points were compared; the ERG considered this a sub-optimal approach to the analysis of such data.

The ERG notes that in the patient population eligible for treatment with letermovir, there is a high mortality risk associated with the underlying disease which is not directly impacted upon by letermovir treatment. Therefore, consideration of non-relapse related mortality and CMV-related mortality might be relevant. Neither of these outcomes was specified in the NICE scope or included in

the CS, but results were presented in the CSR for trial PN001. Non-relapse related mortality is discussed further in Section 4.2.8 of this report. CMV-related mortality was not considered scientifically sound by the EMA assessors and the data were omitted from the EPAR [3]; further details are given in Section 4.2.8.

3.5 Subgroups

The NICE final scope specified that people at high risk of CMV reactivation should be considered as a subgroup (should the evidence allow). This subgroup was included in the CS together with analyses are reported based on risk categories for CMV reactivation, patient characteristics, and conditioning and concomitant immunosuppressive regimen as per study protocol:

- CMV reactivation risk stratum (high/low risk)
- Stem cell source (peripheral blood, bone marrow)
- Donor mismatch (matched related, mismatched related, matched unrelated, mismatched unrelated)
- Haploidentical donor (yes, no)
- Sex (male, female)
- Age (< or ≥median (55 years))
- Race (white vs non-white, Asian vs non-Asian)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region (Europe vs North America, US vs ex-US)
- Weight
- Days from transplantation to randomisation (<2 weeks, ≥2 weeks)
- Conditioning regimen (myeloablative, reduced intensity, non-myeloablative)
- Immunosuppressive regimen (ciclosporin A (CsA), tacrolimus).

These subgroups were considered relevant and informative by the clinical advisors to the ERG. One important subgroup not included in the analysis was whether recipients had undergone T-cell depletion during the trial, which substantially significantly increases the risk of CMV activation. However, this could not be defined a priori, and was not analysed; the number of patients who had received ex-vivo T-cell depletion at baseline was too small to make investigation of this with the current trial data meaningful.

3.6 Other relevant factors

The CS includes a Patient Access Scheme comprising [redacted].

4 Clinical Effectiveness

This section contains a critique of the methods of the review of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results, and the results of any synthesis of studies.

4.1 Critique of the methods of review(s)

A systematic review to identify relevant trials of effectiveness was conducted and reported in Appendix D 1 of the CS.

4.1.1 **Searches**

For the SLR of clinical evidence, searches were conducted using the databases MEDLINE and MEDLINE In Process (via OvidSP), EMBASE (via OvidSP) and the Cochrane Central Register of Controlled Trials [CENTRAL] (via Wiley) on 21st August 2017. The search strategies used and the number of records identified for each database were reported in Tables 2 to 4 Appendix D.

The company also searched trial registers (ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform) and the search strategies used and the number of records identified are provided in Tables 5and 6.

The overall structure of the database search strategies was appropriate: terms for cytomegalovirus and hematopoietic stem cell transplantation were combined with terms for letermovir and other relevant drug interventions (aciclovir, valaciclovir, valganciclovir, ganciclovir, cidofovir, foscarnet). Where required, a search filter was included in the strategy to restrict the results to RCTs. The strategies contained relevant subject headings, text word searches and synonyms. There appears to be no errors in how the search sets are combined or typographical errors within the search terms. The numbers of records identified matches the number reported in the PRISMA diagram (Figure 1 page 74)

4.1.2 Inclusion criteria

The inclusion and exclusion criteria, used to select studies for inclusion in the systematic review of the clinical efficacy and safety of letermovir and other antiviral agents in the prophylaxis of adult CMV-seropositive recipients of an allogeneic HSCT are detailed in Table 7 of Appendix D.1.3 of the CS. The ERG considers these criteria to be appropriate, though the list of interventions to be included in the review was very broad: it included aciclovir, valaciclovir, ganciclovir, valganciclovir, cidofovir and foscarnet as well as letermovir. The inclusion of these other anti-virals as interventions was unnecessary in the context of the decision problem. Placebo and 'no preventive treatment' were also included as interventions which appears to be incorrect; these should have been listed as comparators,

but no comparators were listed. The inclusion criteria for study design specified randomised controlled trials, which is appropriate. Source publications were limited to full journal articles or conference abstracts from the following (2015 or later) conferences: American Society of Hematology (ASH); European Society for Blood and Marrow Transplantation (EBMT); American Society for Blood and Marrow Transplantation (ASBMT). Only English-language studies were included, however, given the rarity of trials of prophylaxis against CMV infection post-HSCT it is likely that good quality studies will be published in major English-language journals.

The methods used to select the studies for inclusion were appropriate as is the presentation of the results of study selection: a PRISMA flow diagram and a list of all studies excluded at the full-paper screening, with reason for exclusion, are given in Appendix D.1.

4.1.3 Critique of data extraction

No methods of data extraction are reported in the CS. However, the data presented in the submission can be checked against that in the relevant CSRs and also the EMA EPAR.

4.1.4 Quality assessment

The quality assessment of the studies identified for inclusion in the systematic review of effectiveness is reported in the Appendix Section D1.1.9. The assessment considered the following factors relating to quality and the risk of bias:

- Was randomisation carried out appropriately?
- Was the concealment of treatment allocation adequate?
- Were groups similar at the outset of the study in terms of prognostic factors?
- Were care providers, participants, and outcome assessors blind to treatment allocation?
- Were there any unexpected imbalances in dropouts between groups?
- Did the authors measure more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis?

This assessment appears to have been appropriate and well conducted based on the specified publications. However, it is unclear to the ERG why a quality assessment of study PN001 based on an abstract (Duarte 2017) was included separately, the full journal article (Marty 2018) and the CSR being more complete descriptions of this trial. Also the Grade assessment was not reported against the CSR report of this trial. Details and further commentary on the results of the assessment are given in Sections 4.2.2.

4.1.5 Evidence synthesis

The relevant trials identified by the systematic review did not readily lend themselves to quantitative evidence synthesis. In Section D 1.5 of the CS, consideration is given to the synthesis of a trial comparing ganciclovir with aciclovir as prophylaxis of CMV infection [4] and the phase II trial of letermovir versus placebo [1] because both trials report the proportion of patients who developed clinically significant CMV infection; because of the lack of a common comparator the CS correctly states no network meta-analysis could be conducted. The ERG notes that a comparison with aciclovir or ganciclovir is not relevant to the decision problem as neither of these antivirals is included as a prophylactic in the decision problem. The ERG also notes that the CS does not consider any standard meta-analysis of the Phase II trial [1] and the phase III pivotal trial PN001. Given the differences between these trials this is appropriate; only a narrative synthesis is presented for the phase III pivotal trial PN001.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Identified studies

Table 2 Publications included in the systematic literature review (adapted from CS Appendix D table 9)

Author, year	Phase	Full reference
Burns, 2002	Not reported	Burns, L.J., Miller, W., Kandaswamy, C., DeFor, T.E., MacMillan, M.L., Van Burik, J. & Weisdorf, D.J. (2002). Randomized clinical trial of ganciclovir vs acyclovir for prevention of cytomegalovirus antigenemia after allogeneic transplantation. *Bone marrow transplantation*. 30 (12). p.pp. 945–951.
Chemaly, 2014	II	Chemaly, R.F., Ullmann, A.J., Stoelben, S., Richard, M.P., Bornhäuser, M., Groth, C., Einsele, H., Silverman, M., Mullane, K.M., Brown, J., Nowak, H., Kölling, K., Stobernack, H.P., Lischka, P., Zimmermann, H., Rübsamen-Schaeff, H., Champlin, R.E. & Ehninger, G. (2014). Letermovir for Cytomegalovirus Prophylaxis in Hematopoietic-Cell Transplantation. *New England Journal of Medicine*. [Online]. 370 (19). p.pp. 1781–1789.
Trial PN001, published as Duarte, 2017 and Marty, 2017	III	Duarte, R., Marty, F., Ljungman, P., Chemaly, R., Maertens, J., Snydman, D., Blumberg, E., Einsele, H., Boeckh, M., Teal, V., Wan, H., Kartsonis, N., Leavitt, R. & Badshah, C. (2017). Letermovir for prevention of cytomegalovirus infection in adult CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. *Haematologica*. 102. p.pp. 331–332.
		Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. N Engl J Med. 2017;377(25):2433-44
		Merck Sharp & Dohme Corp. Week 24 Clinical Study Report: A Phase III Randomized, Placebo-controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-8228 (Letermovir) for the Prevention of Clinically Significant Human Cytomegalovirus (CMV) Infection in Adult, CMV-Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipients. 2017
		Merck Sharp & Dohme Corp. Week 48 Clinical Study Report: A Phase III Randomized, Placebo-controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-8228 (Letermovir) for the Prevention of Clinically Significant Human Cytomegalovirus (CMV) Infection in Adult, CMV-Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipients. 2017

It should be noted that the CS listed the Duarte et al. 2017 [5] and Marty et al. 2017[6] publications as the source of the PN001 trial, but in fact used and referenced mainly the CSRs, as is appropriate given

that the CSRs provide the most comprehensive report of the trial. The ERG were provided with the CSRs.

Trial PN001 provides the main evidence for this appraisal and is described and discussed in the following sections.

4.2.2 Design of Trial PN001

The details of Trial PN001 are presented in Section B2.3.1 of the CS. In brief, PN001 was a phase III randomised, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of letermovir compared to placebo for the prevention of clinically-significant human CMV infection in adult, R+ recipients of an allogeneic HSCT. The trial details are summarized in Table 3 and Figure 1 (both taken from the CS).

Patients were randomised in a 2:1 ratio to receive either letermovir at a dose of 480 mg once daily (adjusted to 240 mg when co-administered with CsA), or placebo. Study medication was continued through to Week 14 (~100 days). Randomization was stratified by study centre and high or low risk for CMV reactivation in order to balance any effects of these variables across treatment groups. The two categories of risk based on available literature[7-10] and input from external experts on the Scientific Advisory Committee (SAC), are as follows:

High risk: Patients meeting one or more of the following criteria at the time of randomisation:

Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or –DR

Haploidentical donor

Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and –DRB1

Use of umbilical cord blood as stem cell source

Use of *ex vivo* T-cell-depleted grafts (including *ex vivo* use of alemtuzumab [Campath™])

Grade 2 or greater graft-versus host disease (GvHD), requiring the use of systemic corticosteroids (defined as the use of ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid)

Low risk: All patients not meeting the definition of high risk.

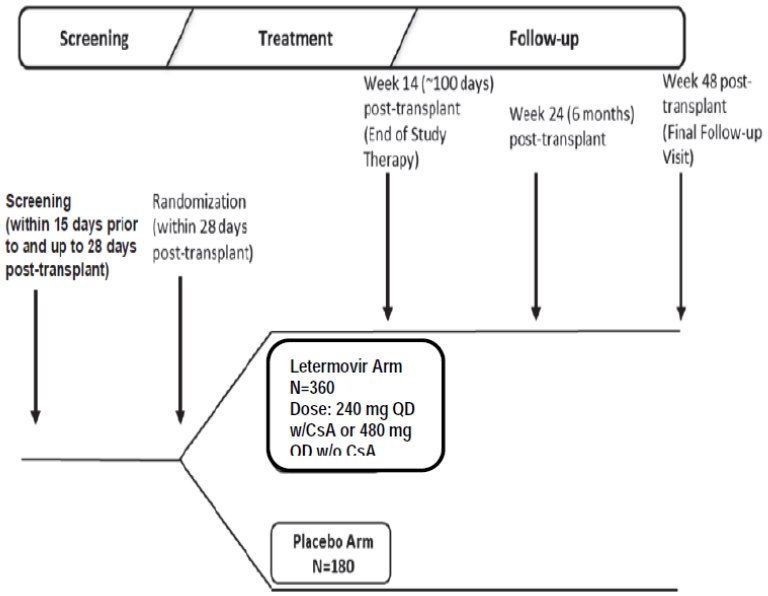
The clinical advisors to the ERG agreed with this categorisation of high and low risk, although noted that in vivo T-cell depletion with ATG or alemtuzumab will confer high risk, and could have been included.

Patients were monitored through to Week 24 post-transplant for the primary efficacy endpoint. Patients who completed the trial Week 24 post-transplant subsequently entered a follow-up phase from Week 24 to Week 48 post-transplant to collect data related to CMV disease, health outcomes, and quality of life (QoL) measures.

Table 3 Summary of design of trial PN001 (adapted from CS Table 8)

Study design	Phase III multicentre and multinational randomised, double-blind, placebo-controlled trial
Population	Adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant
Intervention(s)	Letermovir 480 mg once-daily (OD, adjusted to 240 mg OD if co-administered with CsA)
Comparator(s)	Placebo
Reported outcomes specified in the decision problem	Clinically-significant CMV infection Time to onset of clinically-significant CMV infection Initiation of pre-emptive therapy for documented CMV viraemia Time to initiation of pre-emptive therapy for documented CMV viraemia All-cause mortality Reduction of hospital in-patient days (re-hospitalisation for any reason and for CMV reinfection/disease respectively) Adverse events Health-related quality of life
All other reported outcomes	CMV disease Opportunistic infections Acute and/or chronic GvHD Incidence of CMV viraemia Time to CMV viraemia Incidence of engraftment Time to engraftment

Figure 1 Study Design of PN001



CsA ciclosporin; QD every day.

The main inclusion criteria were that patients:

- Had been ≥18 years of age on the day of signing informed consent.
- Had documented seropositivity for CMV (recipient CMV IgG seropositivity [R+]) within 1 year before HSCT.
- Received a first allogeneic HSCT (bone marrow, peripheral blood stem cell, or cord blood transplant).
- Had undetectable CMV DNA (as confirmed by the central laboratory) from a plasma sample collected within 5 days prior to randomisation.
- Been within 28 days post-HSCT at the time of randomisation

Full details are given in Section 2.3.1.3 of the CS.

The primary outcome of Trial PN001 was the proportion of patients with clinically-significant CMV infection through Week 24 (~ 6 months) post-transplant, defined as the occurrence of either one of the following outcomes:

- Initiation of anti-CMV pre-emptive therapy based on documented CMV viraemia (as measured by the central laboratory) and the clinical condition of the patient. Initiation of pre-

emptive therapy in this study referred to the practice of initiating therapy with ganciclovir, valganciclovir, foscarnet and/or cidofovir

OR

- Onset of CMV end-organ disease

In order to allow standardisation of what constituted 'documented viraemia' in the definition of the primary endpoint, this was defined as any detectable CMV viral DNA on a confirmatory sample obtained immediately prior to (i.e. on the day of) the initiation of treatment for CMV disease or pre-emptive therapy, as measured by a central laboratory using the Roche COBAS® AmpliPrep/COBAS TaqMan® (CAP/CTM) System. The lower limit of quantification (LLoQ) for this assay is 137 IU/ml, which equates to 151 copies/mL[2]. [redacted].

ERG comments of the design of PN001

While the population is appropriate, the requirement for no detectable CMV DNA at baseline is of uncertain relevance to clinical practice. As stated above, the level of detectable CMV DNA is 137 IU/ml, which equates to 151 copies/ml. This is a very low viral load; in clinical practice such patients would still be considered for preventive therapy (prophylaxis) i.e. treatment with letermovir, as were some patients in the trial see Section 4.2.4. Unlike the trial, NHS patients with a positive qPCR test at <1000 copies of viral DNA would not yet typically be eligible for PET,

Although the outcome measure of clinically significant CMV infection included documented viraemia in its definition, the cut offs specified above were used for the initiation of anti-CMV PET in the trial only for high risk patients during the treatment phase. For low risk patients a viral load threshold of 300 copies/ml was recommended. However, this threshold was only a recommendation and did not have to be adhered to in the trial, a decision to initiate PET could be made on an individual basis based on a positive local laboratory test. As long as the result was later confirmed by the standardised central laboratory test, the lower threshold was acceptable (see results Section 4.2.8).

There appears to be some discrepancy between this and clinical practice in the UK. The ERG's clinical advisors agreed that a patient with a viral load of ~200 copies/ml would not be started on pre-emptive therapy, but trends in copy number carefully monitored by testing at least once per Week. If the viral load reaches a high absolute number; at least >1000 copies/ml but highly variable depending on the centre [11]), PET would then be initiated. If the patient shows evidence of CMV disease then

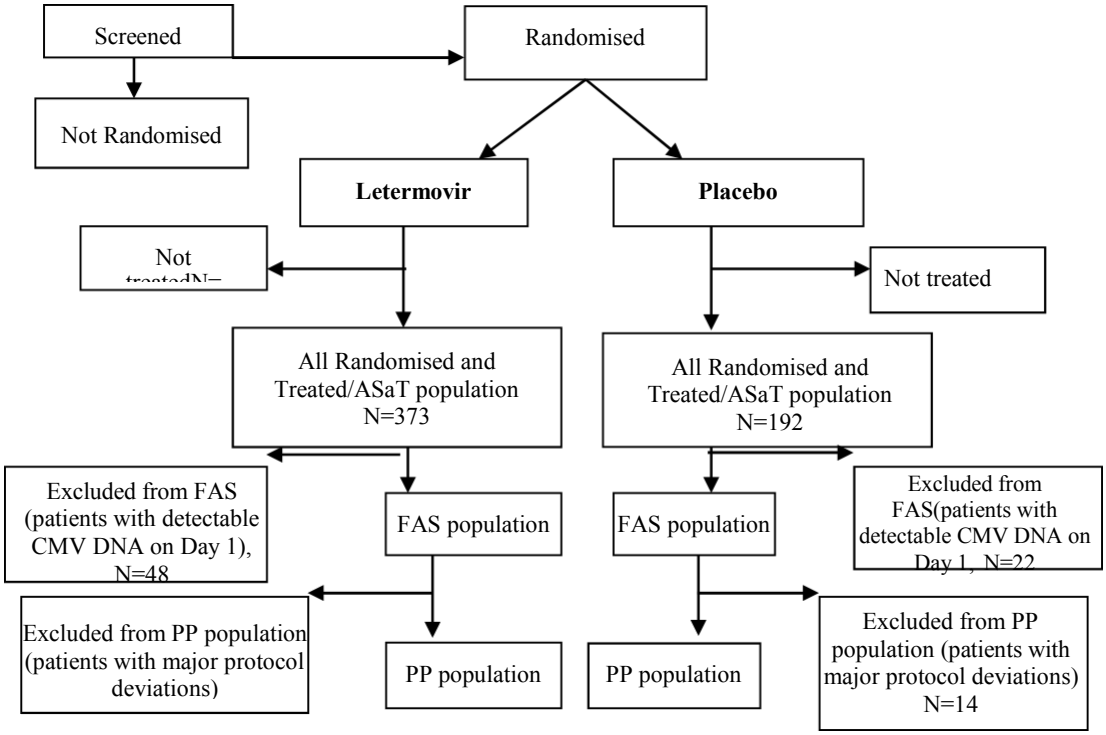
treatment is commenced; however, in practice this would not be expected in the absence of a period of preceding viraemia. As some patients may have stable low levels of CMV activation over a long period, PET is often delayed to allow a natural immune response and avoid exposure to toxic drugs.[11, 12]. However, the clinical advisors stressed that there are no fixed rules; clinical experience and the condition of each individual patient has to be considered. Nevertheless, the initiation criteria for trial patients is unlikely to match those treated in the NHS, and on the whole the trial population probably initiated PET (and therefore stopped taking letermovir) sooner than they would in clinical practice, and some, whose infections would have been cleared with prophylaxis or naturally, have been treated with PET unnecessarily.

The ERG's clinical advisors considered the fixed maximum treatment period of 100 days inappropriate. In clinical practice there would be of patients requiring longer periods of prophylaxis (as is allowed under the product licence), e.g. those undergoing enhanced immunosuppressive treatment for active GvHD with corticosteroids or additional lines of therapy, or at high-risk of CMV re-activation for other reasons, such as a D^- graft, particularly in the context of T-cell depletion. Therefore the trial *may* both underestimate the efficacy and duration of letermovir prophylaxis expected in clinical practice.

4.2.3 Participant flow and analysis populations in PN001

Details of the participant disposition in the trial are taken from the CSR:

Figure 2 Disposition of patients in Trial PN001 (CS Appendix D Figure 3)



ASaT= All Subjects as Treated; FAS= Full Analysis Set; PP= Per Protocol

The CS presents analyses of two populations the All Subjects (patients) as Treated (ASaT) and the Full analysis set (FAS). The ASaT population included all randomised patients who received at least one dose of study medication. The FAS population was the ASaT population minus patients found to have detectable CMV DNA on Day 1: (48 letermovir and 22 to placebo). Therefore the FAS population comprised (325 on letermovir and 170 on placebo).

Over 35% of patients were recruited in the USA (37.2% of the FAS population (Data provided in the clarification response). Only 12 patients (10 in the FAS population) were UK patients.

As discussed in Section 4.2.2, it is uncertain which population (data set) is the most relevant to clinical practice.

The FAS population can be considered the more likely to represent clinical practice in the UK if patients with detectable CMV DNA would not be considered suitable for prophylaxis but would (as according to the trial protocol) be initiated on PET. However, the ERG understands that in UK practice it is unlikely that PET would be initiated in the majority of patients returning a positive qPCR

test unless they were at high-risk of CMV infection, or the viral load was very high or was increasing rapidly to spare patients unnecessary exposure to toxic PET agents. The question is whether in UK practice patients with detectable, but not high levels of CMV-DNA would be considered eligible for letermovir prophylaxis. If that is the case then the ASaT population, that included some patients with detectable CMV DNA at baseline may be more generalisable to the NHS.

Another factor that needs to be considered in this discussion is whether eligible patients with detectable CMV DNA at baseline will exist in clinical practice. It is possible that such patients (protocol violators) emerged due to some investigators delaying letermovir prophylaxis until after engraftment. As the PN001 trial demonstrated that letermovir does not adversely affect engraftment,[6] clinicians are likely to be more confident in beginning prophylaxis immediately post-transplant, therefore the chance of CMV reactivation by the time of treatment initiation would be lower. In that case the FAS data (with patients with detectable CMV-DNA excluded) might be the most generalisable.

Whichever data set is 'preferred' the delay before letermovir initiation seen in the trial (ASaT population mean [redacted] (SD 8.5), median 9, and FAS population 11 days (SD 8.4) median 8 days) would be unlikely in practice.

4.2.4 Patient characteristics in PN001

The CS presented baseline characteristics for the ASaT population (CS Table 9) and found that patient characteristics were generally balanced between the letermovir and placebo groups. The majority of patients were male (327/565 [58%]), white (462/565 [82%]), and with a mean age of around 51 years old. At baseline, 175/565 (31%) of patients were at high risk for reactivation (as defined in the 'Study Design' section above) and 293/565 (52%) were receiving concomitant CsA.

The most common primary reasons for transplant were acute myeloid leukaemia (AML, 142/565 [38%]), myelodysplastic syndrome (MDS, 63/565 [17%]), and lymphoma (47/565 [13%]). The majority of patients had received transplants using peripheral blood stem cells (413/565 [73%]). Baseline aciclovir use for prior HSV prophylaxis was similar across both study groups (311/373 [83%] letermovir group, 152/192 [79%] placebo group; 463/565 [82%] overall).

The ERG requested further information from the company about the line of therapy the HSCT comprised, in order to better understand the patients' underlying health status, as HSCT is indicated at different stages of the disease depending on the condition, and a patient's response to chemotherapy. However, the ERG was informed that other than the fact that in all patients in the trial were undergoing their first HSCT, this information was not collected in this trial.

The median time to initiation of the study drug was 9 days after transplant.

The ERG checked the baseline demographics of the FAS population (reported in the CSR through 24 weeks – note patient characteristics were not provided for the FAS population the CSR through 48 weeks) and found them to be very similar to those of the ASaT population. Comparing the ASaT and FAS populations, the proportion of High Risk patients was slightly lower in the FAS population: 31.4% compared with 32.4% in the ASaT population (Table 4). Also, the proportion of patients with engraftment at baseline was smaller in the FAS population, suggesting that delaying study treatment until after engraftment may have been one reason for the appearance of CMV DNA at baseline (hence engrafted patients removed from the FAS population).

In both the ASaT and FAS populations imbalances were seen for the proportion of patients with a haploidentical donor (ASaT/FAS 16.1%/ 15.8% in the letermovir group and 10.9%/ 10.0% in the placebo group); antithymocyte globulin (ATG) use (ASaT /FAS 37.5%/ 35.7 % in the letermovir group and 30.2%/ 28.8% in the placebo group; and alemtuzumab use (ASaT/FAS 3.2 %/3.4% in the letermovir group and 5.7%/5.3% in the placebo group). The ERG notes that alemtuzumab is used for T-cell depletion to reduce the risk of GvHD; such patients are at a very high risk of CMV reactivation. As shown in Table 4 the number of patients receiving ex-vivo T-cell depletion was very similar in the ASaT and FAS populations.

Additional imbalances in the FAS population were seen for proportion of Asian patients (10.8% letermovir vs 6.5% placebo), and patients from the Asia-Pacific region (9.5% letermovir vs 4.1% placebo). Also in the FAS population there is an imbalance between US/non-US patients across the treatment groups that was not seen in the ASaT population (non-US 64.0% letermovir vs 60.6% placebo).

In summary, the treatment arms were reasonably well balanced with no apparent bias in favour of letermovir. There are some differences between the ASaT and FAS populations, such that it is important to differentiate between these when interpreting the results of the analyses and when considering which data set and results are most generalisable to NHS practice.

Table 4 High risk patients by factors: comparison of FAS and ASaT populations (adapted from clarification response Table 1)

	FAS						ASaT					
	Letermovir n=325		Placebo N=170		Total N=495		Letermovir N=373		Placebo N=192		Total N=565	
High Risk Patients in population	[redacted]											
(percentage of high risk patients)	n	%	n	%	n	%	n	%	n	%	n	%
Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or -DR	[redacted]											
Haploidentical Donor	[redacted]											
Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1	[redacted]											
Use of umbilical cord blood as stem cell source	[redacted]											
Use of ex vivo T-cell-depleted grafts(including ex vivo use of alemtuzumab [Campath™])	[redacted]											
Grade 2 or greater graft-versus-host disease (GvHD), requiring the use of systemic corticosteroids (defined as the use of e 1 mg/kg/day of prednisone or equivalent dose of another corticosteroid	[redacted]											
n (%) = Number (percent) of patients in each sub-category. Note: patients may have more than one high risk factor.												

4.2.5 Statistical analyses

Sample size and power

A sample size of approximately 540 patients was planned using a 2:1 randomisation ratio (~360 patients in the letermovir arm and ~180 patients in the placebo arm), though the actual ASaT

population size was 565. Anticipating the exclusion of 15% patients with detectable CMV DNA on Day 1, the evaluable number of patients in the FAS population would be 459 in total (306 in the letermovir arm and 153 in the placebo arm). With this sample size, the study would have a 90.5% overall power to detect a treatment difference with a 1-sided p-value less than or equal to 0.0249. The actual FAS population size was 495 (325 in the letermovir arm and 170 in the placebo arm).

Primary analysis

The primary hypothesis in study PN001 was that letermovir is superior to placebo in the prevention of clinically-significant CMV infection, as assessed by the proportion of patients with CMV end-organ disease or initiation of anti-CMV pre-emptive therapy based on documented CMV viraemia and the patient's clinical condition through to Week 24 (approx. 6 months) post-transplant.

To test the primary hypothesis, stratum-adjusted Cochran Mantel-Haenszel weights were used to calculate the overall between-group differences. Letermovir was to be considered superior to placebo if the one-sided p-value was less than or equal to 0.0249.

Methods to account for missing data

The CS included a number of analyses with full details given in Section 2.4.2.3. Briefly, the primary missing data approach used for the efficacy analyses in the study was the "non-completer = failure" (NC = F) approach. 'Non-completers' included patients who withdrew from the study and those missing data points. The ERG considers this a conservative assumption that should not bias the relative treatment effect. The main effect of this assumption is to increase the apparent incidence of CMV reactivation in both treatment arms. It should be noted that this primary outcome is not used in the economic model.

A secondary missing data approach was the "data-as-observed" (DAO) approach. With this approach, any patient with a missing value for a particular endpoint was excluded from the analysis. The ERG notes that this analysis ignores any attrition bias.

A post-hoc multiple imputation model was carried out within each risk stratum to impute the occurrence of clinically significant CMV infection in patients who discontinued or had missing data. Two assumptions for missing data were made, referred to as 'missing-at-random' (MAR), and missing-not-at-random (MNAR). The first imputation model (MAR) assumed the clinically significant CMV infection rate = the observed rate for each treatment group, which may introduce bias if missing data did not occur at random. The ERG notes that this would have little (if any) impact on the analysis apart from (unreasonably) narrowing the confidence intervals. The second imputation model (MNAR) assumed the clinically-significant CMV infection rate for both letermovir and

placebo groups = the observed rate in the placebo group. That is, it assumed no treatment benefit of letermovir in missing patients. The ERG considers this a reasonably conservative analysis, although a more sophisticated approach attempting to predict missing data may have yielded more appropriate results; as discussed in Section 5, the approaches to handling missing data impact on efficacy estimates.

4.2.6 Summary of the quality of trial PN001

The quality assessment of Trial PN001 is reported in CS Appendix D.2.1.

Table 5 Quality assessment of Trial PN001 (adapted from CS Tables 67 and 68)

Trial	Assessment in CS (Section D 1.6 and		
	From Marty et al. 2017	Based on Duarte et al.2017	ERG assessment based on CS and CSR
Was randomisation carried out appropriately?	Yes	Patients were randomised stratified by study site and high or low CMV disease risk	Yes – it is stated in the CSR (section 9.4.5) that randomization occurred centrally using an interactive voice response system (IVRS) and integrated web response system (IWRS). Note whilst the information stated under the Duarte paper is correct it does not address the risk of selection bias. Stratification reduces the chance of random imbalance.
Was the concealment of treatment allocation adequate?	Yes	Not reported	Yes– it is stated in the CSR (section 9.4.4) that the subject, the investigator and Sponsor personnel or delegate(s) who were involved in the treatment or clinical evaluation of the subjects were unaware of the treatment group assignments
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Study arms were balanced	Yes but there was some imbalance in the proportion of high risk patients (slightly higher in the letermovir arm)
Were the care providers, patients and outcome assessors blind to treatment allocation?	Yes	Triple masking (patient, investigator and outcomes assessor) used (NCT02137772)	Yes – see concealment of allocation above
Were there any unexpected imbalances in dropouts between groups?	No	Not reported	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Not applicable	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Modified intention-to-treat: Populations analysed for CMV prophylaxis failure reported were lower than the population that received the study drug, although mITT criteria not reported.	No. A modified ITT that included 'All Subjects as Treated', i.e. all randomised who received at least one dose of study medication. The main analysis population (named the 'full analysis population' (FAS)) excluded randomised and treated patients who had detectable CMV DNA at baseline.

The assessment in Table 5 is one of the risk of bias inherent in the trial. Overall the trial was well conducted and risk of bias was low. However there are some deficiencies in the trial design which

make it sub-optimal in addressing the research question / needs of clinical practice. The main limitation is the fixed treatment duration for 100 days, which did not allow prophylaxis to continue until each individual patient was considered at low risk of CMV reactivation. Therefore the trial will not have collected the best data to evaluate the efficacy of letermovir to prevent infection or improve mortality. The lack of follow-up of the occurrence of clinically significant CMV infection beyond Week 24 also limits the information collected on the effect of letermovir.

There are also some questions regarding the statistical analysis of the time to event data, which are discussed further in Section 4.2.8.

4.2.7 Generalisability of trial PN001 to NHS clinical practice

The clinical advisors to the ERG believed that whilst the population in PN001 was not a perfect match to patients in the NHS, it could be considered to be essentially generalisable, despite only 12 patients (ASaT population – 6 in letermovir arm and 6 in placebo) recruited to the trial from UK centres. The UK patient population might be more white, more male, and include more matched unrelated patients than that in the trial. The most important difference relates to the use of T-cell depletion and the agents employed to achieve this. In the UK, the use of T-cell depletion for unrelated donor allo-HSCT is almost universal, while some centres also use T-cell depletion in those with related donors. In UK practice, alemtuzumab is used in up to 85% of patients in some centres. Alemtuzumab is more profoundly T-cell depleting than the main alternative, anti-thymocyte globulin (ATG). The incidence of CMV reactivation is substantially higher with T-cell depletion than without, and is higher with alemtuzumab than with ATG. In the PN001 study only ~40% of patients underwent T-cell depletion in and almost all of these received ATG (33% of FAS population ATG, 4.0% alemtuzumab). We would therefore expect higher rates of CMV reactivation, with lower incidence of GvHD in UK clinical practice; the ERG notes that this also suggests a higher potential need and benefit of letermovir in these patients. The age of the population also has an important influence on estimates of efficacy and cost effectiveness; while patients in the PN001 trial were around 51 years of age on average, results from the HMRN database suggested that allograft recipients in NHS practice would be closer to 45 years.

The generalisability of the trial to NHS practice may also be limited by the 100-day fixed treatment duration of letermovir. This did not allow prophylaxis to continue until each individual patient was considered to be at low risk of CMV reactivation as might occur in clinical practice. It should be noted that the licence permits continued use in high risk patients. Furthermore the delay before initiation of prophylaxis seen in the trial of around 9 days would be unlikely in practice. Therefore,

the treatment duration in practice is likely to be longer than that seen in the trial, limiting generalisability of the results from this trial.

As discussed in Section 2, there is a question over which data analysis set from PN001 (FAS or ASaT) is most generalisable to clinical practice.

The prevalence of CsA use also differed significantly between the trial and NHS clinical practice. While the ERG's clinical advisors suggested 90% of patients would receive CsA-based immunosuppressive therapy, only 51.7% of letermovir patients (ASaT population) in the trial received CsA, with the remainder given tacrolimus-based or other immunosuppressive regimens. This difference may be significant in considering the generalisability of these trial results, due to the effect of CsA upon the bioavailability and effective dose of letermovir, which will also reduce the total amount of letermovir required. Furthermore, it is unclear for how long subjects received concomitant immunosuppression in the trial, and likely varied by country.

The definition of 'Clinically-significant CMV infection' used in the trial may also impact on the generalisability of the trial results to NHS practice. Clinically-significant CMV infection was defined as the occurrence of either initiation of anti-CMV PET based on documented CMV viraemia (as measured by the central laboratory) and the clinical condition of the patient, or onset of CMV end-organ disease. Initiation of PET in this study referred to the practice of initiating therapy with ganciclovir, valganciclovir, foscarnet and/or cidofovir. The threshold for initiation of PET recommended in the trial protocol was the detectable presence of CMV DNA, or ~150 copies/ml using the central laboratory PCR method. However, as discussed earlier, PET is not initiated in NHS practice in the absence of symptoms of CMV disease unless there is a rapidly rising viral load or a threshold (significantly exceeding ~150 copies/ml) is reached. It is reasoned that some patients may have stable low levels of CMV reactivation of <1500 copies/ml for weeks without ill effect, and that many such low level infections may clear in low-risk patients naturally. Therefore trial patients were likely to have initiated PET therapy much earlier than in NHS practice, and the number of NHS patients classed as having CMV infection may be lower, although as discussed above, this is likely to be offset by the increased use of more potent T-cell depletion. Furthermore, in the trial many patients were initiated on PET at CMV DNA level that were even lower than the protocol recommended ones (see Section 4.2.8, Table 9 and associated text).

4.2.8 Summary of efficacy results of PN001

Clinically-significant CMV infection by Week 24 post-transplant

As stated in previous sections, the primary endpoint was incidence of clinically-significant CMV infection by Week 24 post-transplant, as assessed by the proportion of patients with CMV end-organ disease or initiation of anti-CMV pre-emptive therapy based on documented CMV viraemia and the patient's clinical condition. The primary analysis was of the FAS population and used the very conservative assumption that withdrawn patients or missing data points equalled a CMV infection event. The results of this primary endpoint together with the component data are presented in Table 6.

Table 6 Data for clinically-significant CMV infection by Week 24 post-transplant, (FAS) (adapted from CS Table 11 and clarification response Tables 7 and 9)									
	FAS			ASaT			Excluded from FAS (CMV DNA on Day1)		
Parameter	Letermovir (n = 325) n (%)	Placebo (n = 170) n (%)	Difference* (95% CI) (letermovir-placebo), one sided p value	Letermovir (n = 373) n (%)	Placebo (n = 192) n (%)	Difference* (95% CI) (letermovir-placebo), one sided p value	Letermovir (n = 48) n (%)	Placebo (n = 22) n (%)	Difference* (95% CI) (letermovir-placebo), one sided p value
Primary efficacy endpoint (proportion of patients who failed prophylaxis by Week 24 i.e Clinically significant CMV infection by Week 24 with NC+F)[a]	122 (37.5)	103 (60.6)	–23.5 (–32.5 to –14.6) p-value<0.0001	[redacted]	[redacted]	[redacted]	31 (64.6)	20 (90.9)	26.1% (-45.9%, -6.3%), p-value <0.0048
Clinically significant CMV infection by Week 24 (data as observed)	57/[redacted] (17.5% of FAS)	71/[redacted] (41.8% of FAS)	[redacted]	[redacted]	[redacted]		22 (45.8)	17 (77.3)	
Initiation of pre-emptive therapy based on documented CMV viraemia	52 (16.0)	68 (40.0)		[redacted]	[redacted]		21 (43.8)	17 (77.3)	
CMV end-organ disease	5 (1.5)	3 (1.8)		[redacted]	[redacted]		2 (4.2)	1 (4.5)	
Discontinued from study before Week 24	56 (17.2)	27 (15.9)		[redacted]	[redacted]		8 (16.7)	3 (13.6)	
Missing outcome in Week 24 visit window	9 (2.8)	5 (2.9)		[redacted]	[redacted]		1 (2.1)	0 (0.0)	

Table 6 Data for clinically-significant CMV infection by Week 24 post-transplant, (FAS) (adapted from CS Table 11 and clarification response Tables 7 and 9)

	FAS			ASaT			Excluded from FAS (CMV DNA on Day1)		
Parameter	Letermovir (n = 325) n (%)	Placebo (n = 170) n (%)	Difference* (95% CI) (letermovir-placebo), one sided p value	Letermovir (n = 373) n (%)	Placebo (n = 192) n (%)	Difference* (95% CI) (letermovir-placebo), one sided p value	Letermovir (n = 48) n (%)	Placebo (n = 22) n (%)	Difference* (95% CI) (letermovir-placebo), one sided p value

CI = confidence interval; CMV = cytomegalovirus; FAS = full analysis set; NC = F = non-completer = failure.[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed. * Stratum-adjusted treatment difference (95% CI) (letermovir-placebo), One sided p value

The results for the ASaT population and results for those patients who were not included in the FAS population because they had detectable CMV DNA on Day 1 were provided in the company's clarification response and are also included in Table 6. The treatment differences for the primary outcome analysis were similar across the analysis sets, though the number of events was higher in both the letermovir and placebo groups in the data set containing only those patients who were randomized and treated but CMV positive at Day 1. It is noteworthy that there is a statistically significant benefit in these patients.

In addition, a number of sensitivity analyses relating to the methods for imputation in the analysis of the FAS data set were presented in the CS and these are presented in Table 7.

Table 7 Analysis of clinically significant CMV infection by Week 24 (adapted from CS Table 11 and text)

Analysis of clinically significant CMV infection by Week 24	Population	Stratum-adjusted treatment difference (95% CI) (letermovir-placebo)[c] One sided p value
Primary analysis (proportion of patients who failed prophylaxis by Week 24 i.e Clinically significant CMV infection by Week 24 with NC+F)	FAS	–23.5 (–32.5 to –14.6) p-value<0.0001
Data as Observed	FAS	[redacted]
Imputation of missing values using mean value for respective treatment group (MAR)	FAS	-30.7 (95% CI: -34.8, -26.5) p<0.0001
Imputation of missing values using mean value for placebo group for both letermovir and placebo groups (NMAR)	FAS	-24.5 (95% CI: -28.4, -20.7, p<0.0001

The results of the primary and sensitivity analyses demonstrate that letermovir significantly reduces the rate of clinically significant CMV infection. As noted in Section 4.2.5 the NC+F is the most conservative analysis and the DAO the most optimistic, and the MAR analysis closely reflected the DAO as expected

Subgroup analyses of the primary outcome were presented in the CS (Section B2.7 and Appendix E). The consistency of the treatment effect of letermovir in PN001 was assessed across various subgroups (FAS population) based on risk categories for CMV reactivation (risk stratum, stem cell source, degree of donor mismatch, haploidentical transplantation), patient characteristics (age, gender, weight, region, time of randomisation from the day of transplantation), and conditioning and concomitant immunosuppressive regimen (CsA-containing and tacrolimus-containing) used. Overall, the treatment effect consistently favoured letermovir across subgroups based on patient baseline, epidemiological and clinical characteristics.

The ERG notes that in some subgroups the effect size is numerically different from that of the whole trial population: higher in high risk patients; donor mismatch subgroups; haploidentical donors; female subgroups; and with use of non-myeloablative conditioning regimen; and lower in Asian race; Hispanic or Latino ethnicity; US patients; and use of tacrolimus as immunosuppressant. Details are presented in Table 8. No tests for interaction were conducted to evaluate the statistical significance of these subgroup differences. It should be noted that when DAO data are used for these subgroups analyses (as presented in the CSR) numerical differences are seen for fewer subgroups: the observed difference was notably smaller for matched related donors; Asian patients; and use of tacrolimus as immunosuppressant (compared to use of CsA).

Table 8 Noteworthy Subgroup results for clinically significant infection at Week 24 (NC=F FAS population) (adapted from CS Tables 16, 17 and 18)

Risk category	Letermovir		Placebo		Letermovir vs. Placebo % (95% CI)†
	n/N	% (95% CI)	n/N	% (95% CI)	
Total	**122/325**	**37.5 (32.3, 43.1)**	**103/170**	**60.6 (52.8, 68.0)**	**-23.5 (-32.5, -14.6)**
Risk Stratum‡					
High Risk	43/102	42.2 (32.4, 52.3)	33/45	73.3 (58.1, 85.4)	-31.2 (-47.5, -14.9)
Low Risk	79/223	35.4 (29.2, 42.1)	70/125	56.0 (46.8, 64.9)	-20.6 (-31.3, -9.8)
Donor Mismatch					
Matched related	40/114	35.1 (26.4, 44.6)	28/59	47.5 (34.3, 60.9)	-12.1 (-28.1, 3.8)
Mismatched related	16/46	34.8 (21.4, 50.2)	12/16	75.0 (47.6, 92.7)	-40.2 (-66.5, -13.9)
Matched unrelated	43/122	35.2 (26.8, 44.4)	49/72	68.1 (56.0, 78.6)	-31.1 (-45.2, -17.1)
Mismatched unrelated	23/43	53.5 (37.7, 68.8)	14/23	60.9 (38.5, 80.3)	-7.4 (-33.7, 18.8)
Haploidentical Donor					
Yes	19/51	37.3 (24.1, 51.9)	14/19	73.7 (48.8, 90.9)	-36.4 (-61.0, -11.8)
No	103/274	37.6 (31.8, 43.6)	89/151	58.9 (50.7, 66.9)	-21.5 (-31.2, -11.8)
Gender					
Male	72/176	40.9 (33.6, 48.6)	58/104	55.8 (45.7, 65.5)	-15.7 (-27.7, -3.8)
Female	50/149	33.6 (26.0, 41.7)	45/66	68.2 (55.6, 79.1)	-34.8 (-48.5, -21.2)
Race Subgroup					
Asian	18/35	51.4 (34.0, 68.6)	6/11	54.5 (23.4, 83.3)	-3.1 (-39.1, 32.9)
Non-Asian	104/290	35.9 (30.3, 41.7)	97/159	61.0 (53.0, 68.6)	-25.5 (-34.9, -16.2)
Ethnicity					
Hispanic or Latino	12/24	50.0 (29.1, 70.9)	5/10	50.0 (18.7, 81.3)	0.0 (-41.1, 41.1)
Not Hispanic or Latino	107/288	37.2 (31.6, 43.0)	95/154	61.7 (53.5, 69.4)	-25.4 (-34.8, -16.0)
Not Reported	0/4	0.0 (0.0, 60.2)	2/5	40.0 (5.3, 85.3)	NA
Unknown	3/9	33.3 (7.5, 70.1)	1/1	100.0 (2.5, 100.0)	NA
Region					

US	44/117	37.6 (28.8, 47.0)	34/67	50.7 (38.2, 63.2)	-13.1 (-28.1, 1.9)
Ex-US	78/208	37.5 (30.9, 44.5)	69/103	67.0 (57.0, 75.9)	-30.3 (-41.4, -19.2)
Conditioning Regimen					
Myeloablative	60/154	39.0 (31.2, 47.1)	50/85	58.8 (47.6, 69.4)	-20.9 (-33.9, -7.9)
Reduced intensity conditioning	33/86	38.4 (28.1, 49.5)	28/48	58.3 (43.2, 72.4)	-19.9 (-37.7, -2.2)
Non-myeloablative	29/85	34.1 (24.2, 45.2)	25/37	67.6 (50.2, 82.0)	-33.2 (-51.4, -15.0)
Immunosuppressive Regimen‡					
Ciclosporin A	58/162	35.8 (28.4, 43.7)	60/90	66.7 (55.9, 76.3)	-31.1 (-43.2, -19.0)
Tacrolimus	56/145	38.6 (30.7, 47.1)	37/69	53.6 (41.2, 65.7)	-15.5 (-29.8, -1.1)
Other	8/18	44.4 (21.5, 69.2)	5/9	55.6 (21.2, 86.3)	NA
Missing	NA	NA	1/2	50.0 (1.3, 98.7)	NA

Clinically-significant CMV infection by Week 14 post-transplant

Table 9 Clinically significant CMV infection by Week 14 post-transplant (NC=F Approach, FAS population) (From clarification response Table 11)

Parameter	**Letermovir (n = 325) n (%)**	**Placebo (n = 170) n (%)**
Failures	**62 (19.1)**	**85 (50.0)**
Clinically significant CMV infection by Week 14	25 (7.7)	67 (39.4)
Initiation of pre-emptive therapy based on documented CMV viraemia	24 (7.4)	65 (38.2)
CMV end-organ disease	1 (0.3)	2 (1.2)
Discontinued from study before Week 14	33 (10.2)	16 (9.4)
Missing outcome in Week 14 visit window	4 (1.2)	2 (1.2)
Stratum-adjusted treatment difference (letermovir-placebo)		
Difference (95% CI)	–31.3 (–39.9 to –22.6)	
P value	<0.0001	

These tabulated results, which reflect those of the primary endpoint, were provided in the company's response to clarification. These outcome data are used in the economic model.

Initiation of pre-emptive therapy for documented CMV viraemia by Week 24 post-transplant

The results for the FAS population and sensitivity analyses based on the FAS population are presented in

Table 10. In addition, results for the ASaT population are given in Table 11. The results reflect those of the primary endpoint, which is unsurprising given that most clinically significant infection events were initiations of PET.

Table 10 Initiation of pre-emptive therapy for documented CMV viraemia by Week 24 post-transplant (NC=F Approach, FAS Population) (Adapted from CS Table 12 and text)

Parameter	Letermovir (n=325) N (%)	Placebo (n=170) N (%)	Stratum-adjusted treatment difference (Letermovir-Placebo) Difference (95% CI)
Initiation of PET based on Central laboratory (FAS)			
Initiation of pre-emptive therapy for documented CMV viraemia (NC=F Approach)	119 (36.6)	101 (59.4)	-23.3 (-32.3, -14.3) one sided p-value <0.0001
Initiation of pre-emptive therapy based on documented CMV viraemia (no imputation)	52 (16.0)*	68 (40.0)*	-30.6 (-40.2, -21.0) one sided p-value <0.0001
Discontinued from study before Week 24	57 (17.5)	28 (16.5)	
Missing outcome in Week 24 visit window	10 (3.1)	5 (2.9)	
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	

*Percentage based on intention to treat

Table 11 Initiation of pre-emptive therapy for documented CMV viraemia by Week 24 post-transplant (NC=F Approach, FAS Population) (Adapted from CS Table 12 and text)

Parameter	Letermovir (n=373) N (%)	Placebo (n=192) N (%)	Stratum-adjusted treatment difference (Letermovir-Placebo) Difference (95% CI)
Initiation of PET based on Central laboratory (FAS)			
Initiation of pre-emptive therapy for documented CMV viraemia (NC=F Approach)	[redacted]	[redacted]	[redacted]
Initiation of pre-emptive therapy based on documented CMV viraemia (no imputation)	[redacted]	[redacted]	
Discontinued from study before Week 24	[redacted]	[redacted]	
Missing outcome in Week 24 visit window	[redacted]	[redacted]	

The ASaT results were similar to the FAS results but the number of events was higher in the ASAT population – reflecting the fact that those patients excluded from the FAS population were at higher risk of developing a clinically significant infection requiring initiation of PET.

No additional sensitivity analyses were conducted for this outcome to explore the impact of patient withdrawals and missing data. [redacted]. It should be noted that the first of these sensitivity analyses was included in the CS but the second was not: the ERG took the details from the CSR supplied with the CS.

[redacted].

[redacted]

[redacted]

Table 12 PN001- Proportion of Patients with Initiation of Pre-emptive therapy for Documented CMV Viraemia through Week 14 Post-Transplant (NC=F Approach, FAS Population)(From clarification response Table 13)

Parameter	Letermovir (n=325) N (%)	Placebo (n=170) N (%)
Failures	**61 (18.8)**	**84 (49.4)**
Initiation of pre-emptive therapy based on documented CMV viraemia	24 (7.4)	65 (38.2)
Discontinued from study before Week 14	33 (10.2)	17 (10.0)
Missing outcome in Week 14 visit window	4 (1.2)	2 (1.2)
Stratum-adjusted treatment difference (Letermovir-Placebo)		
Difference (95% CI)	-31.0 (-39.6, -22.4)	
p-value	<0.0001	

Proportion of patients with CMV disease by Week 14 post-transplant and Week 24 post-transplant

The results for the proportion of patients with CMV disease are reported in Section 2.6.3.1 of the CS and are presented in Table 13 below. The overall incidence of CMV end-organ disease (FAS population) was low through both the Week 14 and Week 24 post-transplant time points. Therefore, only the DAO analyses was used so as not to classify patients who discontinued before Week 24 post-transplant or had missing data as failures, which could lead to potentially misleading estimates of CMV end-organ disease rates. Using this approach, the rates of CMV end-organ disease were comparable between the groups at both time points.

Table 13 Proportion of patients with CMV disease by Week 14 post-transplant and Week 24 post-transplant (FAS population, DAO analysis only) (adapted from CS Table 18)

Parameter	Letermovir (n=285) N (%)	Placebo (n=145) N (%)	Stratum-adjusted treatment difference (Letermovir-Placebo) Difference (95% CI)
CMV Disease by Week 14 (adjudicated cases only) (no imputation)	1	2	-1.0 (-3.5, 1.5) one-sided p-value of 0.2258
CMV Disease by Week 24 (adjudicated cases only) (no imputation)	5	3	-0.4% (-4.0%, 3.2%), one-sided p-value of 0.4056.

Time to onset of clinically significant CMV infection

The time to onset of clinically-significant CMV infection through Week 24 post-transplant was presented in the CS (Section 2.6.4.1) and summarised using Kaplan-Meier (K-M) plots (Figure 3). A plot for time to Initiation of PET through Week 24 post-transplant was also available from the CSR and is presented in Appendix 10.1 of this report. Given the very small number of CMV disease events it is not surprising that the time to clinically-significant CMV infection curve and the time to initiation of PET curves are very similar. It is the latter data that are included in the economic model.

Figure 3 K-M Plot of Time to Onset of Clinically Significant CMV Infection by Week 24 Post-Transplant (FAS Population) (CS figure 4)

At Week 24 post-transplant, the event rate (95% CI) for clinically-significant CMV infection was 18.9% (14.4%, 23.5%) in the letermovir group versus [redacted] in the placebo group. In response to a request by the ERG, the company undertook a hazard modelling approach to analysing this outcome, producing a hazard ratio (95% CI) of [redacted] for letermovir vs placebo. The distribution of time to event significantly differed between the letermovir and placebo groups (nominal two-sided $p<0.001$), after controlling for stratification of high and low risk of CMV end-organ disease at baseline.

There was a large separation between the curves from Day 0 to Week 14 while patients were on study drug. Once medication was discontinued at Week 14, there was a small rebound effect in the letermovir group. Assessment using a logistic regression model adjusted for baseline risk strata (high or low risk for CMV reactivation at baseline) found that factors associated with CMV DNAemia after cessation of letermovir prophylaxis up to Week 24 post-transplant included high baseline risk for CMV reactivation, GvHD, and corticosteroid. The incidence of late failure in subjects at high risk for CMV reactivation was [redacted] compare to [redacted] in subjects at low risk. The incidence of late failure was [redacted] for subjects who developed GvHD after randomization compared to [redacted] for subjects who did not. In subjects with concomitant steroid use, the incidence of late failures was [redacted] vs. [redacted] in subjects with no concomitant steroid use.

The Kaplan-Meier event rate for time to Initiation of PET through Week 24 post-transplant was [redacted] in the letermovir group versus [redacted] in the placebo group.

All-cause Mortality

Mortality was followed up through Week 48 and reported in the CS (section 2.6.5.1). Separate plots were provided for all-cause mortality through weeks 24 and 48, incidences were provided for the letermovir and placebo groups at 14, 24 and 48 weeks, and nominal log rank p-values (not controlled for multiplicity) were presented for the curves through Week 24 and separately for the curves through Week 48. As the data through Week 48 follow-up represent the longest follow-up, only the results based on these data are summarised below. The ERG understands that these data also include those patients who withdrew early from the trial but whose post-trial vital status was later ascertained. In the analysis, patients of unknown status were assumed to be alive. These results are summarised in Table 14.

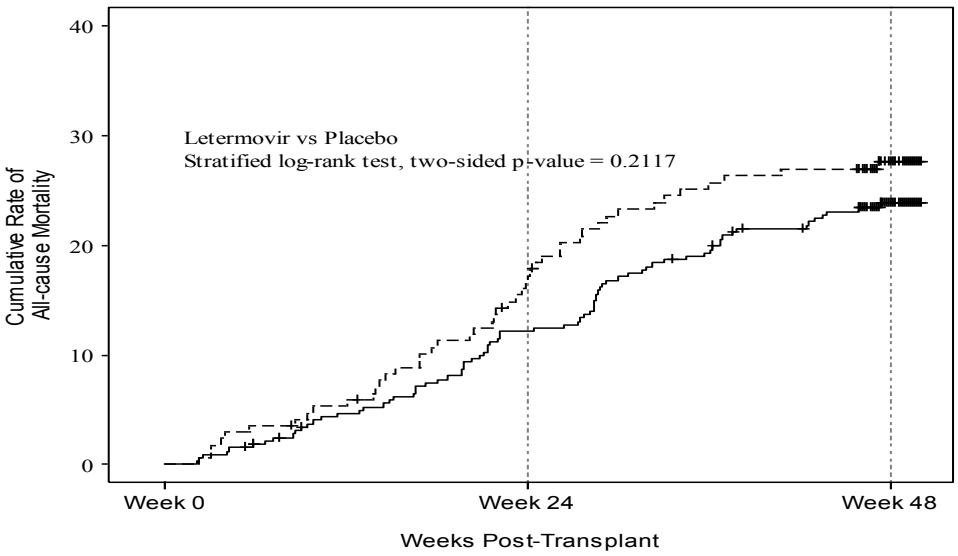
Table 14 Results for All-cause mortality through weeks 14, 24 and 48 (FAS population) (adapted from CS figures 5 and 6 and Response to clarification questions, Tables 15 and 16)

	Incidence of all-cause mortality		K-M event rate		Log Rank test (Stratified 2-sided) P-value for difference
	Letermovir	Placebo	Letermovir	Placebo	
Week 24			From Through Week 48 K_M plot 12.1%; 95% CI 8.6, 15.7**	From Through Week 48 K_M plot 17.2%; 95% CI 11.5, 22.9**	0.0401
Week 48	20.9%, 95% CI: 16.2% to 25.6%	25.5%, 95% CI: 18.6% to 32.5%	23.8%; 95% CI 19.1, 28.5	27.6%; 20.8, 34.4	0.2117
Clin sig CMV infection	9/57 [15.8%])	22/71 [31.0%])			NR
No Clin sig CMV infection	52/268 [19.4%]	18/99 [18.2%]			NR

**These are the most compete results for wk 24 – these are given in the CS on p59 (from CS figure 6 which is reproduced as

Figure 4 below.

Figure 4 K-M plot of time to all-cause mortality at Week 48 post-transplant (including vital status collected post-study, FAS population)



No. at risk: KM estimates % (95% CI)

Letermovir	325	282: 12.1 (8.6, 15.7)	165: 23.8 (19.1, 28.5)
Placebo	170	139: 17.2 (11.5, 22.9)	81: 27.6 (20.8, 34.4)

The ERG requested that an estimate of the treatment difference between the groups using a hazard modelling approach. In the clarification response, the company's Cox proportional hazards model yielded a hazard ratio (95% CI) of 0.57 (0.34, 0.96) for letermovir vs placebo for all-cause mortality risk through Week 24. The ERG note that this analysis was based on the through Week 24 data only (i.e. derived from CS Figure 5 rather than the more complete

Figure 4 above. The hazard ratio may therefore be a slight over estimation of the letermovir effect size. There was no significant association between letermovir and risk of all-cause mortality through Week 48, with a hazard ratio (95% CI) of 0.73 (0.49, 1.09). The ERG notes that the number and percentage of events (deaths) in this analysis does not match those in the original submission. However, the differences are small and the results of the analysis is the same: the reduction in mortality with letermovir at Week 48 is not statistically significant.

The ERG also notes that based on CS Table 14 by Week 48 in the letermovir group 79/325 patients (24.3%) had died compared with 46/170 (28.2%) in the placebo group. These percentages are slightly higher than those in the analyses above. The ERG notes that these numbers are similar to but slightly different to those given in Table 37 of the EPAR (23.4% (76/325) vs 27.1% (46/170).

Finally, this mortality benefit was explored when stratified by prior CMV infection in an additional ad-hoc analysis. This analysis suggested a lower mortality rate through Week 48 in the letermovir group (9/57 [15.8%]) versus the placebo group (22/71 [31.0%]) among patients with clinically-significant CMV infection through Week 24; and similar mortality rates between the letermovir (52/268 [19.4%]) and placebo (18/99 [18.2%]) groups in patients without clinically-significant CMV infection through Week 24. The CS states that:

"Since significantly fewer letermovir-treated versus placebo-treated patients developed clinically-significant CMV infection, the decrease in all-cause mortality observed with letermovir is likely due to prevention of CMV viraemia post-transplant."

The ERG doesn't not consider this a clear explanation. The ERG suggests that the results indicate that letermovir prevents additional CMV-related mortality, despite not completely preventing CMV reactivation.

Non-relapse related mortality

[redacted]

[redacted]

Health-related quality of life

To assess QoL in this study, patients completed two validated tools of patient-reported outcomes (PROs) - the EQ-5D (Version 3L) and the FACT-BMT (Version 4) - at the time of randomisation, Week 14, Week 24, and Week 48 post-transplant. An assessment was also conducted upon CMV infection onset or at the early discontinuation visit, if applicable.

[redacted]

The ERG notes that three of the four assessment points are when the patient is not taking letermovir, and the Week 14 assessment is at the end of the letermovir treatment period. Other than at randomisation, the mean values for EQ-5D and the FACT-BMT scores do not represent any single condition: at weeks 14, 24 and 48 patients will be a mixture of those who have had CMV reactivation and will have commenced PET and those who have not. Difference in the HRQoL scores will reflect the difference between these two health states rather than any direct impact of letermovir on HRQoL. Whilst letermovir will have impacted on the proportion of patients in these two states, other influencing factors such as the specific PET regimen and the patient's ability to tolerate the PET received will impact strongly on the scores.

[redacted]

Table 15 Analysis of treatment effect in EQ-5D and FACT-BMT total score (FAS population)

	Letermovir vs Placebo	
	Mean difference (95% CI)	p-value
EQ-5D UK Index		
Baseline	[redacted]	[redacted]
Week 14 post-transplant	[redacted]	[redacted]
Week 24 post-transplant	[redacted]	[redacted]
Week 48 post-transplant	[redacted]	[redacted]
FACT-BMT total score		
Baseline	[redacted]	
Week 14 post-transplant	[redacted]	[redacted]
Week 24 post-transplant	[redacted]	[redacted]
Week 48 post-transplant	[redacted]	[redacted]

Other exploratory endpoints

The results for other exploratory endpoints (GvHD, re-hospitalisation and opportunistic infections) were presented in the CS - see Table 16 (CS Table 15)

Table 16 Summary of the efficacy analyses for non-mortality exploratory endpoints (FAS population) (CS Table 15 and clarification response Table 17))

	Letermovir (N=325)		Placebo (N=170)	
Exploratory Endpoints	n	% (95% CI)	n	% (95% CI)
Bacterial and/or Fungal opportunistic infection through Week 14 post-transplant	78	24.0 (19.5, 29.0)	37	21.8 (15.8, 28.7)
Bacterial and/or Fungal opportunistic infection through Week 24 post-transplant	87	26.8 (22.0, 31.9)	43	25.3 (19.0, 32.5)
GvHD through Week 14 post-transplant	126	38.8 (33.4, 44.3)	71	41.8 (34.3, 49.6)
GvHD through Week 24 post-transplant	159	48.9 (43.4, 54.5)	93	54.7 (46.9, 62.3)
Re-hospitalisation through Week 14 post-transplant	118	36.3 (31.1, 41.8)	81	47.6 (39.9, 55.4)
Re-hospitalisation for CMV infection/disease through Week 14 post-transplant	2	0.6 (0.1, 2.2)	12	7.1 (3.7, 12.0)
Re-hospitalisation through Week 24 post-transplant	158	48.6 (43.1, 54.2)	94	55.3 (47.5, 62.9)
Re-hospitalisation for CMV infection/disease through Week 24 post-transplant	10	3.1 (1.5, 5.6)	13	7.6 (4.1, 12.7)
Documented CMV viraemia through Week 14 post-transplant	103	31.7 (26.7, 37.1)	118	69.4 (61.9, 76.2)
Documented CMV viraemia through Week 24 post-transplant	186	57.2 (51.7, 62.7)	124	72.9 (65.6, 79.5)
N = Number of patients in analysis population; n = Number of patients with outcome.				

The results presented in Table 5 indicate that bacterial/fungal infections through Week 14 and through Week 24 were numerically slightly higher in letermovir group compared with placebo group. GvHD, re-hospitalisation, re-hospitalisation for CMV infection, and documented CMV viraemia through Week 14 and through Week 24 were all numerically lower in letermovir group compared with placebo group. The result for documented CMV viraemia favoured letermovir by a large margin.

No statistical tests for the significance of these differences were presented.

4.2.9 Phase II trial (Chemaly 2014)[1]

The information presented here on the Phase II trial (Chemaly 2014[1]) is derived from Section 2.8.1 of the CS. CS Section 2.8.1 also included information on a publication by Duarte et al 2017[5], which was of the PN001 trial and so is not repeated here, and a trial by Burns et al 2002[4], comparing ganciclovir with aciclovir, which is not directly relevant to this appraisal and so is also not presented here.

The Phase II trial compared 3 doses of letermovir (60 mg, 120 mg, and 240 mg) once daily with placebo. Treatment duration was 84 days. Only the 240 mg dose is directly relevant to the present appraisal and then only if patients received concomitant CsA. Also the treatment duration in this trial is shorter than the licensed 100 days, which limits the generalisability of any results from this trial.

Ninety eight patients were randomised (distributed evenly across the doses). Patient characteristics are summarised in Table 17 and the results are presented in Table 18.

Table 17. Patient characteristics from the Phase II trial (Chemaly 2014) (adapted from CS Table 20)

Letermovir dose	Male participants, n (%)	Average age (range)	CMV seropositive donor status, n (%)	Bone marrow HSCT, n (%)	Peripheral blood HSCT, n (%)
60 mg	14(42)	55 (24-69)	13 (39)	1 (3)	32 (97)
120 mg	22 (71)	57 (22-68)	17 (55)	0 (0)	31 (100)
240 mg	22 (65)	53.5 (25-67)	21 (62)	1 (3)	33 (97)
Placebo	19 (58)	53 (24-71)	19 (58)	2 (6)	31 (94)

Table 18 Outcomes and results from the Phase II trial (Chemaly 2014) (adapted from CS Table 22)

Author (year)	Intervention	Dose	CS-CMV infection, n (%)	Time to onset of CS-CMV (days)	All-cause prophylaxis failure, n (%)	All mortality, n (%)	CMV-related mortality, n (%)	Non-CMV, non-drug mortality, n (%)	GvHD, n (%)	Infection or infestation, n (%)
Chemaly, 2014	Letermovir	60 mg	7 (21)	1-42	16 (48)	2 (6)	0 (0)	2 (6)	4 (12)	17 (52)
		120 mg	6 (19)	1-15	10 (32)	0 (0)	0 (0)	0 (0)	5 (16)	18 (58)
		240 mg	2 (6)	1-8	10 (29)	1 (3)	0 (0)	1 (3)	4 (12)	23 (68)
	Placebo	-	12 (36)	1-21	21 (64)	1 (3)	0 (0)	1 (3)	5 (15)	25 (76)
CS-CMV= clinically-significant CMV infection; GvHD= graft-versus-host disease; NR= not reported										

All-cause prophylaxis failure (defined as patients who discontinued the study drug because of virologic failure or for any other reason such as an adverse event, non-adherence or withdrawal of consent[1]) is similar to the NC=F analysis of initiation of PET in the PN001 trial.

This study demonstrated that letermovir, as compared with placebo, was effective in reducing the incidence of CMV infection in recipients of allogeneic haematopoietic-cell transplants. The highest dose (240 mg/day) had the greatest anti-CMV activity.

The ERG noted that some patients in this study received CsA concomitantly with the 240 mg dose; this is the licensed dose of letermovir. In their clarification response the company provided results for this post-hoc sub group (Clarification response table 24). Prophylaxis failures numbered [redacted]

[redacted] in the letermovir group compared with [redacted] on placebo. Although these cannot be directly compared with the results form PN001, they are supportive.

4.3 Adverse effects of letermovir

Evidence for the adverse effects of letermovir presented in the CS was derived solely from trial PN001: see Section B2.10. The evaluation of adverse effects in PN001 was based on the ASaT population (n=565). The extent of exposure to study drug is given in Table 19.

Table 19 Extent of Exposure to Letermovir or Placebo by Route of Administration (CS Table 24)

	Letermovir			Placebo		
	Any route of administration	IV	Oral	Any route of administration	IV	Oral
Patients in population	373	99	367	192	48	187
Number of days on therapy (n)						
Mean	69.4	[redacted]	66.7	55.2	13.2	53.2
Median	82	12	78	56	12	54
Range	1 - 113	1 - 47	1 - 109	4 - 115	1 - 88	1 - 112
Each patient who received letermovir or placebo is counted once in the respective 'any route' columns for duration of exposure to study medication. Patients may be counted in multiple columns if they received different routes of administration. IV= intravenous; (Database cut-off: 12SEP2016).						

[redacted].

Adverse events are presented in the CS for the Treatment phase (AEs collected from time of study drug initiation through to 14 days following the last dose of study medication), through to Week 24, and through to Week 48 post-transplant. From Week 16 only drug-related SAEs and SAEs leading to death are reported, though the CS also states that tabulated AE data after Week 16 post-transplant also contain any other types of AEs that were passively reported. The ERG notes that the therapies associated with the underlying disease, plus the initiation of PET upon discontinuation of letermovir or placebo make the interpretation of the AE data extremely difficult.

The AEs reported during the treatment phase of trial PN001 are presented in Table 25 of the CS. These are the most directly relevant AEs being those during the active treatment phase of the trial, though those reported after the termination of letermovir or placebo may be contaminated by PET. Not surprisingly given the indication, almost all patient experienced at least one AE, but overall, the AE profile was similar in the letermovir and placebo groups with the exception of AEs leading to discontinuation of study medication: letermovir (19.3% letermovir; 51.0% placebo). The CS states

that this imbalance was mainly due to a higher proportion of patients discontinuing due to the AE of CMV infection in the placebo group (6.2% in letermovir group compared to 39.1% in the placebo group). Treatment phase AEs reported by 4 or more patients are presented in Table 26 of the CS. The most commonly reported treatment phase AEs, namely graft-versus-host disease (GvHD), nausea, vomiting, diarrhoea, pyrexia and rash, occurred at comparable frequency in patients receiving letermovir or placebo. The incidences of the following treatment phase AEs were significantly higher in the letermovir group compared to the placebo group: Cardiac Disorders (12.6% letermovir vs.6.3% placebo; 6.4% difference [95% CI: 1.1, 11.0]) and Ear and Labyrinth Disorders SOC (4.6% letermovir vs. 1.0% placebo; 3.5% difference [95% CI: 0.5, 6.3]), and AEs of myalgia (5.1% letermovir vs. 1.6% placebo; 3.5% difference (95% CI: 0.2%, 6.5%), hyperkalaemia (7.2% letermovir vs. 2.1% placebo; 5.2% difference (95% CI: 1.4%, 8.6%)), and dyspnoea (8.0% letermovir vs. 3.1% placebo; 4.9% difference (95% CI: 0.8%, 8.6%). Further details of each of these are provided in the CS.

In addition to CMV infection (8.3% letermovir vs. 45.8% placebo; -37.5% difference (95% CI: -45.1%, -30.0%)), the incidence of the following AEs was lower in the letermovir group compared to the placebo group and the corresponding 95% CI for the difference in percentage excluded zero: upper abdominal pain: 4.0% letermovir vs. 8.3% placebo; -4.3% difference (95% CI: -9.4%, -0.3%); Gastroesophageal reflux disease (GORD): 1.1% letermovir vs. 4.7% placebo; -3.6% difference (95% CI: -7.7%, -1.0%); Myopathy: 0.5% letermovir vs. 2.6% placebo; -2.1% difference (95% CI:-5.5%, -0.1%); Dehydration: 0.5% letermovir vs. 2.6% placebo; -2.1% difference (95% CI: -5.5%, -0.1%); and presyncope: 0.3% letermovir vs. 2.1% placebo; -1.8% difference (95% CI: -5.0%, -0.2%). Also the CS states that, "Notably, the proportions of patients with Renal and Urinary Disorders SOC AEs and the acute kidney injury PT AE were numerically lower in the letermovir group compared to the placebo group." The ERG notes that the difference was very small: 21.7% with letermovir compared with 24.0% with placebo (difference -2.2% (95% CI: -9.8, 4.9).

Overall, the proportions of patients with SAEs reported during the treatment Phase were similar in the treatment groups (44.2% letermovir vs. 46.9% placebo; difference -2.6 [95% CI -11.3%, 6.0%]). Cardiac Disorders SOC were reported as SAEs by 6 patients (1.6%) in the letermovir group and 1 (0.5%) in the placebo group.

The adverse events through Week 24 are presented in Section 2.10.6 of the CS (Tables 27 and 28) and those through Week 48 were provided in the company's clarification. As stated in the CS the results of the comparison between letermovir and placebo through weeks 24 were similar to those in the treatment phase. Drug related AEs and SAEs are presented separately in the CS (Section 2.10.7). There were no additional reports of drug-related AEs or SAEs, indicating that there were no delayed

AEs associated with letermovir. However, these results are difficult to interpret due to the toxicities associated with various PET regimens.

Through Week 48

Relevant summaries of adverse effect data were reported through to Week 48 were provided by the company in their response to clarification questions. The ERG checked these for any indication that an adverse effect which appeared to be more common on letermovir during the treatment phase persisted in the longer term. Disutilities for any such effects should be included in the economic model.

The company reported that the AE profile through to Week 48 post-transplant was similar for the letermovir and placebo groups, and is consistent with the profile through Week 24 post-transplant. The majority of patients experienced one or more AEs through Week 48 post-transplant [redacted] in the letermovir group vs. [redacted] in the placebo group). Through Week 48 post-transplant, the proportion of patients with at least one SAE reported was [redacted] in the letermovir group vs. [redacted] in the placebo group. They also reported that a total of [redacted] patients in the letermovir group vs. [redacted] of patients in the placebo group discontinued due to a SAE. There were 6 patients with drug-related SAEs [redacted] in the letermovir group vs. [redacted] in the placebo group) through Week 48 post-transplant; there were no additional drug-related SAEs reported after Week 24 post-transplant. The incidence of AEs associated with fatal outcome was [redacted] in the letermovir group vs. [redacted] in the placebo group.

Through Week 48 there was still a statistically significant higher rate in the letermovir group for [redacted].

Not surprisingly, there was a slight increase in the number of patients with SAEs between Week 24 and Week 48 post-transplant ([redacted] additional patients in the letermovir group, and [redacted] additional patients in the placebo group through Week 48 post-transplant when compared to Week 24 post-transplant).

There were no additional drug-related SAEs (incidence >0% in one or more treatment groups) reported between Week 24 and Week 48 post-transplant.

Through Week 48 the proportion of patients with AEs associated with fatal outcomes was [redacted] in the letermovir group compared to [redacted] in the placebo group through Week 24 post-transplant. There were an additional [redacted] with AEs associated with fatal outcomes in the letermovir group compared to [redacted] in the placebo group between Week 24 post-transplant and Week 48 post-transplant. The incidence of AEs associated with fatal outcomes experienced by patients in the letermovir and placebo groups was [redacted], respectively through Week 48 post-transplant.

The most frequently reported specific AEs associated with fatal outcomes through Week 48 post-transplant (letermovir vs. placebo) were recurrent AML [redacted] GvHD [redacted] pneumonia [redacted] sepsis [redacted] septic shock [redacted] AML [redacted], which are consistent with the Week 24 profile for AEs associated with fatal outcomes.

None of the AEs associated with fatal outcomes was considered to be related to study medication by the investigator.

IV Formulation of letermovir

[redacted].

Overall, exposure to letermovir short and even the treatment phase data are difficult to interpret due to the patients' underlying conditions and treatments. During the treatment phase cardiac disorder; hyperkalaemia; ear and labyrinth disorder; and dyspnoea were more common on letermovir than placebo and the difference persisted through follow-up. The follow-up data are even more difficult to interpret due to the initiation of PET on discontinuation of letermovir in many pts. There are no safety data for letermovir use longer than 100 days.

4.4 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable

4.5 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

4.6 Additional work on clinical effectiveness undertaken by the ERG

4.7 Conclusions of the clinical effectiveness section

Evidence of efficacy comes almost entirely from the PN001; a phase III randomised, double-blind, placebo-controlled trial. PN001 is reasonably well conducted, with a low risk of bias. However, design limitations mean the trial could not fully capture the benefit of letermovir and the results generated are not optimal for decision making.

- The fixed 100 days treatment duration may mean potential treatment benefits are not captured – high-risk patients may require longer periods of prophylaxis.
- The primary outcome of clinically significant CMV infection is defined differently than in UK practice, meaning that trial patients initiated PET sooner than they would in practice, thus, overestimating the CMV infection rate.
- In contrast, the high use of T-cell depletion in NHS practice, with its higher risk of CMV infection suggests the infection rate may have been lower in the trial than would be expected in practice.
- The follow-up duration was limited for evaluation of a mortality benefit, and mortality was only an exploratory analysis.
- There are numerous differences between trial and UK practice in patient population composition, donor matching, immunosuppressive regimens, prevalence and intensity of T-cell depletion (putting UK patients at higher risk of CMV reactivation but lower GvHD incidence), myeloablation use, and criteria for initiation of PET. Very few UK patients were included in trial.
- The primary analysis (NC=F approach) of the primary outcome variable is very conservative. It overstates the incidence of CMV infection in untreated patients.
- It is unclear whether the strict inclusion criteria for the main analysis for no detectable CMV-DNA at baseline was an appropriate reflection of clinical practice;
- However, the delay in initiating prophylactic therapy seen in the trial is unlikely to occur in clinical practice, therefore patients with detectable CMV upon initiation of letermovir are highly unlikely to exist.

The results demonstrated that letermovir significantly reduces incidence of clinically significant CMV infection. This was supported by all sensitivity analyses and subgroup analyses. In some subgroups the letermovir effect size is numerically higher than that of the whole trial population: high risk patients; donor mismatch subgroups; haploidentical donors; female subgroups; and with use of non-myeloablative conditioning regimen. It was numerically lower in Asian race; Hispanic or Latino ethnicity; US patients; and use of tacrolimus as immunosuppressant. No tests for interaction were conducted to evaluate the statistical significance of these subgroup differences.

The reduction in clinically significant CMV infection was driven by a reduction in patients initiating PET; the number of patients developing CMV end organ disease was very small.

An analysis of protocol violators who had detectable CMV DNA at baseline found a treatment benefit of letermovir in these patients also; such patient might be eligible for prophylaxis in clinical practice.

The analysis of time to clinically significant CMV infection showed a large separation between the curves from Day 0 to Week 14 while patients were on study drug. Once medication was discontinued at Week 14, there was a small rebound effect in the letermovir group. Factors associated with CMV infection after cessation of letermovir prophylaxis included high baseline risk for CMV reactivation, GvHD, and corticosteroid use.

All-cause mortality was lower in the letermovir group than in the placebo group at Week 24 (using most complete data letermovir 12.1% (95% CI 8.6, 15.7) compared with placebo 17.2%; 95% CI 11.5, 22.9 (Stratified 2-sided p-value for difference= 0.0401). However, at Week 48 the difference was not statistically significant letermovir 23.8%; 95% CI 19.1, 28.5 vs placebo 27.6%; 20.8, 34.4, p= 0.2117. Therefore a benefit of letermovir on all-cause mortality is not confirmed by the results of PN001.

The trial data showed no significant treatment benefit on HRQoL. Small possible utility benefits on GvHD, rehospitalisation, and opportunistic infections were not formally tested.

Evidence for the adverse effects of letermovir presented in the CS was derived solely from trial PN001. The AEs reported during the treatment phase of trial PN001 are the most directly relevant AEs being those during the active treatment phase of the trial. Almost all patient experienced at least one AE, but overall, the AE profile was similar in the letermovir and placebo groups except for AEs leading to discontinuation of study medication, which were driven by the higher rate of CMV infection in the placebo group. The incidences of Cardiac Disorders, Ear and Labyrinth Disorders myalgia, hyperkalaemia, and dyspnoea were significantly higher in the letermovir group.

The results of the comparison between letermovir and placebo for adverse events through Week 24 and through Week 48 were similar to those in the treatment phase. However, these results are difficult to interpret due to the toxicities associated with various PET regimens.

[redacted].

5 Cost Effectiveness

This section focuses on the economic evidence, submitted by the company, and the additional information provided in response to the ERG's points for clarification. The submission was subject to a critical review, on the basis of the company's report, and by direct examination of the electronic version of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of the economic evaluation and a narrative review to highlight key assumptions and areas of uncertainty. Section 6 presents additional analyses and scenarios, either requested from the company or independently undertaken by the ERG, to further explore these uncertainties.

The company's economic submission included:

- A description of each systematic review conducted to identify published evidence on the cost-effectiveness, health-related quality of life (HRQoL)/utilities and resource usage/costs (CS, Sections B.3.1, 3.4.3, 3.5.1), with further details presented in separate appendices (CS, Appendices G, H, I).
- A report on the de novo economic evaluation, conducted by the company. This report includes a description of the patient population (CS, Section 3.2.1) and the model structure (CS, Section 3.2.2); the clinical parameters used in the economic model (CS, Section B.3.3); the measurement and valuation of health effects and quality-of-life data used in the cost-effectiveness analysis (CS, Section B.3.4); the cost and healthcare resource use identification, measurement, and valuation (CS, Section B.3.5); a summary of the inputs and assumptions used in the model (CS, Section B.3.6); the cost-effectiveness results for the base-case (CS, Section B.3.7) and sensitivity analyses (CS, Section B.3.8); an overview of any subgroup analyses (CS, Section B.3.9); the methods of validation (CS, Section B.3.10); and the final interpretation and conclusion of the economic evidence (CS, Section B.3.11).
- An electronic copy of the company's economic model developed in Microsoft Excel®.

In response to a number of points for clarification raised by the ERG, the company further submitted:

- A descriptive reply to the ERG's points for clarification, alongside additional data and analyses requested by the ERG.
- An updated Excel-based model correcting minor errors and incorporating the additional scenario analyses requested by the ERG.

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Searches

The CS described the search strategies used to identify relevant economic modelling studies cost-effectiveness studies for the prophylaxis and/or treatment of CMV infection.

The databases used for the cost effectiveness systematic literature review are reported as being MEDLINE (segments 1946 to Present, MEDLINE in Process, MEDLINE Epub Ahead of Print, MEDLINE Daily) (all via Ovid SP), EMBASE (via OvidSP), and the Cochrane Library databases - the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment database (HTAD), and the NHS EED database. Additional searches of conference websites (American Society of Hematology (ASH), European Society for Blood and Marrow Transplantation (ESBMT) and the American Society for Blood and Marrow Transplantation (ASBMT)) were conducted to identify additional information. The reference lists of key papers were scanned. The search strategies used in MEDLINE, Embase, EconLIT and the Cochrane Library databases, DARE, HTAD and NHS EED are fully reproduced in Appendix G Published cost-effectiveness studies

The strategies used and databases searched were considered appropriate.

5.1.2 Inclusion/exclusion criteria used for study selection

The inclusion/exclusion criteria are reported in Appendix G (CS appendices, Tables 22, pg. 95-96). Studies that assessed letermovir for the prophylaxis of CMV reactivation and disease were included in the review. Articles were independently assessed by one reviewer against each eligibility criteria. Any uncertainty regarding the inclusion of studies was checked and judged by a second reviewer, with the decision being made by consensus between the two reviewers.

5.1.3 Studies included and excluded in the cost effectiveness review

A total of 2,457 potentially relevant articles were identified in the cost-effectiveness review. Of these 2,354 were subsequently excluded at the primary screening stage. The remaining 103 studies were assessed in full. Only two of these articles was included in the final review that were deemed relevant for economic evaluation, and both were abstracts. These two abstracts (covering one study) presented the results of cost-effectiveness analysis of letermovir as second-line treatment for CMV-specific T-cell therapy and another as a third line treatment option.[13, 14] No previously published studies of the cost-effectiveness of letermovir for the prophylaxis of CMV reactivation and disease were identified.

5.1.4 Conclusions of the cost effectiveness review

The company's search did not identify any relevant economic assessments of letermovir versus relevant anti-viral pre-emptive therapies used in the prophylaxis of CMV infection. Therefore, the ERG considers the *de novo* cost-effectiveness analysis reported in the CS to be the most relevant source of evidence to inform the decision problem.

5.2 ERG's summary and critique of company's submitted economic evaluation

An overall summary of the company's approach, and signposts to the relevant sections in the company's submission, are reported in **Table 20**.

Table 20 Summary of the company's economic evaluation (and signposts to CS)

	Approach	Source / Justification	Signpost (location in company submission)
Model	Cost-effectiveness (cost-utility) analysis using a hybrid model consisting of decision tree and Markov model	No justification given.	Section 3.2.2 pg. 87
States and events	Decision tree: differences in initiation of PET, rehospitalisation, GVHD, opportunistic infection and mortality. Markov model: Alive and Dead.	No justification given.	Section 3.2.2 pg.87
Comparators	The cost-effectiveness model compared the use of letermovir prophylaxis against SoC (no preventative treatment) only.	The CS considers a comparator which aligns with the marketing authorisation in the UK for this indication and did not include aciclovir and valaciclovir as a comparator. Aciclovir and valaciclovir were not considered relevant as neither of these drugs currently has a marketing authorisation in the UK for this indication; there is no relevant UK evidence supporting use of either treatment for CMV prophylaxis in this patient population (based on a systematic literature review (SLR)), and the overall evidence base is not considered to be robust by professional bodies.[2]	Section 3.2.4.1 pg. 91-92
Treatment effectiveness	Clinical outcomes included were initiation of PET, rehospitalisation, GvHD, opportunistic infection. These data were taken from the PN001 data and used the DAO – no imputation of missing data.	Data was sourced from the pivotal RCT PN001. Approach to missing data was noted as being the most likely to reflect the magnitude of healthcare and resource use required. Scenario analysis was presented using the NC=F approach to missing data which was discussed in the clinical section of the CS.	Section 3.1.1.1 pg.94 and 95.

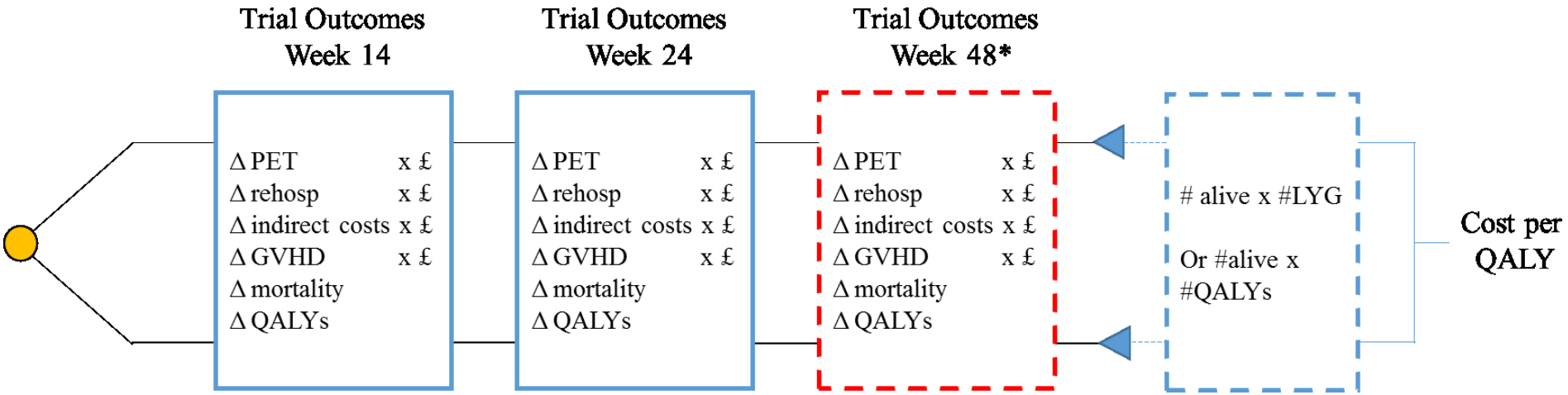
Mortality	Differences in mortality during the decision tree phase (up to 24 weeks) of the model were drawn from the PN001 study. Beyond 24 weeks of the trial no further survival gains from letermovir were assumed and long-term outcomes were extrapolated using mortality rates generated using natural history data on the long-term mortality of patients who had received SCT.	Data on short term mortality sourced from PN001 study. Data on long-term mortality sourced from Wingard *et al*.[15]	Section 3.1.1.1 pg.94 and 97.
Adverse events	No treatment related adverse events were included in the model. Adverse events associated with CMV infection and initiation of PET were included in the model: neutropaenia, thrombocytopaenia, and leukopaenia	Exclusion of treatment related adverse events was based on the assumption that any differences in utilities would be accounted for through the use of trial based utility estimates. Neutropaenia, thrombocytopaenia, and leukopaenia, were noted as the most commonly seen haematological adverse events in allogeneic-SCT patients.	Section 3.4.4 pg.102 and Section 3.5.6 pg. 129.
Health-related quality of life	Health-state utilities were assigned to each arm, and were derived from PN001 trial data and published evidence.	The sources of utilities were obtained from PN001 trial data and were collected using FACT-BMT and the EQ-5D. Aligned to the NICE reference case, the utilities derived from the EQ-5D were applied in the model. The model used EQ-5D utility inputs based on the time point in the trial for each comparator, to adjust life-years based on patient health-related quality of life. The baseline utility at each time point was assumed to be the weighted average EQ-5D index at baseline for letermovir and placebo from PN001. Beyond year one for survivors, the QALYs was estimated as a post-trial utility using the lowest value of either 0.82 from an AML population who underwent a HSCT (Leunis et al., 2014) [16], or the age-specific general population utility (Ara et al., 2011) [17].	Section 3.4.5 pg.101-103
Resource utilisation and costs	The resource use and costs included: drug acquisition costs, drug administration costs, costs of complications that can occur from the onset of clinically-significant CMV infection (including CMV disease, CMV-related re-hospitalisation, opportunistic infection and the costs associated with GvHD), and costs associated with adverse events.	Costs have been sourced from the NHS reference costs [18] and the PSSRU [19]. Costs have been applied using the perspective of the NHS. In accordance with the NICE reference case. Note that the costs to the NHS were included, but PSS costs have not been considered due to the unavailability of data to incorporate this into the model.	Section B.3.5 pg. 104-124
Time horizon	Lifetime analysis based on week 24 outcomes.	In accordance with the NICE reference case.	Section 3.2.2.2 pg. 86
Discount rates	Beyond one year, the costs and benefits were discounted at 3.5% per annum.	In accordance with the NICE reference case.	Section 3.2.2.2 pg. 87

Sensitivity analysis	Probabilistic sensitivity analysis was performed. Deterministic analysis was performed on a series of model parameters. A series of scenario analyses was also performed.	In accordance with the NICE reference case.	Section B.3.8 pg. 132-143
Subgroups	No subgroup analysis was conducted.	N/A	Section B.3.9 pg. 144
Note: CMV=cytomegalovirus; CUA=cost-utility analysis; DSU=decision support unit; FACT-BMT=Functional Assessment of Cancer Therapy – Bone Marrow Transplant; GvHD= Graft-versus-host-disease, HSCT=haematopoietic stem cell transplant; N/A=not-applicable; NHS=National Health Service; NICE=national institute of health and care excellence; PSS=personal social services; PSSRU=personal social services research unit; QALY=quality-adjusted life years; SoC=standard of care			

5.2.1 Model structure

The CS presented a de novo model to estimate the cost-effectiveness of letermovir prophylaxis compared with standard care (no prophylaxis). The model structure consists of a decision tree phase covering the first 24 weeks post SCT (48 weeks in scenario analysis) and Markov model phase covering the remaining time horizon of the model. In the decision tree phase differences in the rate pre-emptive therapy CMV disease, re-hospitalisations, opportunistic infection, GvHD, adverse events (AEs) and mortality were accounted for using cumulative probabilities from the PN001 trial. Patients then move into a simple two state Markov model (alive or dead) to account for the mortality benefits associated with letermovir prophylaxis. The model structure and transitions are depicted in **Figure 5**.

Figure 5: Model structure (adapted from CS Figure 7, pg. 89)



*Scenario analysis only

Costs and QALYs in the decision tree phase of the model were determined at two points, 14 weeks and 24 weeks, based on data from the PN001 trial. Trial clinical endpoints at 24 weeks were then extrapolated to the end of one year, where patients enter the Markov model. In scenario analysis, clinical endpoints at 48 weeks were also used to populate the model; 48 week data was, however, not available for all outcomes, including initiation of pre-emptive therapy which was only available up to week 24. In the Markov phase of the model, a cycle length of one year was used. Half cycle correction was applied to both costs and QALYs in both phases of the model.

ERG comment

The model presented by the company is notable in its simplicity, the primary benefits of this are that the model is very transparent and relatively flexible, allowing exploration of key uncertainties. This simplicity, however, has a number of limitations:

- The model lacks explicit health states to capture differences in QALYs. The problem with this approach is that it does not link the occurrence of CMV events (the primary benefit of letermovir) to the accrual of QALYs. Importantly, there is no structure linking between the rate of CMV and mortality. This is important because nearly all QALYs benefits associated with letermovir are a consequence of differences in mortality. As such it is not possible to explore the impact of uncertainty regarding the difference in the rate of CMV and its impact on subsequent mortality. This also means that direct impact of a CMV event and other clinical events e.g. GvHD on QoL are not captured directly in the model, which instead relies upon trial based utilities to capture differences between treatment groups.
- Related to the above issue, the model structure does capture fully the complexities of post-HSCT treatment in patients who have undergone SCT, this includes both the follow up care and management costs incurred by patients and important clinical events such as relapsed disease; data obtained by the ERG from the HMRN network suggests that [redacted] of patients will relapse in the first 3 years following SCT.(See Appendix 10.3) Capturing the complexities and underlying consequences both in terms of costs and QALYs is potentially important, as while borne by all patients whether receiving letermovir or standard care, these costs and QALYs will impact on incremental QALYs and costs due differences in the number of patients at risk in the two groups (different mortality rates). With respect to this issue the ERG requested that the company provide a scenario analysis including the relapse of the underlying disease into the economic model. See Section 5.2.14 for further details.

These issues aside, the ERG considers the company's model fit for purpose and that it appropriately addresses the decision problem. The ERG, however, implements a number of additional analyses

presented in Section 6 aimed at mitigating the impact of some of the identified weaknesses with the company model.

5.2.2 The company's economic evaluation compared with the NICE reference case checklist

Table 21 summarises the economic submission and the ERG's assessment of whether the company's economic evaluation meets NICE's reference case and other methodological recommendations.

Table 21 Features of de novo analysis

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Comparator(s)	The NICE final scope lists the following comparators • aciclovir (does not currently have a marketing authorisation in the UK for this indication) • valaciclovir (does not currently have a marketing authorisation in the UK for this indication) • no preventative treatment	Partially	The CS does not include aciclovir and valaciclovir as comparators which were outlined in the NICE scope. The ERG and the clinical advisors to the ERG concur with company's justification for not considering these, which cites that neither of these two drugs currently have a marketing authorisation in the UK for this indication; and there is no relevant UK evidence supporting use of either treatment for CMV prophylaxis in this patient population.
Type of economic evaluation	Cost-effectiveness analysis.	Yes	Cost-utility analysis (CUA) with the direct health effects expressed in terms of QALYs.
Perspective on costs	NHS and personal and social services	Yes	PSS costs have been taken into account.
Perspective on outcomes	All health effects on individuals.	Yes	QALY benefits to treated individuals were considered.
Time horizon	Sufficient to reflect any differences in costs or outcomes between the technologies being compared.	Yes	Lifetime analysis based on week 24 outcomes. The time horizon used in the economic model is equivalent to a life-time horizon.
Synthesis of evidence on outcomes	Systematic review.	NA	Not applicable as no other relevant trials of letermovir compared with standard care were identified in the systematic review.
Measure of health effects	QALYs.	Yes	Utility values during the decision tree phase of the model were sourced from PN001 trial which collected EQ-5D data. Utilities in the post-trial period 24 weeks to 1 year) were based on published utilities (EQ-5D (5L) values) Utility values for the post 1 year period were based UK EQ-5D population norms adjusted for age.
Source of data for measurement of HRQoL	Reported directly by patients and/or caregivers.	Yes	
Source of preference data for valuation of changes in HRQoL	Representative sample of the public.	Yes	
Discount rate	Annual rate of 3.5% on both costs and health effects.	Yes	Costs and benefits were discounted at 3.5% per annum.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	No special weighting undertaken.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was undertaken.

5.2.3 Population

The primary source of data used to inform the cost-effectiveness model was the PN001 trial, which recruited adult CMV-seropositive [R+] recipients of an allogeneic HSCT, which is in line with the population defined in the NICE scope.

The modelled population was based on a cohort with age, weight and primary condition primary condition (e.g. AML, ALL, CLL, etc.) based on the ASaT population of the PN001 study. These parameters were used to inform long-term mortality and dosing of therapies used on detection of CMV (PET) and in the treatment of GvHD.

ERG comment

As noted in Section 3.1 the ERG considers the population recruited to the PN001 trial to be in line with that defined in the NICE scope, and is broadly reflective of the population eligible for treatment in the UK. The ERG, however, note that the model results are sensitive both to the mean age of the cohort and distribution of the underlying primary condition. The ERG therefore sought to obtain external data from the HRMN on the validity of these parameters. (See Appendix 10.3 for the data received) The HRMN data is registry of patients with a haematological malignancy within the HRMN region of Yorkshire and Humberside. This data covers broadly the same population as those who would be potentially eligible for treatment with letermovir, though it does not include patients without a haematological malignancy: small number of these, primarily patients with aplastic anaemia would be eligible. The mean age of patients receiving allograft SCT in the HMRN data is 45 (compared with 50.8 in the model) suggesting patients may be somewhat younger on average in practice than in those recruited to the trial; this will act to reduce the ICER. The HRMN data also suggests some slight differences in the underlying distribution of primary conditions, see **Table 22** below.

Table 22 Comparison of primary conditions

	PN001	**HMRN data**
Acute lymphocytic leukaemia	9.20%	18.1%
Acute myeloid leukaemia	37.88%	35.71%
Aplastic anaemia	3.5%	Not eligible
Chronic lymphocytic leukaemia	2.48%	2.86%
Chronic myeloid leukaemia	4.07%	2.38%
Lymphoma	13.27%	10.95%
Myelodysplastic syndrome	15.04%	12.38%
Myelofibrosis	2.65%	2.38%
Plasma cell myeloma	4.2%	8.1%
Other	7.6%	7.14%

The differences between the trial data and HRMN network population may in part explained by changes in the underlying characteristics of HSCT recipients overtime (the HRMN data goes back to 2004), but may also reflect differences in practice and disease incidence in the countries from which

the PN001 trial population were recruited. The ERG therefore considers that the patient's characteristics reported in the HMRN data to be at least as plausible as those in the PN001 trial.

5.2.4 Interventions and comparators

5.2.4.1 Interventions

The cost-effectiveness model compared the use of letermovir prophylaxis against SoC (no treatment). The recommended dosage of letermovir is one 480 mg dose per day, or alternatively 240 mg when taken concomitantly with ciclosporin A (CsA), which significantly increases the bioavailability of letermovir. Letermovir is available as both as an oral formulation and as a solution for intravenous (IV) infusion (240 mg and 480 mg). The oral and IV formulations may be used interchangeably at the discretion of the physician, with no dose adjustment necessary. The expected proportion of patients using each dose and formulation was based on clinical opinion, see Section 5.2.9 for further discussion and comment.

Modelled initiation and duration of treatment was based on mean duration of therapy observed in the ASaT population of the PN001 trial (69.4 days) which permitted initiation of treatment between day 0 (day of HSCT) and 28 days post-transplant. Maximum duration of therapy permitted in the PN001 trial was set at 100 days. This broadly matches the SmPC, though importantly, the SmPC does not mandate any futility rules and instead states:

> *"Prolonged letermovir prophylaxis beyond 100 days post-transplant may be of benefit in some patients at high risk for late CMV reactivation (see section 5.1). Use of letermovir prophylaxis for greater than 100 days requires a careful assessment of the benefit-risk balance."* Pg. 2 of SmPC

ERG comment

The ERG's primary concern with respect to the intervention is the duration of therapy which the ERG consider may be considerably longer than the mean of 69.4 days reported in the ASaT trial population of the PN001 study.

Firstly, reflecting the licence and the clinical experience gained as part the PN001, the ERG deem it likely that clinicians will be more confident to initiate letermovir prophylaxis immediately post-HSCT, as PN001 demonstrated no deleterious interaction with engraftment success. This means that it is unlikely that the mean delay between HSCT and initiation of prophylaxis of [redacted] days would be expected in practice, therefore patients will receive treatment earlier and for longer than in the trial.

Secondly, there is a question over which of the FAS or ASaT population's mean duration of letermovir therapy best reflects clinical practice. Patients excluded from the FAS population are those patients who initiated therapy, but were protocol violators due to having had detectable CMV DNA at Day 1. This might mean that these patients may have tended to discontinued therapy early. However, the results presented in Section 3 for these excluded patients suggest that they were treated as other eligible patients. At the clarification stage the ERG requested further data on the duration of therapy in the FAS population, which was supplied by the company, showing the mean duration of therapy to be 72 days. The mean duration of letermovir treatment in the ASaT population is 69.4 days. Which duration is most relevant to clinical practice depends upon whether or not clinicians initiate prophylaxis with letermovir despite the presence of low levels of CMV DNA (ASaT population) or only in patients with no detectable CMV DNA (FAS population). A further consideration is that if in clinical practice prophylaxis is not delayed as it was in the trial, then fewer patients would have detectable CMV DNA at letermovir initiation (supporting the use of the FAS data).

Thirdly, as outlined in Section 4.2.7, the criteria used to determine initiation of PET in the PN001 trial were somewhat conservative, with the implication that it is likely that the trial population initiated PET sooner and more frequently than would be observed in NHS practice. As initiation of PET results in discontinuation of letermovir prophylaxis, it is therefore likely that the trial underestimates the duration of of letermovir prophylaxis that we would expect in clinical practice. The ERG, however, notes that the trial therefore also likely underestimates the potential benefit of letermovir prophylaxis in clinical practice.

Finally, the ERG notes the lack of any futility rules in the SmPC and considers that in clinical practice it is plausible that patients requiring longer periods of prophylaxis (as is allowed under the product licence) would receive letermovir beyond 100 days. This is likely to include patients undergoing continued immunosuppressive treatment for GvHD, or those at high-risk of CMV reactivation for other reasons. Again, the trial may therefore underestimate total duration of therapy and therefore incremental costs. The ERG, however, notes that this may cause a further underestimation of the efficacy of letermovir prophylaxis in clinical practice.

Given the above uncertainties regarding the duration of letermovir prophylaxis and the generalisability of the clinical data from the PN001 trial, the ERG performed out a series of exploratory analysis in Section 6 considering the impact of alternative assumptions regarding duration of letermovir prophylaxis.

5.2.4.2 Comparators

The NICE final scope listed aciclovir and valaciclovir as well as 'no preventative treatment' as comparators; however, the NICE scope noted that neither active drug had current marketing authorisation for the relevant indication. The CS included only 'no prophylaxis against CMV reactivation', i.e. no active comparators were included. The reasons given for this in the CS were: neither drug currently has a marketing authorisation in the UK for this indication; there is no relevant UK evidence supporting use of either treatment for CMV prophylaxis in this patient population (based on a systematic literature review (SLR)), and the overall evidence base is not considered to be robust by professional bodies [2].

ERG comment

As stated in Section 3.3, the ERG concurs with this reasoning, and does not consider aciclovir and valaciclovir to be relevant comparators for letermovir in this appraisal.

5.2.5 Perspective and time horizon

The economic model adopted a National Health Service (NHS) perspective in accordance with the NICE reference case.

The NICE reference case indicates that the time horizon used for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs and benefits between the technologies being compared. The time horizon used in the economic model, was 101 years; equivalent to a lifetime horizon. The ERG considers this more than adequate to capture any differences between letermovir and standard care.

5.2.6 Discounting

The costs and benefits in the model were discounted at an annual rate of 3.5%, as per the NICE reference case.

5.2.7 Treatment effectiveness and extrapolation

As described in Section 5.2.1 the economic model presented by the company comprises a decision tree up to week 24 (48 in scenario analysis) and a Markov model covering the remaining time horizon of the model. The clinical parameters used in the two distinct parts of the model differ.

Decision tree phase

The decision tree phase of the model utilises six different clinical outcomes with each outcome indicating the occurrence of a clinical event. The seven clinical events included in the economic model are as follows:

- Initiation of PET based on documented CMV viremia
- All-cause mortality
- CMV end-organ disease
- CMV-related re-hospitalization
- Opportunistic infection
- Graft-versus-host disease

In addition to the above the economic model also draw clinical data on the rate of AEs, this is discussed separately in Section 5.2.6.1 below.

The cumulative probability of each of the six events listed above was drawn from the PN001 trial data with events permitted to occur at 14 weeks, 24 weeks and 48 weeks (scenario analysis only). In the base-case analysis the 48 week outcome data is not used for any clinical event and because no data are available for initiation of PET treatment. Instead, 24 week outcomes extrapolate (assuming no further events) to the end of year one where patients enter the Markov model phase.

Each of the six events, with the exception of all–cause mortality is associated with specific cost and therefore collectively these clinical events determine the costs-accrued over the decision tree phase of the model see Section 5.2.9 for details of associated costs.

All-cause mortality which is not associated with any costs and alone determines the accrual of life years and QALYs. Differences in the HRQoL of patients due to differences in rate of CMV infections, are assumed to be captured in the trial base utilities used, see Section 5.2.8 for further details. In terms of their influence on incremental costs and QALYs initiation of PET is the primary driver of incremental costs and all-cause mortality is the primary driver of incremental QALYs.

The probability of each of the clinical endpoints used in the model are presented in **Table 23**. Probabilities were drawn from the FAS population and use the data as observed (DAO); no imputation was used to impute missing data. The values listed in **Table 23** therefore largely do not correspond with the data presented in the clinical section of the company's submission which primarily uses the NC=F method to impute missing data.

Table 23 Clinical event probabilities used in the company base-case model

	14 weeks		24 weeks		48 weeks[a]	
Clinical Outcome	**Letermovir**	**STD care**	**Letermovir**	**STD care**	**Letermovir**	**STD care**
Initiation of PET based on documented CMV viremia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CMV end-organ disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CMV-related rehospitalisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Opportunistic infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Graft-versus-host disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[a] Scenario analysis only; [b] Assumed						

ERG Comment

The ERG has a number of concerns regarding the clinical data used to populate the model, these concern the use of 24 week data over 48 week data, the approach taken to dealing with missing data, and the cut of the PN001 data the clinical outcome data is drawn from.

24 vs 48 week outcome data

The ERG considers that the use of the 24 week data rather than the 48 week data to be generally inappropriate and inadequately justified in the CS, even accounting for the fact that initiation of PET data was not collected beyond 24 weeks. It is clear from the available data that events do occur beyond week 24, including mortality events which have a significant impact on incremental QALYs. The ERG therefore considered that an approach based on making maximum use of the data available to be more reasonable than making the assumption that no further clinical events occur beyond 24 weeks. With respect to CMV events, while ideal to assume no further event post 24 weeks, the ERG notes that based on clinical advice, few patients will initiate PET after 24 weeks, and therefore this is unlikely to be significant source of uncertainty. Particularly, as the model structure is set up such that mortality is the primary driver of incremental QALYs.

Missing data

As noted in Section 4.2.5, there is sizable loss to follow-up in the clinical data available from the PN001 study. Reflecting this, the company present a number of alternative analyses using different

approaches to account for the incomplete follow up. The data used in the model, however, does not adjust for the incomplete follow up, being based instead on only the observed data (DAO data set). The ERG has some concerns regarding this approach as it implicitly makes the assumption that data is missing completely at random (i.e. not related to the either observed or unobserved data). It is, however, not clear that this is the case, and as shown in the alternative analysis presented by the company, alternative approaches to dealing with missing data do impact on the estimated effectiveness of letermovir.

Further, the ERG also notes that the company collected further data on the survival of participants lost to follow-up in a response to request by the FDA. This data is more complete, with just 3.2% patients lost to follow-up compared with 13.5% in the main analysis; these data were provided in the CS and are presented in Section 4.2.8 of this report. The ERG considers this analysis to be preferable to the main analysis requested the company to present a scenario analysis using this data at the clarification stage. The ERG explores the impact of alternative approaches to addressing missing data in Section 6.

FAS vs ASaT data
As discussed in Section 4.2.3, the ERG considers that the FAS data (which is used in the company's base-case) is likely to be the most reflective of current practice as clinicians are likely to initiate prophylaxis sooner in clinical practice than was observed in the PN001 study. The ERG acknowledges that there is some uncertainty regarding this issue; however, alternative clinical input data provided by the company at the clarification stage shows that using the ASaT data in the economic model has minimal impact on the ICER.

Markov model phase
The Markov phase of the model is primarily used to determine the life-expectancy and rate of QALY accrual in patients who are alive the end of the decision tree phase. The only clinical outcome used in this phase of the model is therefore all-cause mortality. The mortality rate applied in this phase of the model is assumed to be the same in both treatment groups and therefore no survival gains are assumed beyond the decision tree phase of the model.

The mortality rate applied is based on data drawn from general population mortality data sourced from the ONS, with a standardised mortality rate (SMR) applied to account for the reduced life expectancy of patients who receive allo-HSCT, primarily due to relapse of the underlying disease and secondary cancers [15, 20] The SMR applied was based on data drawn from Wingard *et al.* (2011) [15]. and was generated using a weighted average of 5 SMR for acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS), severe aplastic anaemia (SAA), and Lymphoma reported in Wingard *et al.* (2011) to account for the impact of the underlying condition on

the probability of future relapse and survival. The weights applied are determined based on the proportion of patients in the ASaT population of the PN001 trial with each underlying condition. Because the Wingard study did not report SMRs for all primary conditions, the economic model makes a number of assumptions to estimate the SMR in these sub populations. For chronic myeloid leukaemia (CML), chronic lymphocytic leukaemia (CLL) and others (not ALL, AML, MDS, SAA, CLL, CML, myelofibrosis or PCM) the SMR applied was assumed equal to that of myelodysplastic syndrome (MDS), for myelofibrosis and plasma cell myeloma (PCM) the SMR applied was assumed equal to SAA.

To account for the fact that mortality risk following SCT changes over time the SMR applied was also assumed to change over time and after 15 years (maximum follow up in Wingard *et al.* (2011)) it was assumed the excess mortality risk would remain constant. Because the Wingard data recruited patients who had survived for 2 years post HSCT, no data was available for the second year of the model and therefore it was assumed that the excess risk of mortality in year 2 was equal to year 3.

ERG Comment

The ERG considered the general approach taken by the company regarding the long-term mortality a reasonable one and that the assumptions made regarding those underlying conditions where data is not available were reasonable. The ERG, however, considers there to be considerable uncertainty associated with the data used by the company. The ERG considers a more relevant source of data for the UK is from the haematological malignancy research network. Specifically, the ERG notes two issues:

Firstly, the ERG notes that company model makes strong assumptions about the mortality of patients in the second year following transplant, assuming to be equal to the mortality in the third year. This is problematic as the mortality risk following HSCT is known to decline substantially over time in the years following HSCT. The mortality rate in the 2nd year is therefore likely to be several times higher than the mortality rate in the third year. This is supported by evidence from the HMRN which reports a mortality rate in the second year following allograft of 19%, compared with just 3% in the company model. To explore the impact of alternative methods of estimating second year survival the ERG requested that the company undertake parametric extrapolation of the Kaplan-Meier data from PN001, which was provided by the company in its clarification response. Unfortunately, this analysis assumed (in contrast with the base-case) that the OS benefits of letermovir persist beyond one year, which the ERG does not consider plausible. The results of this this analysis are presented and discussed further in Section 5.2.11.

Secondly, the ERG notes a number of issues with the mortality data used to calculate the SMR. In particular the data collected in the Wingard study is relatively old, covering the period 1980 to 2003 and therefore its relevance to current practice is unclear. The ERG, however, acknowledges that there is limited evidence of any significant improvement in mortality rates over time in the period covered by the Wingard data. Furthermore, a substantial proportion (>40%) the patients recruited to the Wingard data set were from included paediatric populations and on the whole, the population was much younger than the patients recruited to the PN001 study. This is likely to significantly impact upon the calculation of the relative mortality. Validation of the mortality risk using data obtained by the ERG from the HRMN, shows that this is likely to have led to underestimation of the mortality rate of patients who received allo-HSCT, see **Table 24** for comparison.

Table 24 Comparison of mortality rates

Years post SCT	Company base-case	HRMN data
2	2.7%	19%
3	2.9%	11%
4	3.1%	5%
5	5.4%	6%
6	5.4%	8%

Given the issues highlighted above the ERG explores alternative approaches to modelling long-term mortality in Section 6.

5.2.7.2 Adverse events

The impact of adverse events (AEs) associated with letermovir prophylaxis and standard care were not directly captured in the company's model, which did however include AEs associated with CMV infection and end-organ disease. Event probabilities for AEs associated with CMV infection and end-organ disease were based on the safety profile in the PN001 trial and applied to patients experiencing either of these events. The events selected were based on those most commonly observed in patients undergoing allo-HSCT: neutropenia, thrombocytopenia, and leukopenia.

The adverse event probabilities incorporated into the model are presented in **Table 25**. These were based on the number of patients experiencing each type of event during the PN001 study (week 0 to 48). Patients experiencing multiple instances of a particular adverse event were only counted once.

Table 25: Grade 3/4 adverse events in the model (CS, Table 47, p 129)

Adverse events, % of patients	Letermovir	standard care
Neutropenia	5.3%	5.3%
Thrombocytopenia	7.8%	7.8%
Leukopenia	3.9%	3.9%
CS, company submission		

Because the PN001 study collected utility data on patients irrespective of whether they had experienced an AE, disutilities associated with AE were not included in the model as it was assumed that the trial based utilities already incorporated the impact of AE's. Adverse event rates therefore impacted only on costs included. See Section 5.2.8.3 or details of the costs applied.

ERG comment

The ERG has a few concerns regarding the data use and approach to modelling AEs in the company economic model. Firstly it is not clear why the company chose not to include AEs associated with treatment, as even if differences in HRQoL are included in the trial utilities used in the economic modelling, the costs are not. With respect to this, the ERG notes that there are few differences in the AE's rates for patients receiving letermovir, see Section 4.3. Secondly, the rates of adverse events applied for patients experiencing CMV infection appear to be based on AEs incurred throughout the whole trial period by all patients, and therefore do not reflect AEs incurred only by patients who have experienced a CMV infection or end-organ disease. Thirdly, because the HRQoL data was not collected after CMV infection or end-organ disease, the trial based utilities do not include the impact of these AEs on HRQoL. The ERG does not consider the issues raised important, as the impact of alternative assumptions regarding AEs is likely to be negligible and therefore the ERG presents no further exploratory analysis to address this weakness in the company's approach.

5.2.8 Health related quality of life

The company conducted a systematic literature review to identify the literature on health-related quality of life (HRQoL). The searches used were described and the inclusion/exclusion criteria used in the study selection were presented in Appendix H. While a number of studies were identified as having potentially useful information, none of the studies examined HRQoL in patients with CMV disease (see Table 30 in Appendix H. Therefore, the HRQoL values collected in the trial, using the EQ-5D-3L, were used within the decision tree phase of the model. The HRQoL values used in the Markov model phase were derived from published literature.

5.2.8.1 Trial utilities

In PN001, the EQ-5D questionnaire was administered at the time points of weeks 0, 14 and 24, during the primary study period, and at the conclusion of the follow-up period (week 48) to estimate the treatment-specific utility weights. HRQoL was also measured if early discontinuation or infection occurred.

The baseline utilities used in the company's model were derived from the baseline utilities observed in the PN001 trial. The baseline utility value for letermovir was [redacted] and for SoC was [redacted]. A weighted average of these two values (0.649) was applied to both arms within the model.

In order to calculate the utilities at Week 14, 24 and 48, the mean change from baseline values, as presented in the 48 week CSR, were combined with the baseline utility values to derive the utility values for each time point and are presented in **Table 26** below.

Table 26: Utility time point weights (Table 37 in CS, pg. 104)

Timepoint	Letermovir	Standard of care
Week 14	0.756	0.674
Week 24	0.757	0.689
Week 48	0.813	0.733

ERG Comment

The ERG has two concerns regarding the utility values used in the company's analysis; the capacity of the data collected in the trial to capture HRQoL differences, and the methods of analysis used.

Group differences

The approach taken by the company to modelling the differences in the HRQoL of patients receiving letermovir or standard care assumes that the values obtained in the trial reflect any differences in the HRQoL of these two patient groups. The CS, however, states that in PN001, once a patient had documented CMV viraemia, they were excluded from the analysis and HRQoL data were not collected after this point. Therefore, it is likely that the disutility associated with CMV infection and the resulting ill-health has not been captured in the trial utilities. Given that this is likely to be a primary benefit of letermovir treatment, the ERG feel that this should be accounted for in the estimation of QALYs, however, the magnitude of these benefits is likely to be very small and as such the ERG do not undertake further analysis exploring this issue.

Methods of analysis

The utilities used in the company base-case model appear to be based on unadjusted differences in the EQ-5D data collected in the trial. The ERG, however, notes that the magnitude of the differences

reported here differ substantially from the pre-planned trial analysis, supplied by the company at the PFC stage. This analysis uses a mixed effects regression model adjusted for base-line risk of CMV reactivation and importantly shows no statistically significant differences in HRQoL between the two groups at any time points. The ERG also note that the estimated differences between the two groups are substantially smaller than suggested in this naive analysis of the data. The ERG considers that this analysis is much more likely to reflect the true differences between the groups (the issue outlined above aside) as it takes into account a number of factors including baseline risk differences, the lack of independence of repeat observations, and makes more conservative assumptions with respect to missing observations. Although both of these adjustments enable the trial utilities to better reflect clinical practice, the ERG considers their effect to be very small and so these issues were not explored further.

5.2.8.2 Lifetime utilities

The PN001 trial collected utility values up to 48 weeks. To estimate the utilities for the subsequent time period in the model, the company used published literature estimates for their lifetime utility values. Patient who survive past the trial time period of 48 weeks are estimated to have a utility value of 0.820. This value was derived from Leunis *et al*. [16], which assessed the impact of AML on the HRQoL of patients who had been diagnosed between 1999 and 2011 and were still alive in 2012.

As the patients aged through the model, age-adjusted utilities are applied, as presented in **Table 27** below.

Table 27: General (UK) population utility values (Table 38 of CS, pg. 104)

Age	Utility value EQ-5D (95% CI)
60 to ≤ 65	0.8072 (0.793, 0.821)
65 to ≤ 70	0.8041 (0.790, 0.817)
70 to ≤ 75	0.7790 (0.766, 0.791)
75 to ≤ 80	0.7533 (0.739, 0.767)
80 to ≤ 85	0.6985 (0.677, 0.719)
>85	0.65497 (0.624, 0.675)
CI=confidence interval; EQ-5D=EuroQol-5 Dimension	

These values, as described in Ara and Brazier (2011) [17] are age stratified general population health statuses, where the population has a previous health condition.

ERG Comment

The ERG considers the general approach of the company to modelling post-trial HRQoL to be appropriate, including the adjustments for age, but has some concerns regarding the appropriateness of the post-trial utility value of 0.82 sourced from. Leunis *et al* [16] Firstly, this utility value is based on the EQ-5D-5L which currently does not align with NICE's preferred method of eliciting utilities[21] EQ-5D-3L. Further it has been noted in a recently published study,[22] that EQ-5D-5L estimates tend to be higher than those generated using the EQ-5D-3L instrument, due to the smaller differences in values between the health states in the value set. Secondly, the ERG notes that this implies a utility value higher than that of the general public based on the EQ-5D-3L, which would appear to be inconsistent with the fact these patients have survived a very serious illness. This also is inconsistent with results in the Leunis study which reports results, using the EQ-VAS, that show that survivors of AML have lower HRQoL than age and sex matched members of the general public. Reflecting these concerns the ERG requested that the company present a scenario analysis where a utility decrement from the long-term effects of HSCT has been incorporated: see Section 5.2.12 for further details. The ERG, however, does not consider that this analysis fully captures the long-term utility decrement associated with having undergone SCT as it mixes EQ-5D-5L and EQ-5D-3L values. It also suggests a decrement much smaller than estimated in Leunis based on the EQ-VAS. The ERG explores this issue further in Section 6.

5.2.8.3 Adverse event disutilities

The CS states that the company explored the recent technology appraisals for ALL and AML [23, 24] for impacts of AEs on HRQoL, however this search did not uncover any studies with this information provided. The company noted that as the EQ-5D data collected in the trial was at particular time

points irrespective of when AEs occurred that these data would include a disutility associated with AEs. Therefore no additional disutilities relating to AEs were incorporated in the company's model.

ERG Comment

The ERG disagrees that disutilities relating the AEs would have been captured by the trial utility values. As stated in the CS, the most commonly seen haematological adverse events in allogeneic-HSCT patients are neutropenia, thrombocytopenia and leukopaenia and these are associated with the initiation of PET. The CS also states that when documented CMV viraemia occurs leading to the initiation of PET, HRQoL data is no longer collected for that patient. Therefore, there is a strongly likelihood that disutility due to PET AEs have not been included. However, given the small utility decrements that these AEs will incur, this scenario is not explored further.

In addition, as noted in Section 4.3, it is possible that adverse events associated with letermovir use may be applicable. However, this is difficult to disentangle and not explored further.

5.2.8.4 Disutilities due to GvHD

GvHD is serious and common complication associated with allo-HSCT that is associated with significant morbidity and mortality. The CS did not include any disutility associated with GvHD in the base-case analysis, but did present a scenario analysis where a proportion of chronic (c)GvHD (those who suffer GvHD one year or more after the HSCT) suffered a disutility. The disutility applied was based on a published study [25], which estimated the HRQoL for cGvHD disease survivors and this was converted to an EQ-5D value using Ara and Brazier (2011) [17] resulting in a disutility value of 0.09 being estimated. This disutility was applied in year 1 and 2 after the trial period for 30% of survivors.

ERG Comment

The ERG considers it appropriate to include a disutility associated with GvHD, and consider that this disutility should be included in the company's base-case analysis.

5.2.9 Resources and costs

The CS provided a description of the resources and incurred over time. These included:

- Drug acquisition and administration costs;
- CMV disease monitoring costs;
- Pre-emptive therapy costs;
- Health state costs;
- Adverse event costs

To identify the cost and resource-use data to be used, the company carried out a systematic review of healthcare resource utilisation and cost studies. As discussed in Section 5.1, the review appears to have been appropriately undertaken.

5.2.9.1 Drug acquisition and administration costs

In the CS base-case model, the cost per day was calculated for letermovir, taking into account the drug cost, administration cost and concomitant dosing adjustments. The unit costs per day were calculated accounting for both route of administration (oral or IV), and the dose administered (240mg and 480mg). Oral administration of therapy was assumed to be associated with no administration costs while IV administration was assumed to incur a unit cost sourced from NHS Reference costs: Deliver Simple Parenteral Chemotherapy at First Attendance. The total unit costs per day of treatment associated with each route of administration and dose are presented in **Table 28** below and include the company's proposed PAS, which equates to a [redacted]% discount on the list price of letermovir.

Table 28: Letermovir cost breakdown (Table 31 in CS, pg. 92)

Letermovir	**Oral**		**IV Infusion**	
	240mg (concomitant with CsA)	**480mg**	**240mg (concomitant with CsA)**	**480mg**
List Price	[redacted]	[redacted]	[redacted]	[redacted]
PAS Price	[redacted]	[redacted]	[redacted]	[redacted]
CsA=ciclosporin A; IV=intravenous; PAS=patient access scheme				

The proportion of the patient receiving concomitant ciclosporin A (CsA) was assumed to be 95%, the vast majority of patients were therefore assumed to require a 240mg, rather than a 480mg, dose of letermovir. The proportion of patients receiving concomitant CsA was based on expert opinion which suggested more widespread use of CsA as an immunosuppressive agent than was observed in the PN001 trial, in which 42% of patients were treated with tacrolimus, which does not require a dose reduction of letermovir. To explore the uncertainty regarding this assumption, the CS also presented a scenario analysis where the proportion of patients concomitantly using CsA was varied from 71% to 100%.

With the base case analysis the company assumes that 5% of patients will receive initial IV infusion, this reflects the administration route observed in the 12 UK patients in the PN001 trial (100% PO; MSD, Data on file) and the assumption that a proportion of patients would not be able to tolerate oral administration initially, due to gastrointestinal complications and would receive letermovir initially via IV infusion. Patients who initial receive IV are not assumed to continue to receive IV infusion

throughout the duration of letermovir prophylaxis, but assumed to revert to receiving oral letermovir after [redacted] days. The duration of [redacted] days was based on the mean duration of IV letermovir within the PN001 trial.

When the drug costs, administration costs, mode of administration and concomitant dosing adjustments were taken into account, the company estimated that the letermovir cost per day was [redacted].

ERG Comment

The ERG considers that, for the most part, the assumptions used to estimate the letermovir cost per day are appropriate including the assumptions made regarding the proportion of patients receiving concomitant CsA. Clinical advice received by the ERG confirmed that tacrolimus is rarely used in the UK and that the vast majority of patients would receive concomitant CsA throughout the maximum 100 day treatment period. However, the ERG has concerns regarding the proportion of patients assumed to receive IV letermovir. The ERG also thinks it inappropriate that no administration costs have been include for oral letermovir therapy.

The ERG considers that the proportion observed in the trial (27%) receiving IV letermovir is more likely to be representative of UK practice than the assumption of 95% made in the company base-case. Firstly, the company's justification based on the UK trial participants is at odds with the value used; 100% of UK patients received oral therapy. Secondly, the use of IV therapy is primarily driven by the ability of patients to tolerate an oral administration rather than clinician or patient preference. It is therefore unclear why the proportion would vary with location unless patients differed in their ability to tolerate oral therapy by region. The ERG therefore considers it more reasonable to assume that the proportion of patients unable to tolerate oral administration will align with the PN001 trial. A scenario based on this assumption is presented in Section 6.

With respect to the administration costs associated oral treatments (both letermovir and valganciclovir), the ERG considers that some administration costs should be included to reflect the resource required give patients instructions on how and when to take the tablets as well dispensing costs to cover pharmacists' time. Inclusion of administration costs for oral therapy is also consistent with Committees' preferred assumptions in several previous appraisals of oral cancer therapies; TA395, TA406, TA 422 and TA500. The ERG, therefore presents a scenario based on applying an administration cost for patients receiving oral letermovir Section 6.

5.2.9.2 CMV disease monitoring costs

The company's base-case analysis includes twice-weekly CMV viral load monitoring for both the letermovir and SoC arms of the model. The model also allows for a scenario where CMV viral load monitoring was incorporated on a weekly basis. The cost of the PCR test was estimated to be £32.62, this estimate was derived from Nottingham University Hospital. For modelling purposes, whether patients received monitoring was based on their survival. An average proportion of patients in each arm being monitored was estimated based on survival rates half-way through the model's time period.

ERG Comment

As noted in Section **Error! Reference source not found.**, there is a degree of variation in clinical ractice with respect to PCR testing, with the majority of centres undertaking PCR once a week, and smaller proportion of centres undertaking twice weekly testing. Further, the ERG's clinical advisor noted that in centres undertaking twice weekly monitoring, this would not continue for the entire duration of patients' post-transplant care, with monitoring being reduced to weekly when patients leave hospital. It is therefore likely that the company have slightly overestimated the monitoring required. Altering the frequency of testing, however, has minimal impact on the ICER and this issue is not explored further.

5.2.9.3 Pre-emptive therapy costs

When the CMV viral load monitoring detects CMV viraemia or clinically-significant CMV infection, patients begin pre-emptive therapy (PET). The rates of initiation of PET for the letermovir and SoC arms of the model for the 14 week and 24 week outcomes were derived from the PN001 trial, see Section 5.2.9.3 for further details.

The company's model includes three PET CMV antivirals: ganciclovir, valganciclovir and foscarnet. Cidofovir was a PET received by patients in the PN001 trial but was not included in the company's model for this submission, due to its lack of use in NHS clinical practice. Ganciclovir and foscarnet are both administered intravenously and therefore the model includes a drug administration cost for these therapies of £236.19 per infusion (the same administration cost as applied for IV letermovir). Because ganciclovir and foscarnet require multiple infusions per day (ganciclovir requires an infusion twice daily; foscarnet requires an infusion thrice daily) these costs was multiplied by the number of infusions required per day for the two treatments. The drug costs, administration costs and proportions of patients receiving each treatment used in the model are presented in **Table 29**. The CS assumes that patients receive PET for a mean duration of 21 days.

Table 29: Pre-emptive therapy therapies (based on Table 43 and Table 44 of CS, pg. 122-3)

Pre-emptive therapy therapies	Dosing	Source	% of patients receiving this treatment in the company's model	Drug cost	Drug administration cost
Valganciclovir	900mg (PO) twice daily	eMC SmPC Valcyte (valganciclovir) [26]	37.5%	£28.84	N/A
Ganciclovir	5mg/kg infusion once every 12 hours (twice daily)	eMC SmPC Cymevene (ganciclovir) [27]	37.5%	£45.60	£472.38*
Foscarnet	60mg/kg infusion once every 8 hours (thrice daily)	eMC SmPC Foscavir (foscarnet) [28]	25%	£275.42	£708.57*
PO=per oral; eMC=electronic Medicines Compendium; SmPC=Summary of Product Characteristics *Based on patient weight of 76.6kg obtained from PN001 week CSR (ref 29)					

The CS includes additional hospital stay costs for patients receiving foscarnet, which is assumed to require an inpatient stay; valganciclovir and ganciclovir are both assumed to be outpatient treatments. Costs are applied are assumed to be equal to £305.72 per day based on a weighted average of elective and non-elective excess bed days, obtained from the NHS Reference Costs 2015/16 [29].

Taking the drug costs, drug administration costs and additional inpatient and outpatient days required due to PET, the total cost of pre-emptive therapy included in the CS was estimated at £11,077.

ERG Comment

The ERG are satisfied with the arguments for cidofovir to have been excluded from the company's model. As stated in the CS, cidofovir had its European marketing authorisation withdrawn in 2014 [30], and there is no list price available from the BNF. In addition, it is likely that a very small number of patients, if any, would receive this drug in clinical practice (the company's clinical advisor suggested 5%; the ERG's clinical advisors both noted that this would be a third-line PET treatment).

The CS assumption that patients receive PET for a mean duration of 21 days is lower than that observed in the PN001 trial (mean duration was 60.4 days in the letermovir arm and 58.5 days in the SoC arm) and was based on correspondence with the company's clinical expert. This is a conservative assumption, as increasing the duration of PET has the effect of reducing the ICER for letermovir. The ERG's clinical advisors considered the assumed mean duration of 21 days to be reasonable and in line with UK practice.

The ERG has a number of concerns regarding the proportion of patients receiving foscarnet and the administration costs associated with each kind of PET.

Foscarnet use

With respects to the proportion of the of patients receiving foscarnet, the ERG notes clinical advice suggested that foscarnet would not be used as first-line PET, unless a patient is ineligible or intolerant to (val)ganciclovir. This is due to the requirement for an inpatient stay and the significant toxicities associated with foscarnet treatment. As such the ERG's clinical advisors suggested that a lower proportion of patients would therefore receive foscarnet than is assumed in the company's base case (25%), with one clinical advisor estimating that around 5% of patients would receive foscarnet, and the other estimating that approximately 10 to 15% would receive foscarnet. The ERG notes that this aligns with the PN001 trial, where 10.8% of patients received foscarnet as pre-emptive therapy. The ERG explores additional analyses in Section 6 where the proportion of patients receiving foscarnet is reduced.

Valganciclovir administration costs

The ERG considers that valganciclovir, which is an oral therapy, should be associated with an administration costs for the same reasons as stated above with respect to letermovir. Further analysis applying these additional costs is applied in Section 6.

Ganciclovir and foscarnet administration costs

The ERG considers that the company's approach to modelling the administration costs of ganciclovir and foscarnet by multiplying the costs of single infusing is overestimating the total costs of PET and that there would be economy of scale involved in delivering multiple simple infusions in single day. As such, the ERG considers that it may be more reasonable to apply a proportionally greater cost associated with a single, more complex and prolonged infusion rather than the costs of multiple simple infusions. The ERG also notes that the costs applied with respect to the administration costs for ganciclovir and foscarnet do not distinguish between the fact that ganciclovir is received on an outpatient basis while foscarnet is received on an inpatient basis. The ERG presents scenario analysis in Section 6 considering these alternative assumptions.

5.2.9.4 Health State Costs

The economic model presented by the company does not include any specific health state costs, but does include further costs related to clinical complications that can occur after the onset of clinical significant CMV infection. These include:

1. CMV end-organ disease
2. CMV-related re-hospitalisation
3. Opportunistic infection

4. GvHD

The rates at which these events occur were based on the clinical inputs derived from the PN001 trial, see Section 5.2.9.4 for further details.

CMV end-organ disease

CMV end-organ disease was assumed to be associated with the same total cost as pre-emptive therapy (i.e. £11,077), as per the British guidelines on CMV management [11]. The company consider this to be an underestimate; they expect patients would be treated with more intensive medicines and would incur more serious conditions such as renal damage and cytopaenia, which would require additional resources.

CMV-related re-hospitalisation

The company's model also includes the cost associated with extra days in hospital due to pre-emptive therapy/CMV disease. The inpatient cost was assumed to be the same as that assumed for PET costs detailed above. The average number of extra inpatient days required was assumed to be 13.9 days in the model. This was based on Jain *et al.* (2014) [31] which assessed the costs associated with CMV. The company stated that no additional costs associated with treatments/procedures were included apart from this excess bed day cost, and therefore, this may be an underestimate of the true cost. Using these estimates, the company calculated that the CMV-related rehospitalisation cost was £4,250.

Opportunistic infection

The company estimated the cost of opportunistic infection based on a published study [32] and NHS reference costs. The three most common opportunistic infections, as per Krüger *et al*. were included. The proportion of patients contracting each infection, along with the associated costs, are presented in **Table 30**.

Table 30: Costs associated with Opportunistic infection (adapted from tabl 39, pg. 106-110 in CS)

Variable	Parameter	Reference
% of patients with FUO	63.7%	Krüger *et al* (1999) [32]
% of patients with pneumonia	18.7%	Krüger *et al* (1999) [32]
% of patients with septicaemia	17.6%	Krüger *et al* (1999) [32]
FUO cost	£1,020	NHS reference costs WJ07A-D
Pneumonia cost	£1,905	NHS reference costs DZ11KI-V
Septicaemia cost	£2,164	NHS reference costs WJ06A-J
Total cost of opportunistic infection	£1,387	

GvHD

The costs associated with GvHD were split into the costs associated with acute GvHD (GvHD which occurs during the first 100 days following SCT) and chronic GvHD (GvHD which occurs during the period subsequent to the 100 days post-transplant). The proportion of patients contracting aGvHD was derived from the PN001 clinical inputs. The proportion of patients contracting cGvHD was assumed to be 30% of the survivors of the HSCT. This was based on the NHS England Clinical Commissioning Policy. [33]

Both types of GvHD were assumed to be treated with methylprednisolone, which is a first line systemic steroid that is administered intravenously. This is the first-line treatment recommended in the Commissioning Policy. For aGvHD, IV methylprednisolone is administered daily for 40 days; for cGvHD, 1mg/kg administered in the first year on alternate days, 0.5mg/kg administered in the second year on alternate days.

ERG Comment

The ERG considers the costs applied in relation to CMV end-organ diseases, CMV-related re-hospitalisations, and opportunistic infections appropriate. With respect to CMV end-organ diseases, the ERG agrees that the costs applied are conservative and likely underestimate the additional resources that may be required to manage the wide range of conditions that would come under CMV end-organ disease. The ERG also agrees that the incidence of these more serious conditions is likely to be rare and unlikely to impact on the estimated ICER significantly.

While the CS submission does include some costs associated with treating GvHD, the ERG are concerned that these costs may have been underestimated. The use of IV methylprednisolone for treatment of GvHD was based on recommendations from Dignan *et al.* (2012).[34] However, this paper recommends corticosteroids as a first-line treatment, and presents several options for second- and third-line treatments, depending on the symptoms of GvHD that present in the patient. At the clarification stage, the ERG asked the company to present a scenario analysis where second-line treatments for GvHD were included. This scenario is presented in Section 5.2.15.

Finally, the ERG are concerned that a major cost category has been omitted from the CS, that is, the costs associated with the patients' underlying disease condition. This cost category includes both the ongoing care costs associated with having received a HSCT, and the costs associated with a relapse in disease following HSCT. Published studies[35] and recent technology appraisals in AML and ALL (ID893 and ID894), have all included ongoing care costs for several years post-HSCT. Published studies[36] have also shown that a significant proportion of people with haematological cancers will

experience relapse in their underlying disease following HSCT and incur additional costs, as well as associated disutilities. While these costs are incurred by both the letermovir arm and the standard care arm of the model, the mortality benefits observed in the letermovir arm relative to the standard care arm mean that a greater number of patients will incur these additional costs and this cost difference should be included in the model. At clarification, the ERG asked the company to justify the omission of these costs and also to present additional scenario analyses where these costs are included. The results of these additional analyses are presented in Section 5.2.14.

5.2.9.5 Adverse event costs

The company's model includes the costs associated with the most commonly occurring haematological adverse events, as observed in the PN001 trial.[37] These were: neutropenia, thrombocytopenia and leukopenia. These adverse event rates were conditional on having confirmed CMV viraemia or CMV end-organ disease and are only applied to the proportion of patients who receive PET. This proportion of PET-initiated patients are then assumed to incur the costs associated with these adverse events, as presented below, in **Table 31**. These costs were derived from NHS Reference costs. [29]

Table 31: Adverse event costs (from company's Model)

Adverse event	Cost
Neutropenia	£1,142.90
Thrombocytopenia	£636.19
Leukopenia	£1,142.90

ERG Comment

Due to the method chosen to implement adverse events within the model, with the assumption that only those patients who initiate PET experience adverse events, very small rates of AE are observed in the model, with very small associated costs.

5.2.10 Cost effectiveness results

In this section, the results of cost-effectiveness analyses (including PAS) are presented for the deterministic base-case analysis, probabilistic sensitivity analysis, deterministic sensitivity analyses and scenario analyses.

5.2.10.1 Base-case incremental cost-effectiveness analysis results

The base-case results are presented in **Table 32**. The company's base-case found letermovir to be more costly (cost difference of £5,014), but also more effective (gain of 0.46 QALYs), compared with SoC. The resulting deterministic ICER was £10,904 per QALY gained.

Table 32 Base-case incremental cost-effectiveness ratios for letermovir compared to SoC (including PAS) (CS, executable model)

Technology (and comparators)	Total costs	Total life-years	Total QALYs	Incremental costs	Incremental life-years	Incremental QALYs	ICER
SoC	£28,805	7.91	6.73	-	-	-	-
Letermovir	£33,819	8.43	7.19	£5,014	0.52	0.46	£10,904
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; SoC, standard of care							

5.2.10.2 Results of sensitivity analysis and scenario analysis

Probabilistic sensitivity analysis results

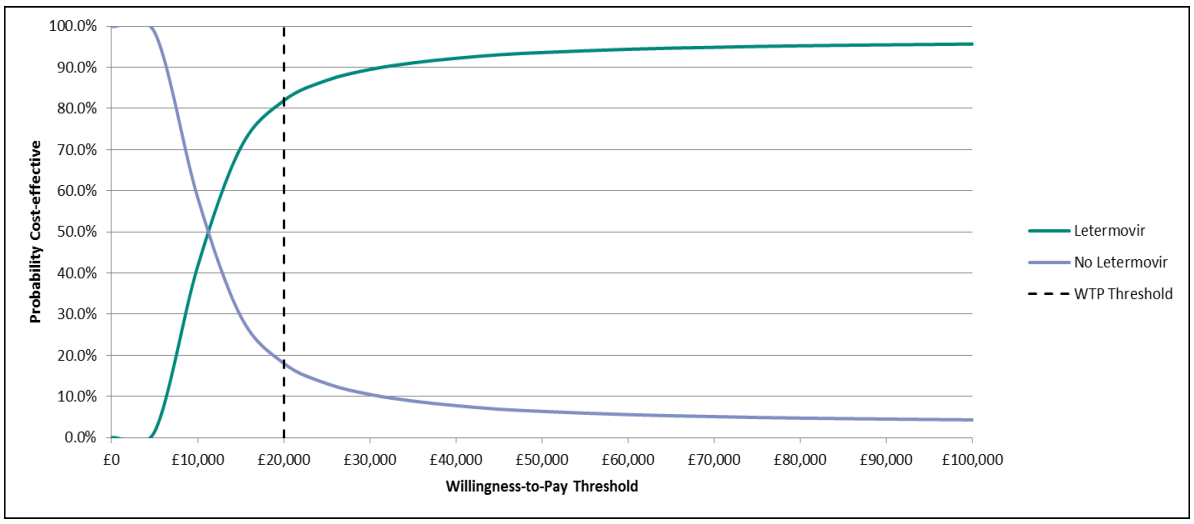
The average QALYs gained with letermovir compared with SoC were 0.46. The average incremental cost was £5,036, resulting in an average ICER of £10,913 per QALY gained. The results of the PSA were similar to those of the deterministic analysis (compare **Table 32** and **Table 33**).

Table 33 Probabilistic sensitivity analysis results (including PAS) (CS, executable model)

Technology (and comparators)	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
SoC	£28,790	6.72			
Letermovir	£33,826	7.19	£5,036	0.46	£10,913
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; SOC, standard of care					

A cost-effectiveness acceptability curve (CEAC) is presented in Figure 6. The results indicate that letermovir has 81.92% chance of being the cost-effective treatment, at the £20,000 willingness-to-pay (WTP) threshold, and 89.49% chance at the £30,000 WTP threshold.

Figure 6 Cost-effectiveness acceptability curve (including PAS) (CS, executable model)

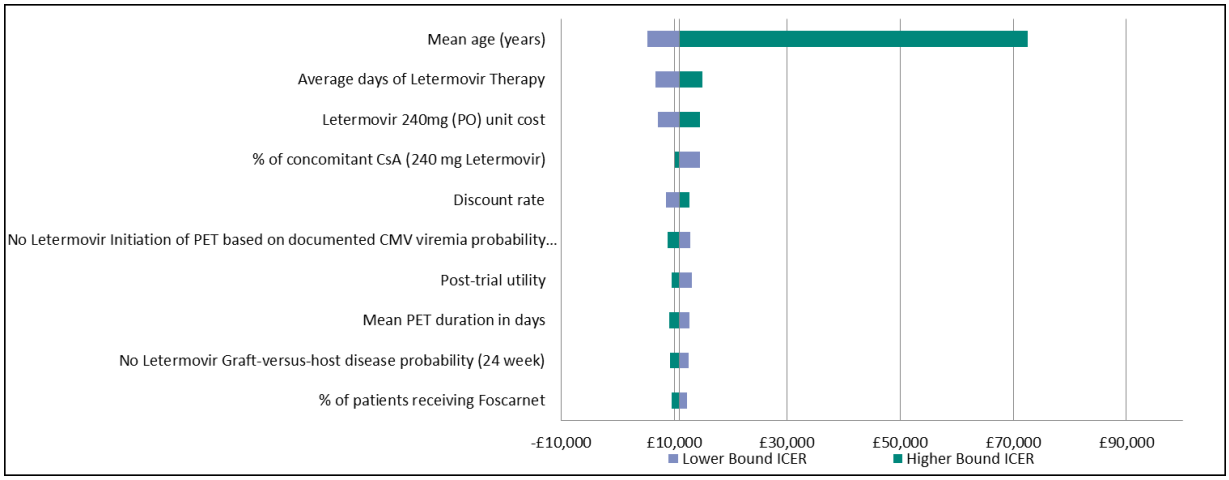


WTP=willingness-to-pay

Deterministic sensitivity analysis results

The company presented a series of deterministic sensitivity analyses to assess the impact of varying key model input parameters on the ICER. Figure 7 shows a tornado diagram, summarising the influential parameters reported by the company. The results indicate that mean age has the largest impact on the ICER, following average days of letermovir therapy and unit cost of letermovir 240mg (PO).

Figure 7 Deterministic sensitivity analysis results (cost per QALY; including PAS) (CS, executable model)



CsA=ciclosporin A; ICER=incremental cost-effectiveness ratio; WTP=willingness-to-pay; PO=Oral

Two-way sensitivity analysis was conducted for mortality parameters to show the robustness of ICER estimates to plausible combinations of these input parameters. The Figure 8 shows the impact on ICER where each input parameter was varied across the 95% confidence interval, in increments of

0.5%. Cells in Figure 8 shaded green display ICERs below £20,000 per QALY, bright yellow between £20,000 and £30,000 per QALY, brown-yellow above £30,000 per QALY and red when standard of care dominates a letermovir strategy. This two-way sensitivity analysis shows that letermovir is cost-effective at £20,000 per QALY, as long as the difference in mortality rate exceeds 2.5% and is cost-effective at £30,000 per QALY as long as the mortality difference exceeds 1.5%. The ERG notes that both these values are well within the estimated 95% confidence interval for the mortality difference.

Figure 8 Results of two-way sensitivity analysis (including PAS) - all-cause mortality parameters

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

Scenario analysis results

The submission also included series of scenario analyses to check the robustness of the model results with different assumptions. The first assumption related to key model parameters used to derive letermovir and pre-emptive therapy costs, the second related to key parameters used to derive the QALY estimates, the third related to the time horizon used to inform the QALY estimates, and the fourth related to the method missing patient data approach used in PN001 to estimate the probability of initiation of pre-emptive therapy and CMV end-organ disease.

The results of the scenarios are presented in **Table 34**. The results were notably most sensitive to variations in average days of letermovir therapy and percentage of patients receiving 240mg letermovir. All the scenarios suggest letermovir is cost-effective with ICERs never exceeding £20,000 per QALY.

Table 34 Results of scenario analyses (including PAS) (CS, executable model)

Model input	Parameter value	Reference	ICER	Changes from base-case ICER (%)
Base-case			£10,904	
Average days of letermovir therapy	81	Median therapy length of UK trial population (MSD, data on file) [38]	£13,679	£2,775 (25%)
Average days of letermovir therapy	100	As per letermovir SmPC [39]	£18,226	£7,322 (67%)
% of patients receiving letermovir Therapy (PO)	73%	As per letermovir ASaT trial population	£12,432	£1,528 (14%)
Percentage of patients receiving oral letermovir therapy (PO)	100%	As per letermovir UK trial population (MSD data on file) [38]	£10,556	-£348 (3%)
Average days of letermovir IV therapy	28	>90% of IV therapy in trial was 4 weeks or less (Table 12-1 CSR) [37]	£11,285	£381 (3%)
Percentage of patients receiving 240mg Letermovir	51.9%	As per trial population - Table 10-13 CSR	£17,471	£6,567 (60%)
Average days of pre-emptive therapy	59	Mean duration of pre-emptive therapy treatment as per trial - Table 11-29 CSR [37]	Letermovir dominant	n/a
Beyond trial mortality in year 1 and 2 based on probability of mortality between 24-week and 48-week	11.5%	Derived from 24-week and 48-week trial data (Week 48 CSR) [40]	£13,629*	£2,725 (25%)
cGvHD disutility	0.090	Pidala J et al. 2011 [25]; Ara & Brazier 2011 [17]	£10,871	-£33 (0%)
Medicine dose and duration				
Percentage of concomitant CsA (240 mg letermovir)	51.9%	Table 10-13 CSR [37]	£14,962	£4,058 (37%)
Percentage of IV letermovir	27%	Page 21 CSR [37]		
Average days of pre-emptive therapy	59	Table 11-29 CSR [37]		
NC=F approach for missing data				
Letermovir initiation of pre-emptive therapy	16.0%	Table 11-2 week 24 CSR [37]	£12,204	£1,300 (12%)
Letermovir CMV disease	1.5%			
SoC initiation of pre-emptive therapy	40.0%			
SoC CMV disease	1.7%			

CMV=cytomegalovirus; CSR=clinical study report; ICER=incremental cost-effectiveness ratio; IV=intravenous; NC=F=non-completer=failure; PO=oral; SoC=standard of care; SmPC=Summary of Product Characteristics
*Model run based on week 48 data

In addition to the above, an exploratory analysis was conducted to show impact on ICERs when alternative time horizons using the base-case were assumptions. The results are presented in **Table 35**. Letermovir is cost-effective at £30,000 per QALY compared to SoC in all time horizons considered, with the ICER falling as the time horizon is increased.

Table 35 Results of alternative time horizon assumptions (including PAS) (CS, main submission Table 54 pg. 142 & executable model)

Model time horizon		Reference	ICER	Changes from base-case ICER (%)
Base-case			£10,904	
Lifetime based on week 24 data	At 5 years	Table 11-1 week 24 CSR and calculation	£21,723	£10,819 (99%)
	At 10 years	Table 11-1 week 24 CSR and calculation	£14,274	£3,370 (31%)
	At 20 years	Table 11-1 week 24 CSR and calculation	£11,132	£228 (2%)
Lifetime based on week 48 data	At 5 years	Table 11-2 week 48 CSR and calculation	£22,662	£11,758 (108%)
	At 10 years	Table 11-2 week 24 CSR and calculation	£15,355	£4,451 (41%)
	At 20 years	Table 11-2 week 24 CSR and calculation	£12,135	£1,231 (11%)
	Lifetime	Table 11-2 week 24 CSR and calculation	£11,897	£993 (9%)
CSR=clinical study report; ICER=incremental cost-effectiveness ratio				

5.2.11 Company scenario analyses

At the clarification stage, the ERG requested a series of additional scenario analyses, a brief description of each of these along with the results of this analysis are presented in the subsequent sections.

5.2.11.1 FAS population and time to event data

In the PfCs, the ERG requested the company to present an analysis where the clinical inputs were all derived from the FAS population and all derived from the ASaT population. In addition, the ERG requested present the analysis for both these populations where the clinical inputs used in the model are based on unadjusted "data as observed" (DAO) analysis, where the all clinical inputs use the missing-not-at random analysis method to adjust for missing data. The company presented the FAS and the ASaT populations using DAO analysis. However, the missing-not-at random analysis method was not used as the company did not have a mechanism of getting hold of the missing data. Instead, the FAS and ASaT populations were presented where the clinical inputs use the time-to-event analysis methods. The results of these different analyses in the two populations are presented in **Table 36**.

Table 36: FAS/ASaT populations using TtE/DAO analyses

Scenarios/Model input	ICER (Lifetime based on 24-week)	Changes from base-case ICER (%)
Base-case	£10,904	
All clinical inputs using DAO analysis using ASaT population	£11,888	£984 (9%)
All clinical inputs using DAO analysis using FAS population	£11,966	£1,062 (10%)
All clinical inputs using missing-not-at-random analysis method to adjust of missing data and using the ASaT population	£13,329	£2,425 (22%)
All clinical inputs using missing-not-at-random analysis method to adjust of missing data and using the FAS population	£12,602	£1,698 (16%)

All of the scenarios presented increase the base case ICER. The ERG consider the FAS population using DAO analysis as the most appropriate to include in the ERG's preferred base case analysis.

5.2.11.2 Extrapolation of OS

At the PfC stage the ERG requested that the company consider alternative approaches to extrapolating OS including the use of parametric survival modelling. The company presented results using both the FAS and ASaT populations. The results of these different analyses in the two populations are presented in Table 37. The ERG while considering this a potentially valid approach has two concerns with the company's approach to implementing this request. Firstly, the company has chosen in this analysis to relax the assumption that there are no survival benefits attributable to letermovir beyond the 24 week data from PN001; it would have more appropriate to retain this assumption and extrapolate a combined KM curve. Secondly, the company's approach relies on using the extrapolated curves for the whole post decision tree phase rather than moving to natural history data at an appropriate point e.g. 2 years post HSCT.

Table 37 Parametric extrapolations of OS

Scenarios/Model input	ICER (Lifetime based on 24-week)	Changes from base-case ICER (%)
Base-case	£10,904	
Extrapolating survival data		
Exponential distribution – AsaT population	£8,598	-£2,306 (21%)
Weibull distribution - ASaT population	£11,453	£549 (5%)
Lognormal distribution - ASaT population	£6,379	-£4,525 (41%)
Loglogistic distribution - ASaT population	£7,920	-£2,984 (27%)
Gompertz distribution - ASaT population	£14,309	£3,405 (31%)
Exponential distribution - FAS population	£7,910	-£2,994 (27%)
Weibull distribution - FAS population	£10,279	-£625 (6%)
Lognormal distribution - FAS population	£5,645	-£5,259 (48%)
Loglogistic distribution - FAS population	£7,158	-£3,746 (34%)
Gompertz distribution - FAS population	£10,531	-£373 (3%)

5.2.11.3 48 Week trial data

As described in Section 5.2.7 the analysis set that the company used in the model included significant missing data and was based on 24 week outcome. Several clinical inputs were, however, available at Week 48 in the PN001 trial, and the ERG consider it more appropriate to include this additional data. Further, the ERG noted that the mortality data in the model, based on the Kaplan-Meier data for the trial was subject to significant censoring as a substantial number of participants were lost to follow up. Due to this, as discussed in the CS, the FDA requested additional follow-up data to be presented, which the ERG requested be included in the model in the PfCs. The results of this analysis are presented in **Table 38**.

Table 38: Results using 48 week data from PN001 trial

Scenarios/Model input	ICER (Lifetime based on 24-week)	Changes from base-case ICER (%)
Base-case	£10,904	
48 week data – DAO_ASaT population	£11,168	£264 (2.42%)
48 week data – DAO_FAS population	£13,069	£2,165 (19.86%)
Revised mortality data - DAO_ASaT population	£10,687	-£217 (-1.99%)
Revised mortality data - DAO_FAS population	£15,071	£4,167 (38.22%)

5.2.12 Long-term disutility

As described in Section 5.2.8, the ERG is concerned that the utilities used by the company in the Markov phase the model do not reflect the long-term impact of SCT on health. Reflecting these

concerns the ERG requested that the company present a scenario analysis where a utility decrement from the long-term effects of HSCT has been incorporated. The results of which are presented in **Table 39**. The disutility applied in this analysis is 0.0114 per year and is calculated based on the difference between the utility reported in Leunis *et al.* (2014) and general population mortality source from Ara *et al*. The ERG considers this an inconsistent approach which mixes EQ5D-5L and EQ-5D-3L values, and is also inconsistent with the value reported in Leunis *et al* (2014) based on EQ-5D VAS scores of 0.046.

Table 39 Long-term disutility following SCT

Scenarios/Model input	ICER (Lifetime based on 24-week)	Changes from base-case ICER (%)
Base-case	£10,904	
Long term utility decrement applied to the general population utilities	£10,959	£55 (1%)

5.2.13 Long-term care costs following SCT

During the PfCs, the ERG requested that the company present a scenario where the long term care costs associated with HSCT are incorporated. Although it is the case that the long-term care costs following a HSCT are borne by both patients receiving letermovir and receiving standard of care, given that letermovir patients are estimated to have lower mortality following SCT, it is important to include the long-term cost implications of this additional survival. The ERG consider the costs included in the PfC response, which were based on TA451, to be appropriate and the results of this scenario analysis is presented in **Table 40**.

Table 40: Long-term care costs following SCT

Scenarios/Model input	**ICER (Lifetime based on 24-week)**	**Changes from base-case ICER (%)**
Base-case	£10,904	
Long-term follow-up costs from allogeneic-HSCT scenario analysis [Follow-up cost year 1 post SCT =£12,378; Follow-up cost year 2 post SCT =£3,565]	£12,322	£1,418 (13%)

5.2.14 Relapse after SCT

The company presented several scenarios where both additional costs and disutilities associated with patients relapsing after SCT are incorporated. The company presented several scenarios for incorporating this data, assuming survival is 6 months, one year or two years. In all scenarios, 10% of patients are assumed to relapse; a relapse is assumed to be associated with a 0.0114 disutility and with a per-cycle cost of £6,460. The ERG considers the range of scenarios presented by the company as

useful exploration of the uncertainty, but note a number of issues. Firstly, there is a small error in the company's model which assumes that all patients incur the disutility associated with relapse rather than just the 10% of patients experience relapsed disease. The corrected scenario (which only has a small effect on the ICER), is presented in **Table 41** below. Secondly, the ERG considers that this scenario underestimates both the disutility associated with relapse and the rate of relapse. The disutility associated with relapse is expected to have only minimal impact on the ICER and therefore is not explored further. However, an alternative rate of relapse is explored further in Section 6.3.

Table 41: Relapse after SCT

Scenarios/Model input	ICER (Lifetime based on 24-week)	Changes from base-case ICER (%)
Base-case	£10,904	
Relapse after stem-cell transplant scenario – 6 month survival	£11,041	£137 (1.26%)
Relapse after stem-cell transplant scenario - 1 year survival	£11,156	£252 (2.31%)
Relapse after stem-cell transplant - 2 year survival	£11,387	£483 (4.43%)

5.2.15 Costs and disutilities associated with GvHD

The company presented a scenario where the cost associated with a patient requiring second-line treatment (in addition to the steroid use currently included in the model) for both aGvHD and cGvHD. The company assumed that 10% of patients developed aGvHD and 6% of patients acquired cGvHD. The ERG consider both the costs included and rate assumed to be appropriate. However, the ERG noted an error with the implementation of this scenario in the company's model. All the costs associated with GvHD were included in the trial time period, which is inappropriate as cGvHD usually manifests after a year post-SCT. Therefore, in **Table 42** below, the ERG present a cost scenario where:

1. The cost of 10% of patients with aGvHD requiring second line treatment is added to the aGvHD costs in the model (an additional cost of £1,810.63);
2. The cost of 6% of patients with aGvHD requiring second line treatment is added to the cGvHD costs in the model (an additional cost of £325.91).

The company also presented a scenario where a disutility of 0.09 is applied in year 1 and year 2 after the trial period for 30% of survivors relating to GvHD. Again, the ERG noted an error with the implementation of this disutility as only 1 year of disutility was included.

The ERG's version is presented in **Table 42**. **Table 42** also presents the results with both the additional costs and the disutilities are included together.

Table 42: Second-line treatment costs for GvHD and disutility for GvHD

Scenarios/Model input	ICER (Lifetime based on 24-week)	Changes from base-case ICER (%)
Base-case	£10,904	
Additional costs for aGvHD and cGvHD included	£10,793	-£111 (-1.02%)
Additional disutility for aGvHD and cGvHD included	£10,977	£73 (0.67%)
Both additional costs and disutility included	£10,866	-£38 (-0.35%)

5.2.15.1 Conclusions

The analyses show that letermovir is cost-effective at the £20,000 WTP threshold with deterministic ICER of £10,904 per QALY. The probabilistic analysis base-case found that letermovir has an 81.92% chance of being the cost-effective treatment at the £20,000 WTP threshold and an 89.49% chance at the £30,000 WTP threshold. The deterministic sensitivity analyses results and pre-defined scenario testing demonstrate that the ICER is most sensitive to the mean age of the cohort, average duration of letermovir therapy, the proportion of patients receiving 240mg letermovir, and the magnitude of the mortality benefit associated with letermovir.

5.2.16 Model validation and face validity check

Validation carried out by the company

The CS reports that several levels of model validation were undertaken as part of the model development process. These included assessment by clinical experts working in the NHS of modelling assumptions, and quality assessment of the model carried out, including validation of model inputs and functionality by an external health economist.

Internal validation carried out by the ERG

The ERG undertook a review of the company's base-case and sensitivity analyses. This included the use of a checklist to carry out a series of black-box tests, to evaluate the internal validity of the model. These black-box tests examined the internal logic of the model, as well checking the predictive validity of the parameter inputs (e.g. that increasing the effectiveness of the treatment lowers cost-effectiveness). Further to this, the code of the model was examined for potential errors, this included tracking how the parameters fed into the model and an examination of the main calculation sheets, with a view to understanding how the QALYs and costs were accumulated in the model. This review identified a number of relatively minor calculation errors and inconsistencies, which do not affect the ICER value.

5.3 Conclusions of the cost effectiveness section

The economic analysis presented by the company was considered to meet the decision problem specified in NICE's scope. However, the ERG identified a number of key uncertainties. The main concerns identified by the ERG include:

1. *Over simplified modelling approach*

The ERG considers that the modelling approach taken by company, although transparent and relatively flexible, is potentially too simplistic. The ERG is particularly concerned that the model makes a number of structural assumptions such that there is no link between the rate of CMV events (the principal benefit of letermovir) and mortality which is the key driver of cost-effectiveness. This means that uncertainty relating to difference between the CMV events in the two groups cannot be fully explored.

2. *Care cost and relapse disease*

The ERG are concerned that a major cost category has been omitted from the CS, that is, the costs associated with the patients' underlying disease condition. This cost category includes both the ongoing care costs associated with having received a HSCT, and the costs associated with a relapse in the underlying-condition following HSCT. This is problematic as, while these costs would be borne by both groups, these costs will not be equal in the two groups due to differences in the proportion of patients alive.

3. *Clinical inputs based on 24 week data*

The clinical inputs used in the company's base-case were based on 24 week outcome despite the availability of data up to 48 weeks for most outcomes (the exception being initiation of PET). The ERG considered that an approach based on making maximum use of the data available is more reasonable than making the assumption that no further clinical events occur post 24 weeks, which is implied in the company's base-case.

4. *Missing data*

The clinical data collected in PN001 was subject to sizable attrition and reflecting this the company present and number of alternative analyses using different approaches to account for the incomplete follow up. The data used in the model, however, does not adjust for the incomplete follow up, being based instead on only the observed data (DAO data set). The ERG has some concerns regarding this approach as it implicitly makes the assumption that data is missing completely at random (i.e. not

related to the either observed or unobserved data). Further, the ERG also notes that the company collected further data on the survival of participants lost to follow in a response to a request by the FDA. This data is more complete with just 3.2% patients lost to follow compared with 13.5% in the main analysis.

5. *Uncertainty in mortality benefits*

The ERG considers that there is significant uncertainty around the difference in mortality between the two treatment groups and notes that the mortality benefits observed in the PN001 trial were not statistically significant. This is important because almost all of the QALY benefits associated with letermovir prophylaxis derive from improved survival and sensitivity analysis implemented by the company demonstrates that there is wide range of plausible values for which letermovir would not be considered cost-effective based on threshold of £30,000 per QALY.

6. *Uncertainty in duration of Letermovir prophylaxis*

The ERG notes that there is considerable uncertainty regarding the duration over which letermovir prophylaxis will be administered. Specifically, the ERG notes that in the clinical trial there was a significant delay following HSCT before letermovir prophylaxis (mean [redacted] days) was initiated. This was likely due to concerns that initiating letermovir prophylaxis may effect graft response. The ERG, however, thinks it is likely that clinicians will be more confident to administer letermovir prophylaxis immediately post HSCT as PN001 demonstrated that letermovir does not impact on graft response. Further, the ERG notes the lack of any futility rules in the SmPC and considers that in clinical practice it is plausible that patients requiring longer periods of prophylaxis (as is allowed under the product licence) would receive prophylaxis beyond 100 days.

7. *Costs of Letermovir and PET*

The ERG noted a number of issues relating to the administration costs associated with both letermovir and PET as well as further issue relating to the composition of PET. These concerned the proportion of patients that would receive IV letermovir; the administration costs associated with oral therapies (letermovir and valganciclovir); the administration costs applied with respect to ganciclovir and foscarnet; and, the proportion of patients initiating PET who would receive foscarnet.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section details the ERG's further exploration of the assumptions and uncertainties raised in the ERG's review and critique of the company's cost-effectiveness analysis. This section is organised in four parts. Section 6.2 details the corrections made by the ERG to the company's additional scenario analyses undertaken in the main submission and during the clarification stage. Section 6.3 details the additional scenario analyses undertaken by the ERG.

The scenario analyses undertaken by the ERG focus on exploring the following issues and uncertainties:

- Duration of letermovir prophylaxis;
- Administration costs for letermovir and PET;
- Cost of PET- Foscarnet use;
- Probability of relapse after HSCT;
- Disutilities associated with HSCT;
- Mortality in the Markov phase.

In Section 6.3, the ERG base-case is presented based on a combination of the company's scenario analyses provided either at the points for clarification stage and the additional scenario analyses undertaken by the ERG presented in Section 6.3. Further exploratory analysis is also presented exploring the impact of alternative assumptions in the context of the ERG base-case. These further analyses explore the following issues:

- Duration of letermovir prophylaxis;
- Approaches to addressing missing data;
- Mortality benefit of letermovir prophylaxis at 48 weeks.

Section 6.4 presents a brief conclusion summarising the ERG's additional analyses. It is important to note that all of the analyses presented in Section 6 include the company's proposed PAS discount of [redacted]. Due to time constraints, ICERs based on the deterministic analysis are presented throughout this section.

6.2 ERG corrections of Company's analysis

As noted in Section 5.2.11, the ERG noted some errors within the company's scenario analyses. The scenarios with errors and the errors identified were:

1. The long-term disutility calculated for survivors of HSCT;
2. The disutility associated with a relapse in the patients' underlying condition; and
3. The costs and disutilities associated with aGvHD and cGvHD.

Scenario 1 and 3 above are included in the ERG's preferred base-case analysis, with the ERG's corrections incorporated. For details on these errors, please refer back to Section 5.2.11.

6.3 ERG exploratory analyses

6.3.1 Duration of therapy

The duration of therapy assumed in the company's base case analysis is 69.4 days. However, this mean value was derived from the ASaT population. As discussed in Section 5, the ERG requested that the company present a scenario analysis where all clinical inputs, including duration of therapy, are derived from the FAS population. The mean duration of therapy derived from the FAS population was 72.1 days. Furthermore, the company's submission, noted that patients waited an average of [redacted] days post-transplant before beginning letermovir prophylaxis; a delay that the ERG think is unlikely to occur in clinical practice. The ERG therefore presents a scenario where patients are assumed to begin treatment with letermovir on the day of transplantation. As presented in Table 43, the results of this analysis are associated with higher incremental costs and a higher ICER of £14,158 per QALY.

As described in Section 5, the ERG notes the lack of any futility rules in the SmPC and considers that in clinical practice it is plausible that, where required some patients may receive prophylaxis beyond 100 days. To explore this uncertainty the ERG runs a number of scenario is in which it is assumed that (45%) patients receiving letermovir prophylaxis at 100 days continue to receive therapy for fixed period of time. Three scenarios are run, assuming an additional 2, 4 and 6 weeks of therapy post 100 days. Note the ERG only adjusts costs in these scenarios and it is likely that extending the duration of letermovir prophylaxis will improve effectiveness. These ICERs therefore are likely to overestimate the true ICER. The results of this analysis show that ICER is quite sensitive to any increase in the mean duration of therapy with the ICER increasing to £18,681 per QALY in the scenario where a further 6 weeks of therapy is assumed.

Table 43: Duration of treatment with Letermovir

Technologies	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's base case (including PAS)					
SoC	28,805	6.73	-	-	-
Letermovir	33,819	7.19	5,014	0.46	10,904
FAS population duration of therapy					
SoC	28,805	6.73	-	-	-
Letermovir	34,116	7.19	5,311	0.46	11,550
Additional [redacted] days duration of therapy and FAS population duration of therapy					
SoC	28,805	6.73	-	-	-
Letermovir	35,315	7.19	6,510	0.46	14,158
Maximum duration of therapy assumed to be 100 days + 2 weeks					
SoC	28,805	6.73	-	-	-
Letermovir	36,008	7.19	7,204	0.46	15,666
Maximum duration of therapy assumed to be 100 days + 4 weeks					
SoC	28,805	6.73	-	-	-
Letermovir	36,668	7.19	7,864	0.46	17,101
Maximum duration of therapy assumed to be 100 days + 6 weeks					
SoC	28,805	6.73	-	-	-
Letermovir	37,395	7.19	8,590	0.46	18,681

ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; SoC=standard of care; FAS=Full Analysis Set; TtE=Time to Event

6.3.2 Administration costs for letermovir and PET

This section focuses on three issues:

- The proportion of letermovir patients assumed to receive IV letermovir;
- The administration costs associated with providing oral letermovir and valganciclovir;
- The IV administration costs applied for foscarnet and ganciclovir.

As discussed in Section 5, the ERG considers the use of IV letermovir to be underestimated in the company's base-case analysis. The ERG therefore explores a scenario where 27% of patients, receive

IV letermovir in line with the PN001 trial. The results of this scenario, present in Table 44 show an increase in incremental cost with the ICER increasing to £12,432 per QALY.

The ERG considers it likely that some administration costs would be incurred to provide oral letermovir and valganciclovir. Therefore a one-off administration cost has been included of £183.50 based on NHS reference costs [SB11Z - "Deliver Exclusively Oral Chemotherapy"]. This was applied to 98% of patients (the proportion of patients receiving oral letermovir in PN001) and all patients receiving valganciclovir. The impact of implementing administration cost for oral therapies is to increase both the total costs associated with providing letermovir and standard care, with a net impact of small increase in incremental costs. This results in a small increase in the ICER to £11,251per QALY.

The company's approach to estimating the costs associated with administering the multiple infusions required per day by patients receiving PET was to multiply the administration cost by the number of infusions required. The ERG considers this to be potentially overly simplistic and likely to overestimate the costs of providing PET. The ERG, therefore presents and alternative scenario in which the cost of single complex infusion is applied instead; £383.13 SB14Z - "Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance". This cost is only applied once per day of treatment, regardless of the setting and number of IV doses required. The results of this scenario are presented in Table 44 and shows marked increase incremental costs. This is because the costs avoided due reduced use of PET in the letermovir treatment group are now smaller. The resulting ICER is £12,452 per QALY.

Table 44: Administration cost for Letermovir.

Technologies	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's base case (including PAS)					
SoC	28,805	6.73	-	-	-
Letermovir	33,819	7.19	5,014	0.46	10,904
IV Letermovir Use – per PN001					
SoC	28,805	6.73	-	-	-
Letermovir	34,522	7.19	5,717	0.46	12,432
Administration cost included					
SoC	28,840	6.73	-	-	-
Letermovir	34,013	7.19	5,173	0.46	11,251
Alternative IV costs for PET					
SoC	27,564	6.73	-	-	-
Letermovir	33,290	7.19	5,726	0.46	12,452
ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; SoC=standard of care					

6.3.3 Costs of PET- Foscarnet use

The ERG are concerned that the assumed use of foscarnet in the company's model is too high. Following discussions with the ERG's clinical advisors, it was assumed that only 15% of patients would receive foscarnet rather than the 25% assumed in the company's base-case analysis. The impact of using alternative assumptions for the rate of foscarnet use is to increase the ICER to £12,274 per QALY. This occurs because foscarnet has higher administration costs and requires an inpatient stay than other PET therapies. Reducing the rate of foscarnet therefore acts to reduce the average cost of PET.

Table 45: Foscarnet use

Technologies	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's base case (including PAS)					
SoC	28,805	6.73	-	-	-
Letermovir	33,819	7.19	5,014	0.46	10,904
Assuming foscarnet use is 15%					
SoC	27,707	6.73	-	-	-
Letermovir	33,351	7.19	5,644	0.46	12,274
ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; SoC=standard of care					

6.3.4 Relapsed disease

HMRN data suggests that 47% of patient who receive HSCT will relapse, this is much higher than the 10% assumed by the company in a scenario analysis in which the costs and QALYs associated with relapse were included in the model. The ERG therefore implements an alternative scenario in which a higher relapse rate is assumed based on the HMRN data. The resulting ICER from this adjustment is presented in, Table 46 and results in the ICER increasing to £11,449 per QALY. Note this scenario assumes that patients will spend 6 months in a relapsed state.

Table 46: Relapse rates

Technologies	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's base case (including PAS)					
SoC	28,805	6.73	-	-	-
Letermovir	33,819	7.19	5,014	0.46	10,904
Company's Relapse Scenario					
SoC	29,585	6.73	-	-	-
Letermovir	34,651	7.19	5,067	0.46	11,020
Relapse Scenario using HMRN relapse rate					
SoC	32,471	6.72	-	-	-
Letermovir	37,733	7.18	5,262	0.46	11,449
ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; SoC=standard of care					

6.3.5 Disutility associated with HSCT

The company's base-case analysis assumes that patients will experience HRQoL in line with the general population. The ERG, however, noted evidence from Leunis et al[16], that suggest that following HSCT patients will tend to have lower HRQoL. The ERG therefore requested that the company implement an analysis in which utilities in Markov phase of the model are adjusted to take account for this lower HRQoL The ERG, however, considers that the company's approach to estimating the long-term disutility associated with HSCT to be inappropriate as it mixes EQ-5D-5L and EQ-3L value. The ERG therefore implements an alternative disutility based on the difference between the mean utility of patients in the PN001 trial at 48 weeks and general population utilities obtained from Ara et al. The results of this analysis are presented in Table 47, and show a small increase in the ICER to £11,092 per QALY.

Table 47 Alternative HSCT disutility

Technologies	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's base case (including PAS)					
SoC	28,805	6.73	-	-	-
Letermovir	33,819	7.19	5,014	0.46	10,904
Company's survivor disutility Scenario					
SoC	28,805	6.65	-	-	-
Letermovir	33,819	7.10	5,014	0.45	11,030
ERG's survivor disutility Scenario					
SoC	28,805	6.61	-	-	-
Letermovir	33,819	7.06	5,014	0.45	11,092

6.3.6 Mortality data in the Markov phase

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

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

Table 48: HMRN mortality data for first 5 year and Martin multiplier for relative risk

Technologies	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's base case (including PAS)					
SoC	28,805	6.73	-	-	-
Letermovir	33,819	7.19	5,014	0.46	10,904
HMRN mortality data and Wingard multiplier					
SoC	27,108	5.27	-	-	-
Letermovir	32,007	5.63	4,899	0.36	13,563
HMRN mortality data and Martin multiplier					
SoC	27,108	6.37	-	-	-
Letermovir	32,007	6.81	4,899	0.44	11,242
ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; SoC=standard of care					

6.4 ERG preferred analysis

Table 49 presents the results of the ERG alternative base-case analysis. These incorporate a number of changes to key model parameters and assumptions, which were previously explored individually in Section 6.2, along with a range of scenarios presented by the company. The ERG alternative base-case analysis includes the following changes to the company base-case analysis:

10. FAS population used for all clinical parameters;
11. 48 Week trial data used together with post-hoc analysis of mortality;

12. Mean duration of therapy assumed to be 83 days;
13. Inclusion of medium-term care costs for survivors of HSCT and (ERG)survivor disutility;
14. Revisions to assumptions regarding GvHD costs and QALYs;
15. Inclusion of relapse disease based on HMRN rate of relapse;
16. Revisions to administration cost for letermovir and PET and IV letermovir use;
17. Foscarnet use assumed to be 15%;
18. Mortality data in the Markov phase of the model based on date from HMRN and relative risk from Martin et al.

Under the ERG's alternative set of assumptions, the deterministic ICER for letermovir prophylaxis versus standard care is £27,536 per QALY.

Table 49: ERG preferred base-case analysis

Technologies	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's base case (including PAS)					
SoC	28,805	6.73	-	-	-
Letermovir	33,819	7.19	5,014	0.46	10,904
ERG preferred base-case analysis					
SoC	29,250	5.35	-	-	-
Letermovir	37,683	5.65	8,433	0.31	27,536
ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; SoC=standard of care					

6.5 Scenario analysis on the ERG preferred base-case

This section presents additional scenario analyses considering uncertainty surrounding three assumptions/inputs used in the model. These concern the duration of letermovir therapy, the approach used to model missing data, and mortality at 48 weeks.

6.5.1 Duration of therapy

As noted above, their some uncertainty as to whether all patients receiving letermovir prophylaxis will discontinue therapy at 100 days as was mandated in the clinical trial given the lack of any futility rules in the SmPC. To explore this uncertainty the ERG reruns a number of scenarios presented in Section 6.3.1 on the ERG's base-case model. These scenarios assumed that those patients receiving letermovir prophylaxis at 100 days continue therapy for a fixed period 2, 4 and 6 weeks post 100 days. As above, no adjust is made to account for the fact extending duration of therapy will likely improve effectiveness. These ICERs therefore are likely to overestimate the true ICER. Table 50

presents the results of this analysis. The impact of using alternative durations of therapy is significant, with the ICERs ranging from £29,776 per QALY to £34,255 per QALY.

Table 50 Scenario analyses – Duration of treatment with Letermovir

Technologies	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG preferred base-case analysis					
SoC	29,250	5.35	-	-	-
Letermovir	37,683	5.65	8,433	0.31	27,536
Maximum duration of therapy assumed to be 100 days + 2 weeks					
SoC	29,250	5.35	-	-	-
Letermovir	38,369	5.65	9,119	0.31	29,776
Maximum duration of therapy assumed to be 100 days + 4 weeks					
SoC	29,250	5.35	-	-	-
Letermovir	39,022	5.65	9,772	0.31	31,909
Maximum duration of therapy assumed to be 100 days + 6 weeks					
SoC	29,250	5.35	-	-	-
Letermovir	39,741	5.65	10,491	0.31	34,255
ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; SoC=standard of care					

6.5.2 Alternative approaches to handling missing data

As outlined in Section 4 and 5 there is sizable loss to follow in the clinical data available from the PN001 study. Reflecting this, the CS includes a number of alternative analyses using different approaches to account for the incomplete follow up. The company's base-case mode, however, does not make use of these adjusted analyses and instead uses the time to event data from the PN001. To explore the impact of alternative approaches to handling missing data the ERG implements two approaches used by the company to modelling missing data NC=F and MNAR. These scenarios are more conservative than the approach taken the company base-case as they respectively assume that either all missing observations are failures or that the event rate is equivalent to the standard care arm. The ERG considers that MNAR approach is the more plausible of the two approaches, and while conservative is not an unrealistic interpretation of the clinical evidence available. The results of the analysis are presented in Table 51. Both alternative approaches to handling missing data have modest influence on resulting ICER, resulting in the ICER increasing to £30,179 per QALY using the NC=F approach and £30,567 using the MNAR approach.

Table 51 Alterative approaches to handling missing data

Technologies	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG preferred base-case analysis					
SoC	29,250	5.35	-	-	-
Letermovir	37,683	5.65	8,433	0.31	27,536
Missing data = failure (NC=F)					
SoC	30,073	5.19	-	-	-
Letermovir	39,060	5.49	8,987	0.30	30,179
Missing data = standard care arm (MNAR)					
SoC	29,250	5.35	-	-	-
Letermovir	38,359	5.64	9,109	0.30	30,567

6.5.3 Week 48 mortality

As highlighted in Section 4 and 5 the mortality benefits observed in the PN001 are not statistically significant and there is considerable uncertainty regarding the magnitude of any mortality benefits. This is particularly important as mortality differences are the primary diver of QALY benefits in the economic model. To explore this further the ERG implements one-way sensitivity analysis in which alternative values for the mortality benefit associated with letermovir are considered. The results of this sensitivity analysis are presented in Table 52 and show that even small changes to the mortality magnitude of the mortality benefit have quite a significant impact on the ICER, with a 1% difference each way producing a range from £34,471 per QALY to £23,124 per QALY.

Table 52 Alterative difference in mortality

Technologies	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG preferred base-case analysis (difference +3.8%)					
SoC	29,250	5.35	-	-	-
Letermovir	37,683	5.65	8,433	0.31	27,536
Mortality difference = +2.8%					
SoC	29,362	5.38	-	-	-
Letermovir	37,571	5.62	8,209	0.24	34,471
Mortality difference = +3.3%					
SoC	29,306	5.36	-	-	-
Letermovir	37,627	5.64	8,321	0.27	30,570
Mortality difference = +4.3%					
SoC	29,183	5.33	-	-	-
Letermovir	37,728	5.67	8,545	0.34	25,110
Mortality difference = +4.8%					
SoC	29,138	5.31	-	-	-
Letermovir	37,795	5.69	8,657	0.37	23,124

6.6 Conclusions from ERG analyses

The ERG has presented a number of additional analyses considering a range of issues raised in Section 5. These scenario analyses addressed the following issues:

- Duration of letermovir prophylaxis;
- Administration costs for letermovir and PET;
- Cost of PET- Foscarnet use;
- Probability of relapse after HSCT;
- Disutilities associated with HSCT;
- Mortality in the Markov phase.

All of the changes implemented by the ERG resulted in an increase to the ICER, although the scenarios were not associated with substantial differences to the ICER. The scenarios associated with the greatest impact on cost-effectiveness outcomes related to changes made by the ERG to duration of

letermovir prophylaxis and administration costs for letermovir and PET. This exploration of alternative modelling assumptions and parameter values was concluded with the ERG presenting a base-case with a preferred set of assumptions. This included a range of alternative assumptions based on both the analysis implemented by the ERG and a number of scenarios that had been implemented by the company.

The ERG base-case analysis estimated letermovir prophylaxis to be more costly (cost difference £8,433) and more effective (0.31 QALY gain) compared with standard of care and suggests that the ICER for letermovir prophylaxis compared with SOC is around £27,536 per QALY.

A further series of exploratory analyses explored the impact of alternative assumptions regarding the duration of therapy, the approach used to model missing data, and the magnitude of the mortality benefit associated with letermovir. These indicate that small changes to key assumption have disproportionately large impact on the ICER. In particular even a small change to the mortality benefit associated with letermovir, results in very significant changes to the ICER. As such the ERG base-case is subject to considerable uncertainty with the true ICER likely to lie within a broad range of £23,124 to £34,471 per QALY, assuming the ERG's base case assumptions.

7 End of life

These criteria do not apply to this appraisal.

8 Overall conclusions

8.1 Clinical effectiveness

Evidence from the well-conducted pivotal RCT PN001 demonstrated that letermovir prophylaxis is effective at reducing the incidence of clinically significant CMV infection in CMV seropositive allo-HSCT recipients and reducing the need for pre-emptive therapy. Through 24 weeks of prophylactic treatment with letermovir, the proportion of patients who had clinically significant CMV infection was significantly lower than in those receiving placebo. The adverse and serious adverse event profile of letermovir was broadly similar to placebo during the treatment phase, although some AEs (including cardiac disorders) were more common to letermovir patients. The impact of letermovir on all-cause mortality is the primary driver of incremental QALY gain; however, the trial showed no statistically significant mortality benefit by Week 48. [redacted].

The design of the trial PN001 was not optimal for decision-making in that the treatment period was fixed at 100 days and the follow-up for the primary efficacy endpoint was limited to 24 weeks. Also the requirement for no detectable CMV DNA at baseline is of uncertain relevance to clinical practice. I the conduct of the trial there was a delay in between HSCT and start of prophylaxis: this is unlikely to occur in practice.

In addition, PN001 was subject to potentially significant generalisability issues relating to NHS practice: In particular, the prevalence and intensity of T-cell depletion differed markedly between the trial and UK practice; with higher rates of CMV reactivation and lower incidence of GvHD expected as a result. However, the level of CMV-DNA at which PET was initiated in the trial (and prophylactic treatment withdrawn) was considerably lower than is seen in clinical practice in the UK and thus started pre-emptive therapy (and therefore stopped taking letermovir) sooner than they would in clinical practice, and those patients whose infections would have been cleared naturally may have been treated with PET unnecessarily. Trial patients also initiated letermovir later, and discontinued earlier than would be expected in clinical practice. However, the ERG judged that issues of generalisability were unlikely to bias the apparent treatment effectiveness in favour of letermovir, and were likely to underestimate its potential benefits in NHS clinical practice.

The economic evidence presented by the company primarily consisted of a *de novo* model. The model structure consists of a decision tree phase covering the first 24 week post HSCT (48 weeks in scenario analysis) and Markov model phase covering the remaining time horizon of the model. The company found letermovir prophylaxis to be more costly (cost difference of £5,014) and more effective (0.46

QALY gain) compared with standard care. The deterministic base-case incremental cost-effectiveness ratio (ICER) was £10,904 per QALY, and the mean probabilistic ICER was £10,913 per quality-adjusted life year (QALY). The predicted probability that letermovir prophylaxis was cost-effective compared with standard care was 81.92% at a cost-effectiveness threshold of £20,000 per QALY and 89.49% at a cost-effectiveness threshold of £30,000 per QALY.

8.2 Cost-effectiveness

The ERG considers that the economic analysis presented by the company addressed the decision problem specified in NICE's scope; however, there were some areas of uncertainty that the ERG did not feel were fully explored. The ERG's key concerns related to the structure of the model; uncertainty with respect to the magnitude of any morality benefit and uncertainty with reatgd the duration of the therapy.

The model structure while providing predictions that aligned with the clinical trial, contained a number of structural assumptions such that there no link between the rate of CMV events (the principal benefit of letermovir) and mortality which is the key driver of cost-effectiveness. This means that uncertainty relating to difference between the CMV events in the two groups cannot be fully explored and the ERG was unable to address this issue.

The ERG noted that there is significant uncertainty around the difference in morality between the two treatment groups and that the values use in the company's base-case model, which are based on outcomes at 24 week data, are an overly optimistic interpretation of the available evidence. The ERG in particular notes that 48 week outcome were available and that a post-hoc analysis of vitality status requested by the FDA includes more complete mortality data with fewer patients lost to follow up. The ERG also notes that the morality benefits observed in the PN001 trial were not statistically significant and are subject to significant uncertainty. This is important because almost all of the QALY benefits associated with letermovir prophylaxis derive from improved survival and sensitivity analysis implemented by the company demonstrates that there is wide range of plausible values for which letermovir would not be considered cost-effective based on threshold of £30,000 per QALY.

The ERG also notes that there is considerable uncertainty regarding the duration over which letermovir prophylaxis will be administered. Specifically, the ERG notes that in the clinical trial there was significant delay following HSCT before letermovir prophylaxis (mean [redacted] days) was initiated, likely due to concerns that it may effect graft response. The ERG, however, thinks it is likely that clinicians will be more confident to administer letermovir prophylaxis immediately post HSCT as PN001 demonstrated that letermovir does not impact on graft response. Further, the ERG notes the

lack of any futility rules in the SmPC and considers that in clinical practice it is plausible that patients requiring longer periods of prophylaxis (as is allowed under the product licence) would receive prophylaxis beyond 100 days.

The ERG was unable to fully address all the identified issues with the company's model structure, but was able to carry out a number of analyses using assumptions and data inputs it believes are more plausible than those used in the company's base-case analysis. The ERG base-case analysis estimated letermovir prophylaxis to be more costly (cost difference £8,433) and more effective (0.31 QALY gain) compared with standard of care and suggests that the ICER for letermovir prophylaxis compared with SOC is around £27,536 per QALY. A further series of exploratory analyses explored the impact of alternative assumptions regarding the magnitude of the mortality benefit associated with letermovir indicate that this ICER is likely to be subject to considerable uncertainty and that the true ICER is likely to lie within a broader range of £23,124 to £34,471 per QALY, assuming the ERG's base case assumptions.

8.3 Implications for research

Investigation is required to determine the effect of treatment with letermovir until clinically determined futility. This should also provide data on the safety of longer than 100 days letermovir.

Relevant to the NHS context would be a study of letermovir when T cell depletion with alemtuzumab is used routinely in HSCT, in line with current UK practice.

Further assessment of all-cause mortality is needed as PN001 was not powered for this outcome. Also, longer- term follow-up data of all-cause mortality are needed.

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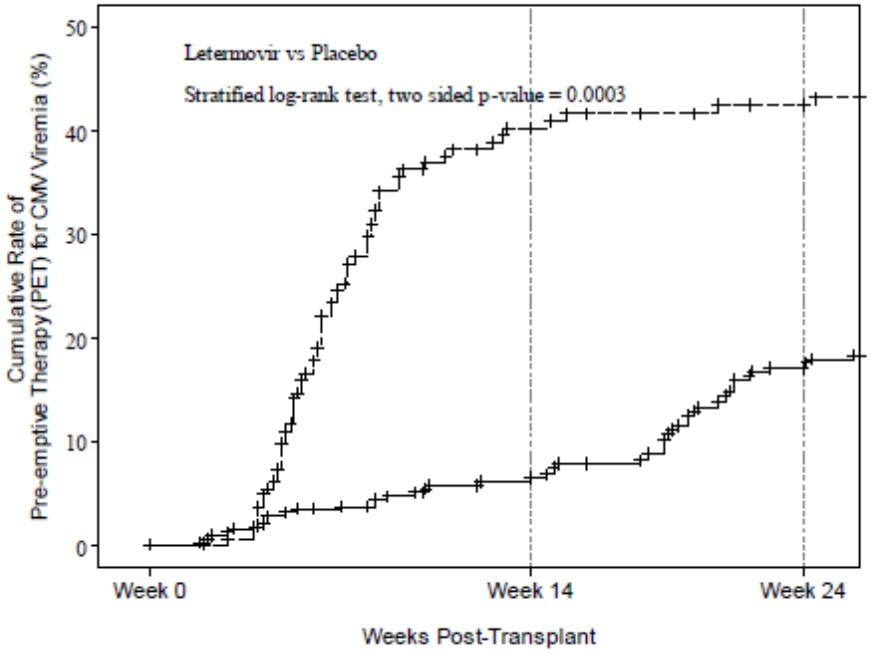
10 Appendices

10.1 Appendix Time to Initiation of PET through Week 24 post-transplant (from CSR to wk 24 Figure 11-3)

Kaplan-Meier Plot of Time to Initiation of Pre-emptive Therapy (PET) for CMV Viremia Through Week 24 Post-Transplant
(FAS Population)



No. at risk: KM estimates % (95% CI)			
Letermovir	325	271: 6.5 (3.7, 9.2)	215: 17.2 (12.8, 21.6)
Placebo	170	86: 40.2 (32.6, 47.9)	72: 42.4 (34.7, 50.2)

Source: [P001V01: analysis-adtte]

10.2 Appendix Health related quality of life results from CSR (Week 48) (tables 11-12 to 11-17)

10.3 Appendix Clinical data provided from the HRMN

[redacted]

Table 53: Relapse/Response data

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Figure 9: Overall Survival data

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from the Centre for Reviews and Dissemination and Centre for Health Economics – York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 21 May 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Wording on recommended dosage of letermovir (1)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11 of ERG report "*The recommended dosage of letermovir is one 480 mg tablet once daily*." This statement does not reflect the fact that the recommended dose may also be administered via 2 x 240 mg tablets.	MSD proposes amending this statement to "*The recommended dosage of letermovir is 480 mg once daily*".	The proposed amendment reflects the fact that the recommended daily dosage may also be administered via two 240 mg tablets, and also aligns with other sections of the document that better reflect the proposed amended language.	We have amended in errata as suggested.

Issue 2 Overall proportion of patients with myelodysplastic syndrome prior to transplant

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 12 of ERG report "*The most common primary reasons for transplant were…myelodysplastic syndrome (MDS) (17%)…*" The figure of 17% in this context is incorrect as it only reflects the letermovir treatment arm, and the paragraph is summarising baseline characteristics for the entire study population.	MSD proposes amending the percentage to 15%, which reflects the 85 patients from both treatment arms out of the entire ASaT population (n=565) with this baseline characteristic.	As the surrounding paragraph is summarising baseline characteristics for the entire study population, the figure of 17% misrepresents the overall proportion of PN001 patients who presented with MDS prior to transplant.	We have amended in errata as suggested.

Issue 3 Pre-emptive therapy initiation in the placebo study group

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 13 of ERG report For the FAS population (NC=F approach), the proportion of placebo group patients who initiated pre-emptive therapy based on documented CMV viraemia is incorrectly reported as 103/170 (60.6%); this figure represents the overall proportion of placebo group patients who met the primary endpoint (i.e. failed prophylaxis by Week 24).	The correct figure for the number of placebo group patients who initiated pre-emptive therapy based on documented CMV viraemia is 68/170 (40.0%).	Reflects the findings of the PN001 study and avoids overstating the degree of pre-emptive therapy initiation in the placebo study group.	We have amended in errata as suggested.

Issue 4 Clinically-significant CMV infection in patients with positive CMV DNA on Day 1 ("protocol violators")

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 13 of ERG report The description of clinically-significant CMV infection by Week 24 in patients with positive CMV DNA on Day 1 only reports the adjusted treatment difference between study groups and the 95% confidence intervals; study group proportions have been omitted.	For completion, MSD proposes inserting the proportions of letermovir patients (31/48 [64.6%]) and placebo patients (20/22 [90.9%]) respectively with clinically-significant CMV infection by Week 24.	Allows for complete reporting of the proportions of patients meeting the primary endpoint in this analysis.	We have amended in errata as suggested.

Issue 5 P-value for event rate for clinically-significant CMV infection at Week 24

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 13 of ERG report A nominal two-sided p-value of p<0.001 has been stated for the clinically-significant CMV infection event rate at Week 24 post-transplant; this figure is incorrect.	The correct p-value is p=0.0005 (as reported in Section 2.6.4.1 of the original submission).	Consistency with trial data.	We have amended in errata as suggested.

Issue 6 Description of the letermovir treatment duration (1)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 16 of ERG report "*The main limitation is the fixed treatment duration of 100 days…*" This is incorrect as neither the PN001 study nor the SmPC mandate an absolute treatment duration.	MSD proposes the following alternative wording: "*The main limitation is the fixed maximum treatment duration of 100 days…*"	The proposed amendment reflects the fact that the letermovir marketing authorisation only specifies a *fixed* maximum treatment duration and not an *absolute* duration. Other references to treatment duration in the ERG report accurately reflect this distinction.	We have amended in errata as suggested.

Issue 7 Wording on recommended dosage of letermovir (2)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 27 of ERG report "*The recommended dosage of letermovir is one 480 mg tablet once daily*." This statement does not reflect the fact that the recommended dose may also be administered via 2 x 240 mg tablets.	MSD proposes amending this statement to "*The recommended dosage of letermovir is 480 mg once daily*".	The proposed amendment reflects the fact that the recommended daily dosage may also be administered via two 240 mg tablets, and also aligns with other sections of the document that better reflect the proposed amended language.	We have amended in errata as suggested.

Issue 8 Summary baseline characteristics of the total study population

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 39 of ERG report The figures summarising the three most common primary reasons for transplant (AML, MDS and lymphoma) quote numerators for the letermovir group only, while the final percentages for each condition represent both study groups combined. MSD acknowledges that these errors were made in the original submission.	MSD proposes amending the figures for the three indications as follows: • AML: 214/565 (38%) • MDS: 85/565 (15%) • Lymphoma: 75/565 (13%)	As the context of the surrounding paragraph is to summarise baseline characteristics for the entire study population, the originally reported numerators are incorrect as they only represent letermovir group patients.	We have amended in errata as suggested.

Issue 9 Comparison of baseline high risk in the FAS and ASaT populations

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 40 of ERG report The percentages of 31.4% and 32.4 stated for the proportions of high risk patients in the FAS and ASaT populations respectively are incorrect, as they only account for the letermovir group and not for both study groups.	The percentages of high risk patients across both study groups were 29.7% for the FAS population and 31% for the ASaT population.	The proposed amendment accurately reflects baseline high risk across both study groups in both analysis populations, and fits with the context of the surrounding paragraph.	We have amended in errata as suggested.

Issue 10 Comparison of baseline haploidentical donors in the ASaT and FAS populations

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 40 of ERG report The quoted figure of 15.8% haploidentical donors for the letermovir group in the FAS population is incorrect.	The correct percentage is 15.1% (49/325- as per Table 1 of the clarification response).	Accurate reflection of letermovir group patients in the FAS population with a haploidentical donor.	We have amended in errata as suggested.

Issue 11 Description of the letermovir treatment duration (2)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 44 of ERG report "The main limitation is the fixed treatment duration of 100 days…"	MSD proposes amending the wording for both quoted statements to reflect a 100-day fixed *maximum* treatment duration of letermovir.	The proposed amendment reflects the fact that the letermovir marketing authorisation only	We have amended in errata as suggested.

This is incorrect as neither the PN001 study nor the SmPC mandate an absolute treatment duration. "The generalisability of the trial to NHS practice may also be limited by the 100-day fixed treatment duration of letermovir." Again, this statement is incorrect as the SmPC does not mandate an absolute treatment duration of letermovir.		specifies a ***fixed*** maximum treatment duration and not an ***absolute*** duration. Other references to treatment duration in the ERG report accurately reflect this distinction.	

Issue 12 Missing data approach (NC=F)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 47 of ERG report Table 6 refers to NC+F, which is incorrect.	MSD proposes amending this to NC=F in order to accurately reflect the non-completer=failure missing data approach.	Accurately reflect the NC=F missing data approach.	We have amended in errata as suggested.

Issue 13 Missing data approach (MNAR and NC=F)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 48 of ERG report Table 7 refers to NMAR, which is incorrect. Additionally, the text	MSD proposes correcting these two acronyms to MNAR and NC=F in order to accurately	Accurately reflect the MNAR and NC=F missing data approaches.	We have amended in errata as suggested.

below Table 7 repeats the incorrect mention of NC+F as per Issue 12 above.	reflect the missing not at random and non-completer=failure approaches, respectively		

Issue 14 Initiation of pre-emptive therapy for documented CMV viraemia by Week 24 post-transplant

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 52 of ERG report Table 11 heading states that the values were adapted from Table 12 and the accompanying text of the original submission.	The values in Table 11 of the report were not presented in the original submission but can be found in Table 8 of the clarification response.	Ensure cross-referencing with the correct documentation (clarification response).	We have amended in errata as suggested.

Issue 15 CMV disease data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 54 of ERG report Table 13 heading states that CMV disease values were adapted from Table 18 of the original submission.	The values in Table 13 of the report were actually reported in Table 11 and the Section 2.6.3.1 text of the original submission.	Ensure cross-referencing with the correct section of the original submission.	We have amended in errata as suggested.

Issue 16 Late treatment failure incidences and K-M event rate for time to initiation of pre-emptive therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 55 of ERG report The late failure incidence percentages quoted for high risk versus low risk patients, GvHD versus no GvHD post-randomisation and concomitant steroid use versus no concomitant steroid use, have not been marked as AIC. The K-M event rate for time to initiation of pre-emptive therapy through Week 24 post-transplant and associated 95% confidence intervals have not been marked as AIC.	Please mark all the late failure incidence percentages and K-M event rates with associated 95% confidence intervals as AIC.	These data are not currently available in the public domain.	We have amended in errata as suggested.

Issue 17 AIC marking of study drug exposure

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 62 of ERG report The patient population figures for letermovir (any route of administration, IV and oral respectively) and placebo (any route of administration) have been marked as AIC.	These figures represent publicly available data and therefore need not be marked as AIC.	These figures were not marked as AIC in the original submission as they represent publicly available data.	We have amended in errata as suggested.

The mean and median days on therapy for letermovir (any route of administration) have also been marked as AIC.			

Issue 18 Description of the letermovir treatment duration (3)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 66 of ERG report "*The fixed 100 days treatment duration…*" This is incorrect as neither the PN001 study nor the SmPC mandate an absolute treatment duration.	MSD proposes the following alternative wording: "The fixed ***maximum*** 100 day treatment duration…"	The proposed amendment reflects the fact that both PN001 and the letermovir marketing authorisation only specify a ***fixed*** maximum treatment duration and not an ***absolute*** duration. Other references to treatment duration in the ERG report accurately reflect this distinction.	We have amended in errata as suggested.

Issue 19 Page numbers for adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 72 of ERG report Sections 3.4.4 and 3.5.6 have been incorrectly stated as appearing on pages 102 and 129 of the submission, respectively.	The correct page number for section 3.4.4 is 101 and for section 3.5.6 is 124.	Ensures cross-referencing with the correct section of the original submission.	We have amended in errata as suggested.

Issue 20 Mean delay between HSCT and initiation of letermovir prophylaxis (FAS population)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 79 of ERG report Mean delay between HSCT and letermovir prophylaxis initiation of [redacted] (FAS population) is not marked as AIC.	Please mark this figure as AIC.	These data are not currently available in the public domain.	We have amended in errata as suggested.

Issue 21 Description of the decision tree phase (clinical events included in the economic model)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 81 of ERG report Introduction to the "decision tree phase" section mentions seven clinical events included in the economic model but then only goes on to list six.	Please either amend the introductory sentence to state six clinical events, or otherwise clarify the additional clinical event.	Support understanding of clinical inputs included in the economic model.	We have amended in errata as suggested.

Issue 22 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 86 of ERG report Table 25 references page 129 of the original submission.	The figures are actually reported on page 124 of the original submission.	Ensures cross-referencing with the correct section of the original submission.	We have amended in errata as suggested.

Issue 23 Utility time point weights

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 87 of ERG report Table 26 heading states that the utility time point weights were derived from page 104 (Table 37) of the original submission.	Table 37 is on page 103 of the original submission.	Ensures cross-referencing with the correct section of the original submission.	We have amended in errata as suggested.

Issue 24 General (UK) population utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 89 of ERG report Table 27 heading states that the utility values were derived from page 104 (Table 38) of the original submission.	Table 38 is on page 103 of the original submission.	Ensures cross-referencing with the correct section of the original submission.	We have amended in errata as suggested.

Issue 25 Letermovir cost breakdown

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 91 of ERG report List prices are not marked CIC in the report.	Please mark the list prices as CIC.	List prices were marked CIC in the original submission as they are confidential until product launch.	We have amended in errata as suggested.

Issue 26 Duration of intravenous letermovir

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 92 of ERG report Duration of IV letermovir [redacted] has not been marked as AIC.	Please mark the figure of [redacted] as AIC.	This data was marked AIC in the original submission as it is not currently available in the public domain.	We have amended in errata as suggested.

Issue 27 ERG comment on initiation of IV letermovir

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 92 of ERG report "*The ERG therefore considers it more reasonable to assume that the proportion of patients unable to tolerate oral administration will align with the PN001 trial*". Inability to tolerate oral administration is primarily applicable to prophylaxis initiation and does not denote the formulation that will be used for the entirety of the treatment duration.	MSD proposes amending this statement to: "The ERG therefore considers it more reasonable to assume that the proportion of patients unable to *initially* tolerate oral administration will align with the PN001 trial".	Inability to tolerate oral administration is primarily applicable to prophylaxis initiation and does not denote the formulation that will be used for the entirety of the treatment duration.	We have amended in errata as suggested.

Issue 28 ERG comment on CMV disease monitoring costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 93 of ERG report ERG comment section begins with "*As noted in Section Error! Reference source not found*" (syntax error).	The corresponding section in the original submission is section 3.5.7 (page 124).	Ensures cross-referencing with the correct section of the original submission.	We have amended in errata as suggested.

Issue 29 Pre-emptive therapies

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 94 of ERG report Table 29 heading states that the values were derived from page 122-3 (Tables 43 and 44) of the original submission.	Tables 43 and 44 are on pages 117-118 of the original submission.	Ensures cross-referencing with the correct section of the original submission.	We have amended in errata as suggested.

Issue 30 Costs associated with opportunistic infection

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 96 of ERG report Table 30 heading states that the values were adapted from pages 106-110 (Table 39) of the original submission.	Table 39 is on pages 105-109 of the original submission.	Ensures cross-referencing with the correct section of the original submission.	We have amended in errata as suggested.

Issue 31 Description of the letermovir treatment duration (4)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 119 of ERG report "*As noted above, their [sic] some uncertainty as to whether all patients receiving letermovir prophylaxis will discontinue therapy at 100 days*".	MSD proposes that is more accurate to say "*day 100 post-transplant*".	The phraseology "*100 days*" still implies a fixed treatment duration as opposed to a fixed *maximum* duration.	We have amended in errata as suggested. The typo have also been amended

1 Summary

1.1 Critique of the decision problem in the company's submission

The company's submission (CS) considered the population specified in the final NICE scope, i.e. adults with seropositive cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant. The licensed therapeutic indication is as follows; 'PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT)'. There is some lack of clarity regarding whether patients with detectable CMV DNA but a low viral load would be initiated on letermovir in clinical practice.

The intervention specified in the final NICE scope and the CS is letermovir. The licence for letermovir states that prophylaxis should be started after HSCT, between the day of transplant and no later than 28 days post-transplant. It states that prophylaxis with letermovir should continue through 100 days post-transplant. Letermovir can be started before or after engraftment occurs.

The recommended dosage of letermovir is 480 mg once daily. The dosage of letermovir should be reduced to 240 mg once daily when co-administered with ciclosporin A (CsA). Letermovir is also available as concentrate for solution for intravenous (IV) infusion (240 mg and 480 mg), and the oral and IV formulations may be used interchangeably at the discretion of the physician, with no dose adjustment necessary.

The NICE final scope listed aciclovir and valaciclovir as well as 'no preventative treatment' as comparators; however, it noted that neither active drug had current marketing authorisation for the relevant indication. The CS therefore included only 'no prophylaxis against CMV reactivation', i.e. no active comparators were included. The ERG and the clinical advisors to the ERG agreed that aciclovir and valaciclovir are not relevant comparators for letermovir in this appraisal.

The outcomes listed in the company's decision problem are based on the outcomes reported in the pivotal Phase III trial (PN001). They adequately reflect those listed in NICE's final scope. The ERG noted that criteria for initiation of PET, and therefore the definition of 'clinically significant CMV infection' differed between the trial and NHS clinical practice.

The NICE final scope specified that people at high risk of CMV reactivation should be considered as a subgroup (should the evidence allow). This subgroup was included in the CS together with analyses based on risk categories for CMV reactivation, patient characteristics, and conditioning and concomitant immunosuppressive regimen as per study protocol.

1.2 Other relevant factors

A Patient Access Scheme was included in the submission – [redacted].

1.3 Summary of clinical effectiveness evidence submitted by the company

PN001 was a phase III randomised, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of letermovir compared to placebo for the prevention of clinically-significant human CMV infection in adult, R+ recipients of an allogeneic HSCT. Adult patients with documented seropositivity for CMV but no detectable CMV DNA at baseline, within 28 days of a first HSCT were randomised in a 2:1 ratio to receive either letermovir at a dose of 480 mg once daily (adjusted to 240 mg when co-administered with CsA), or placebo. Study medication was continued through to week 14 (~100 days). Randomization was stratified by study centre and high or low risk for CMV reactivation

Patients were monitored through to week 24 post-transplant for the primary efficacy endpoint. Patients who completed the trial subsequently entered a follow-up phase from week 24 to week 48 post-transplant to collect data related to CMV disease, health outcomes, and quality of life (QoL) measures.

The primary outcome of trial PN001 was the proportion of patients with clinically-significant CMV infection through Week 24 (~ 6 months) post-transplant, defined as the occurrence of either one of the following outcomes:

- Initiation of anti-CMV pre-emptive therapy based on documented CMV viraemia (as measured by the central laboratory) and the clinical condition of the patient. Initiation of pre-emptive therapy in this study referred to the practice of initiating therapy with ganciclovir, valganciclovir, foscarnet and/or cidofovir

OR

- Onset of CMV end-organ disease.

The majority of patients were male (327/565 [58%]), white (462/565 [82%]), and with a mean age of around 51 years old. At baseline 31% of patients were at high risk for reactivation and 52% were receiving concomitant CsA. The most common primary reasons for transplant were acute myeloid leukaemia (AML) (38%), myelodysplastic syndrome (MDS) (15%), and lymphoma (13%). No information was available regarding the line of therapy. The majority of patients had received

transplants using peripheral blood stem cells (73%). The median time to initiation of the study drug was 9 days after transplant.

The results of the primary and sensitivity analyses demonstrate that letermovir significantly reduces the rate of clinically significant CMV infection through 24 weeks. The proportion of patients who failed prophylaxis by Week 24 i.e. had clinically significant CMV infection (NC=F; FAS population) was 122/325 (37.5%) in the letermovir group vs 68/170 (40.6%) in those receiving placebo, with a stratum-adjusted treatment difference of (letermovir-placebo, 95% CI) -23.5 (-32.5 to -14.6) and one sided p-value of <0.0001. Most prophylaxis failures initiated PET based on documented CMV viraemia (52/325 [16.0%] versus 103/170 [60.6%]); very few patients developed CMV end-organ disease (5/325 [1.5%] vs 3/170 [1.8%]).

The ERG noted that patients who tested positive for CMV DNA on Day 1 (who were protocol violators and therefore not included in the primary analysis) also benefited from letermovir treatment (Clinically significant CMV infection by Week 24 (NC=F) 31/48 (64.6%) letermovir patients vs 20/22 (90.9%) placebo patients, treatment difference: 26.1% (-45.9%, -6.3%), one sided p-value <0.0048).

Subgroup analyses of the primary outcome showed that the treatment effect consistently favoured letermovir across subgroups based on patient baseline, epidemiological, and clinical characteristics. The ERG notes that in some subgroups the effect size is numerically different from that of the whole trial population: higher in high-risk patients; donor mismatch subgroups; haploidentical donors; female subgroups; and with use of non-myeloablative conditioning regimens; and was lower in Asian race; Hispanic or Latino ethnicity; US patients; and use of tacrolimus as immunosuppressant. No tests for interaction were conducted to evaluate the statistical significance of these subgroup differences.

The time to onset of clinically-significant CMV infection through Week 24 post-transplant and time to initiation of PET through Week 24 post-transplant were summarised using Kaplan-Meier (K-M) plots. Given the very small number of CMV end-organ disease events it is not surprising that the time to clinically-significant CMV infection curve and the time to initiation of PET curves are very similar.

At Week 24 post-transplant, the event rate (95% CI) for clinically-significant CMV infection was 18.9% (14.4%, 23.5%) in the letermovir group versus 44.3% (36.4%, 52.1%) in the placebo group groups (nominal two-sided p<0.0005), after controlling for stratification of high and low risk of CMV end-organ disease at baseline) (hazard ratio (95% CI) of 0.29 (0.21, 0.42) for letermovir vs placebo).

There was a large separation between the curves from Day 0 to Week 14 while patients were on study drug. Once medication was discontinued at Week 14, there was a small rebound effect in the

[redacted].

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Trial design and patient characteristics

The PN001 trial was of good quality (low risk of bias) but had some deficiencies in the trial design which make it sub-optimal for addressing the research question and understanding the implications for clinical practice.

- The main limitation is the fixed maximum treatment duration of 100 days, which did not allow prophylaxis to continue until each individual patient was considered at low risk of CMV reactivation. Therefore the trial will not have collected the best data to evaluate the efficacy of letermovir to prevent infection and reduce mortality.
- The lack of follow-up of the occurrence of clinically significant CMV infection beyond Week 24 also limits the information collected on the effect of letermovir.
- While the population is appropriate, the requirement for no detectable CMV DNA at baseline is of uncertain relevance to clinical practice.

In addition, there were some additional issues of generalisability of the trial to NHS practice which may impact the expected treatment efficacy.

- The clinical advisors to the ERG believed that whilst the population in PN001 was not a perfect match to patients in the NHS, it could be considered to be essentially generalisable, despite only 12 patients (ASaT population – 6 in letermovir arm and 6 in placebo) recruited to the trial from UK centres. The UK patient population might be younger, more white, more male, and include more matched unrelated patients than that in the trial.
- The prevalence and intensity of T-cell depletion differed markedly between the trial and UK practice, with only 4% of trial patients receiving the profoundly T-cell depleting agent alemtuzumab versus ~85% in some UK centres. As the incidence of CMV reactivation is substantially higher in T-cell depleted patients, the trial likely underestimates CMV reactivation rates, and overestimates incidence of GvHD, which is suppressed by T-cell depletion.
- The prevalence of CsA use also differed significantly between the trial and NHS clinical practice. While the ERG's clinical advisors suggested 90% of patients would receive CsA-based immunosuppressive therapy, only 51.7% of letermovir patients (ASaT population) in the trial received CsA, with the remainder given tacrolimus-based or other immunosuppressive regimens.

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valganciclovir as the preferred treatment option in current practice under normal circumstances to keep patients out of hospital, or to prevent the additional visits necessary to administer IV ganciclovir as an outpatient, though out-patient ganciclovir pumps are available if there is any concern about gastrointestinal absorption, compliance or response to valganciclovir.

3 Critique of company's definition of decision problem

3.1 Population

The population specified in the final NICE scope was adults who are sero-positive for cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant and this is reflected exactly in the CS. The licensed therapeutic indication is as follows; 'PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT)'. There is some lack of clarity regarding whether patients with detectable CMV DNA but a low viral load who would not yet be considered eligible for pre-emptive therapy would be initiated on letermovir in clinical practice. However, given that patients would be commenced on the day of infusion, the ERG consider it unlikely that patients would have detectable viraemia at that time. This has implications for which analysis and results from the key trial are most relevant to the decision problem; an issue discussed further in Section **Error! Reference source not found.**.

3.2 Intervention

The intervention specified in the CS is letermovir and this matches the final NICE scope. The SmPC for letermovir states that prophylaxis should be started after HSCT, from the day of transplant and no later than 28 days post-transplant. It states that prophylaxis with letermovir should continue through 100 days post-transplant. Letermovir can be started before or after engraftment.

The recommended dosage of letermovir is 480 mg once daily. A 240 mg tablet is also available. Letermovir is also available as concentrate for solution for intravenous (IV) infusion (240 mg and 480 mg), and the oral and IV formulations may be used interchangeably at the discretion of the physician, with no dose adjustment necessary. However, the dosage of letermovir should be reduced to 240 mg once daily when co-administered with ciclosporin A (CsA), which significantly increases the bioavailability of letermovir. This is an important drug interaction as CsA is used in approximately 90% of patients in clinical practice in England and Wales.

test unless they were at high-risk of CMV infection, or the viral load was very high or was increasing rapidly to spare patients unnecessary exposure to toxic PET agents. The question is whether in UK practice patients with detectable, but not high levels of CMV-DNA would be considered eligible for letermovir prophylaxis. If that is the case then the ASaT population, that included some patients with detectable CMV DNA at baseline may be more generalisable to the NHS.

Another factor that needs to be considered in this discussion is whether eligible patients with detectable CMV DNA at baseline will exist in clinical practice. It is possible that such patients (protocol violators) emerged due to some investigators delaying letermovir prophylaxis until after engraftment. As the PN001 trial demonstrated that letermovir does not adversely affect engraftment,[6] clinicians are likely to be more confident in beginning prophylaxis immediately post-transplant, therefore the chance of CMV reactivation by the time of treatment initiation would be lower. In that case the FAS data (with patients with detectable CMV-DNA excluded) might be the most generalisable.

Whichever data set is 'preferred' the delay before letermovir initiation seen in the trial (ASaT population mean [redacted] (SD 8.5), median 9, and FAS population 11 days (SD 8.4) median 8 days) would be unlikely in practice.

4.2.4 Patient characteristics in PN001

The CS presented baseline characteristics for the ASaT population (CS Table 9) and found that patient characteristics were generally balanced between the letermovir and placebo groups. The majority of patients were male (327/565 [58%]), white (462/565 [82%]), and with a mean age of around 51 years old. At baseline, 175/565 (31%) of patients were at high risk for reactivation (as defined in the 'Study Design' section above) and 293/565 (52%) were receiving concomitant CsA.

The most common primary reasons for transplant were acute myeloid leukaemia (AML, 214/565 [38%]), myelodysplastic syndrome (MDS, 85/565 [17%]), and lymphoma (75/565 [13%]). The majority of patients had received transplants using peripheral blood stem cells (413/565 [73%]). Baseline aciclovir use for prior HSV prophylaxis was similar across both study groups (311/373 [83%] letermovir group, 152/192 [79%] placebo group; 463/565 [82%] overall).

The ERG requested further information from the company about the line of therapy the HSCT comprised, in order to better understand the patients' underlying health status, as HSCT is indicated at different stages of the disease depending on the condition, and a patient's response to chemotherapy. However, the ERG was informed that other than the fact that in all patients in the trial were undergoing their first HSCT, this information was not collected in this trial.

The median time to initiation of the study drug was 9 days after transplant.

The ERG checked the baseline demographics of the FAS population (reported in the CSR through 24 weeks – note patient characteristics were not provided for the FAS population the CSR through 48 weeks) and found them to be very similar to those of the ASaT population. Comparing the ASaT and FAS populations, the proportion of High Risk patients was slightly lower in the FAS population: 29.7% compared with 31.0% in the ASaT population (**Error! Reference source not found.**). Also, the proportion of patients with engraftment at baseline was smaller in the FAS population, suggesting that delaying study treatment until after engraftment may have been one reason for the appearance of CMV DNA at baseline (hence engrafted patients removed from the FAS population).

In both the ASaT and FAS populations imbalances were seen for the proportion of patients with a haploidentical donor (ASaT/FAS 16.1%/ 15.1% in the letermovir group and 10.9%/ 10.0% in the placebo group); antithymocyte globulin (ATG) use (ASaT /FAS 37.5%/ 35.7 % in the letermovir group and 30.2%/ 28.8% in the placebo group; and alemtuzumab use (ASaT/FAS 3.2 %/3.4% in the letermovir group and 5.7%/5.3% in the placebo group). The ERG notes that alemtuzumab is used for T-cell depletion to reduce the risk of GvHD; such patients are at a very high risk of CMV reactivation. As shown in **Error! Reference source not found.** the number of patients receiving ex-vivo T-cell depletion was very similar in the ASaT and FAS populations.

Additional imbalances in the FAS population were seen for proportion of Asian patients (10.8% letermovir vs 6.5% placebo), and patients from the Asia-Pacific region (9.5% letermovir vs 4.1% placebo). Also in the FAS population there is an imbalance between US/non-US patients across the treatment groups that was not seen in the ASaT population (non-US 64.0% letermovir vs 60.6% placebo).

In summary, the treatment arms were reasonably well balanced with no apparent bias in favour of letermovir. There are some differences between the ASaT and FAS populations, such that it is important to differentiate between these when interpreting the results of the analyses and when considering which data set and results are most generalisable to NHS practice.

make it sub-optimal in addressing the research question / needs of clinical practice. The main limitation is the fixed maximum treatment duration for 100 days, which did not allow prophylaxis to continue until each individual patient was considered at low risk of CMV reactivation. Therefore the trial will not have collected the best data to evaluate the efficacy of letermovir to prevent infection or improve mortality. The lack of follow-up of the occurrence of clinically significant CMV infection beyond Week 24 also limits the information collected on the effect of letermovir.

There are also some questions regarding the statistical analysis of the time to event data, which are discussed further in Section 4.2.8.

4.2.7 Generalisability of trial PN001 to NHS clinical practice

The clinical advisors to the ERG believed that whilst the population in PN001 was not a perfect match to patients in the NHS, it could be considered to be essentially generalisable, despite only 12 patients (ASaT population – 6 in letermovir arm and 6 in placebo) recruited to the trial from UK centres. The UK patient population might be more white, more male, and include more matched unrelated patients than that in the trial. The most important difference relates to the use of T-cell depletion and the agents employed to achieve this. In the UK, the use of T-cell depletion for unrelated donor allo-HSCT is almost universal, while some centres also use T-cell depletion in those with related donors. In UK practice, alemtuzumab is used in up to 85% of patients in some centres. Alemtuzumab is more profoundly T-cell depleting than the main alternative, anti-thymocyte globulin (ATG). The incidence of CMV reactivation is substantially higher with T-cell depletion than without, and is higher with alemtuzumab than with ATG. In the PN001 study only ~40% of patients underwent T-cell depletion in and almost all of these received ATG (33% of FAS population ATG, 4.0% alemtuzumab). We would therefore expect higher rates of CMV reactivation, with lower incidence of GvHD in UK clinical practice; the ERG notes that this also suggests a higher potential need and benefit of letermovir in these patients. The age of the population also has an important influence on estimates of efficacy and cost effectiveness; while patients in the PN001 trial were around 51 years of age on average, results from the HMRN database suggested that allograft recipients in NHS practice would be closer to 45 years.

The generalisability of the trial to NHS practice may also be limited by the 100-day fixed maximum treatment duration of letermovir. This did not allow prophylaxis to continue until each individual patient was considered to be at low risk of CMV reactivation as might occur in clinical practice. It should be noted that the licence permits continued use in high risk patients. Furthermore the delay before initiation of prophylaxis seen in the trial of around 9 days would be unlikely in practice. Therefore,

Table 1 Data for clinically-significant CMV infection by Week 24 post-transplant, (FAS) (adapted from CS Table 11 and clarification response Tables 7 and 9)

	FAS			ASaT			Excluded from FAS (CMV DNA on Day1)		
Parameter	Letermovir (n = 325) n (%)	Placebo (n = 170) n (%)	Difference* (95% CI) (letermovir-placebo), one sided p value	Letermovir (n = 373) n (%)	Placebo (n = 192) n (%)	Difference* (95% CI) (letermovir-placebo), one sided p value	Letermovir (n = 48) n (%)	Placebo (n = 22) n (%)	Difference* (95% CI) (letermovir-placebo), one sided p value
Primary efficacy endpoint (proportion of patients who failed prophylaxis by Week 24 i.e Clinically significant CMV infection by Week 24 with NC=F)[a]	122 (37.5)	103 (60.6)	–23.5 (–32.5 to –14.6) p-value<0.0001	[redacted]	[redacted]	[redacted]	31 (64.6)	20 (90.9)	26.1% (-45.9%, -6.3%), p-value <0.0048
Clinically significant CMV infection by Week 24 (data as observed)	57/[redacted] (17.5% of FAS)	71/[redacted] (41.8% of FAS)	[redacted]	[redacted]	[redacted]		22 (45.8)	17 (77.3)	
Initiation of pre-emptive therapy based on documented CMV viraemia	52 (16.0)	68 (40.0)		[redacted]	[redacted]		21 (43.8)	17 (77.3)	
CMV end-organ disease	5 (1.5)	3 (1.8)		[redacted]	[redacted]		2 (4.2)	1 (4.5)	
Discontinued from study before Week 24	56 (17.2)	27 (15.9)		[redacted]	[redacted]		8 (16.7)	3 (13.6)	
Missing outcome in Week 24 visit window	9 (2.8)	5 (2.9)		[redacted]	[redacted]		1 (2.1)	0 (0.0)	

CI = confidence interval; CMV = cytomegalovirus; FAS = full analysis set; NC = F = non-completer = failure.[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed. * Stratum-adjusted treatment difference (95% CI) (letermovir-placebo), One sided p value

The results for the ASaT population and results for those patients who were not included in the FAS population because they had detectable CMV DNA on Day 1 were provided in the company's clarification response and are also included in Table 1. The treatment differences for the primary outcome analysis were similar across the analysis sets, though the number of events was higher in both the letermovir and placebo groups in the data set containing only those patients who were randomized and treated but CMV positive at Day 1. It is noteworthy that there is a statistically significant benefit in these patients.

In addition, a number of sensitivity analyses relating to the methods for imputation in the analysis of the FAS data set were presented in the CS and these are presented in Table 2.

Table 2 Analysis of clinically significant CMV infection by Week 24 (adapted from CS Table 11 and text)

Analysis of clinically significant CMV infection by Week 24	Population	Stratum-adjusted treatment difference (95% CI) (letermovir-placebo)[c] One sided p value
Primary analysis (proportion of patients who failed prophylaxis by Week 24 i.e Clinically significant CMV infection by Week 24 with NC=F)	FAS	–23.5 (–32.5 to –14.6) p-value<0.0001
Data as Observed	FAS	[redacted]
Imputation of missing values using mean value for respective treatment group (MAR)	FAS	-30.7 (95% CI: -34.8, -26.5) p<0.0001
Imputation of missing values using mean value for placebo group for both letermovir and placebo groups (MNAR)	FAS	-24.5 (95% CI: -28.4, -20.7, p<0.0001

The results of the primary and sensitivity analyses demonstrate that letermovir significantly reduces the rate of clinically significant CMV infection. As noted in Section **Error! Reference source not found.** the NC+F is the most conservative analysis and the DAO the most optimistic, and the MAR analysis closely reflected the DAO as expected

Subgroup analyses of the primary outcome were presented in the CS (Section B2.7 and Appendix E). The consistency of the treatment effect of letermovir in PN001 was assessed across various subgroups (FAS population) based on risk categories for CMV reactivation (risk stratum, stem cell source, degree of donor mismatch, haploidentical transplantation), patient characteristics (age, gender, weight, region, time of randomisation from the day of transplantation), and conditioning and concomitant immunosuppressive regimen (CsA-containing and tacrolimus-containing) used. Overall, the treatment effect consistently favoured letermovir across subgroups based on patient baseline, epidemiological and clinical characteristics.

Table 3 Initiation of pre-emptive therapy for documented CMV viraemia by Week 24 post-transplant (NC=F Approach, FAS Population) (Adapted from PfC response Table 8 and text)

Parameter	Letermovir (n=373) N (%)	Placebo (n=192) N (%)	Stratum-adjusted treatment difference (Letermovir-Placebo) Difference (95% CI)
Initiation of PET based on Central laboratory (FAS)			
Initiation of pre-emptive therapy for documented CMV viraemia (NC=F Approach)	[redacted]	[redacted]	[redacted]
Initiation of pre-emptive therapy based on documented CMV viraemia (no imputation)	[redacted]	[redacted]	
Discontinued from study before Week 24	[redacted]	[redacted]	
Missing outcome in Week 24 visit window	[redacted]	[redacted]	

The ASaT results were similar to the FAS results but the number of events was higher in the ASAT population – reflecting the fact that those patients excluded from the FAS population were at higher risk of developing a clinically significant infection requiring initiation of PET.

No additional sensitivity analyses were conducted for this outcome to explore the impact of patient withdrawals and missing data. [redacted]. It should be noted that the first of these sensitivity analyses was included in the CS but the second was not: the ERG took the details from the CSR supplied with the CS.

[redacted]

[redacted]

[redacted]

Table 4 Proportion of patients with CMV disease by Week 14 post-transplant and Week 24 post-transplant (FAS population, DAO analysis only) (adapted from CS Table 11 and text)

Parameter	Letermovir (n=285) N (%)	Placebo (n=145) N (%)	Stratum-adjusted treatment difference (Letermovir-Placebo) Difference (95% CI)
CMV Disease by Week 14 (adjudicated cases only) (no imputation)	1	2	-1.0 (-3.5, 1.5) one-sided p-value of 0.2258
CMV Disease by Week 24 (adjudicated cases only) (no imputation)	5	3	-0.4% (-4.0%, 3.2%), one-sided p-value of 0.4056.

Time to onset of clinically significant CMV infection

The time to onset of clinically-significant CMV infection through Week 24 post-transplant was presented in the CS (Section 2.6.4.1) and summarised using Kaplan-Meier (K-M) plots (Figure 1). A plot for time to Initiation of PET through Week 24 post-transplant was also available from the CSR and is presented in Appendix **Error! Reference source not found.** of this report. Given the very small number of CMV disease events

it is not surprising that the time to clinically-significant CMV infection curve and the time to initiation of PET curves are very similar. It is the latter data that are included in the economic model.

Figure 1 K-M Plot of Time to Onset of Clinically Significant CMV Infection by Week 24 Post-Transplant (FAS Population) (CS figure 4)

At Week 24 post-transplant, the event rate (95% CI) for clinically-significant CMV infection was 18.9% (14.4%, 23.5%) in the letermovir group versus [redacted] in the placebo group. In response to a request by the ERG, the company undertook a hazard modelling approach to analysing this outcome, producing a hazard ratio (95% CI) of [redacted] for letermovir vs placebo. The distribution of time to event significantly differed between the letermovir and placebo groups (nominal two-sided $p<0.001$), after controlling for stratification of high and low risk of CMV end-organ disease at baseline.

There was a large separation between the curves from Day 0 to Week 14 while patients were on study drug. Once medication was discontinued at Week 14, there was a small rebound effect in the letermovir group. Assessment using a logistic regression model adjusted for baseline risk strata (high or low risk for CMV reactivation at baseline) found that factors associated with CMV DNAemia after cessation of letermovir prophylaxis up to Week 24 post-transplant included high baseline risk for CMV reactivation, GvHD, and corticosteroid. The incidence of late failure in subjects at high risk for

CMV reactivation was [redacted] compare to [redacted] in subjects at low risk. The incidence of late failure was [redacted] for subjects who developed GvHD after randomization compared to [redacted] for subjects who did not. In subjects with concomitant steroid use, the incidence of late failures was [redacted] vs. [redacted] in subjects with no concomitant steroid use.

The Kaplan-Meier event rate for time to Initiation of PET through Week 24 post-transplant was [redacted] in the letermovir group versus [redacted] in the placebo group.

All-cause Mortality

Mortality was followed up through Week 48 and reported in the CS (section 2.6.5.1). Separate plots were provided for all-cause mortality through weeks 24 and 48, incidences were provided for the letermovir and placebo groups at 14, 24 and 48 weeks, and nominal log rank p-values (not controlled for multiplicity) were presented for the curves through Week 24 and separately for the curves through Week 48. As the data through Week 48 follow-up represent the longest follow-up, only the results based on these data are summarised below. The ERG understands that these data also include those patients who withdrew early from the trial but whose post-trial vital status was later ascertained. In the analysis, patients of unknown status were assumed to be alive. These results are summarised in **Error! Reference source not found.**.

Ninety eight patients were randomised (distributed evenly across the doses). Patient characteristics are summarised in Table 5 and the results are presented in Table 6.

Table 5. Patient characteristics from the Phase II trial (Chemaly 2014) (adapted from CS Table 20)

Letermovir dose	Male participants, n (%)	Average age (range)	CMV seropositive donor status, n (%)	Bone marrow HSCT, n (%)	Peripheral blood HSCT, n (%)
60 mg	14(42)	55 (24-69)	13 (39)	1 (3)	32 (97)
120 mg	22 (71)	57 (22-68)	17 (55)	0 (0)	31 (100)
240 mg	22 (65)	53.5 (25-67)	21 (62)	1 (3)	33 (97)
Placebo	19 (58)	53 (24-71)	19 (58)	2 (6)	31 (94)

Table 6 Outcomes and results from the Phase II trial (Chemaly 2014) (adapted from CS Table 22)

Author (year)	Intervention	Dose	CS-CMV infection, n (%)	Time to onset of CS-CMV (days)	All-cause prophylaxis failure, n (%)	All mortality, n (%)	CMV-related mortality, n (%)	Non-CMV, non-drug mortality, n (%)	GvHD, n (%)	Infection or infestation, n (%)
Chemaly, 2014	Letermovir	60 mg	7 (21)	1-42	16 (48)	2 (6)	0 (0)	2 (6)	4 (12)	17 (52)
		120 mg	6 (19)	1-15	10 (32)	0 (0)	0 (0)	0 (0)	5 (16)	18 (58)
		240 mg	2 (6)	1-8	10 (29)	1 (3)	0 (0)	1 (3)	4 (12)	23 (68)
	Placebo	-	12 (36)	1-21	21 (64)	1 (3)	0 (0)	1 (3)	5 (15)	25 (76)
CS-CMV= clinically-significant CMV infection; GvHD= graft-versus-host disease; NR= not reported										

All-cause prophylaxis failure (defined as patients who discontinued the study drug because of virologic failure or for any other reason such as an adverse event, non-adherence or withdrawal of consent[1]) is similar to the NC=F analysis of initiation of PET in the PN001 trial.

This study demonstrated that letermovir, as compared with placebo, was effective in reducing the incidence of CMV infection in recipients of allogeneic haematopoietic-cell transplants. The highest dose (240 mg/day) had the greatest anti-CMV activity.

The ERG noted that some patients in this study received CsA concomitantly with the 240 mg dose; this is the licensed dose of letermovir. In their clarification response the company provided results for this post-hoc sub group (Clarification response table 24). Prophylaxis failures numbered 6/18 (33.3%) in the letermovir group compared with 10/19 (52.6%) on placebo. Although these cannot be directly compared with the results form PN001, they are supportive.

4.4 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable

4.5 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

4.6 Additional work on clinical effectiveness undertaken by the ERG

4.7 Conclusions of the clinical effectiveness section

Evidence of efficacy comes almost entirely from the PN001; a phase III randomised, double-blind, placebo-controlled trial. PN001 is reasonably well conducted, with a low risk of bias. However, design limitations mean the trial could not fully capture the benefit of letermovir and the results generated are not optimal for decision making.

- The fixed maximum 100 days treatment duration may mean potential treatment benefits are not captured – high-risk patients may require longer periods of prophylaxis.
- The primary outcome of clinically significant CMV infection is defined differently than in UK practice, meaning that trial patients initiated PET sooner than they would in practice, thus, overestimating the CMV infection rate.
- In contrast, the high use of T-cell depletion in NHS practice, with its higher risk of CMV infection suggests the infection rate may have been lower in the trial than would be expected in practice.
- The follow-up duration was limited for evaluation of a mortality benefit, and mortality was only an exploratory analysis.
- There are numerous differences between trial and UK practice in patient population composition, donor matching, immunosuppressive regimens, prevalence and intensity of T-cell depletion (putting UK patients at higher risk of CMV reactivation but lower GvHD incidence), myeloablation use, and criteria for initiation of PET. Very few UK patients were included in trial.
- The primary analysis (NC=F approach) of the primary outcome variable is very conservative. It overstates the incidence of CMV infection in untreated patients.
- It is unclear whether the strict inclusion criteria for the main analysis for no detectable CMV-DNA at baseline was an appropriate reflection of clinical practice;
- However, the delay in initiating prophylactic therapy seen in the trial is unlikely to occur in clinical practice, therefore patients with detectable CMV upon initiation of letermovir are highly unlikely to exist.

Mortality	Differences in mortality during the decision tree phase (up to 24 weeks) of the model were drawn from the PN001 study. Beyond 24 weeks of the trial no further survival gains from letermovir were assumed and long-term outcomes were extrapolated using mortality rates generated using natural history data on the long-term mortality of patients who had received SCT.	Data on short term mortality sourced from PN001 study. Data on long-term mortality sourced from Wingard *et al*.[15]	Section 3.1.1.1 pg.94 and 97.
Adverse events	No treatment related adverse events were included in the model. Adverse events associated with CMV infection and initiation of PET were included in the model: neutropaenia, thrombocytopaenia, and leukopaenia	Exclusion of treatment related adverse events was based on the assumption that any differences in utilities would be accounted for through the use of trial based utility estimates. Neutropaenia, thrombocytopaenia, and leukopaenia, were noted as the most commonly seen haematological adverse events in allogeneic-SCT patients.	Section 3.4.4 pg.101 and Section 3.5.6 pg. 124.
Health-related quality of life	Health-state utilities were assigned to each arm, and were derived from PN001 trial data and published evidence.	The sources of utilities were obtained from PN001 trial data and were collected using FACT-BMT and the EQ-5D. Aligned to the NICE reference case, the utilities derived from the EQ-5D were applied in the model. The model used EQ-5D utility inputs based on the time point in the trial for each comparator, to adjust life-years based on patient health-related quality of life. The baseline utility at each time point was assumed to be the weighted average EQ-5D index at baseline for letermovir and placebo from PN001. Beyond year one for survivors, the QALYs was estimated as a post-trial utility using the lowest value of either 0.82 from an AML population who underwent a HSCT (Leunis et al., 2014) [16], or the age-specific general population utility (Ara et al., 2011) [17].	Section 3.4.5 pg.101-103
Resource utilisation and costs	The resource use and costs included: drug acquisition costs, drug administration costs, costs of complications that can occur from the onset of clinically-significant CMV infection (including CMV disease, CMV-related re-hospitalisation, opportunistic infection and the costs associated with GvHD), and costs associated with adverse events.	Costs have been sourced from the NHS reference costs [18] and the PSSRU [19]. Costs have been applied using the perspective of the NHS. In accordance with the NICE reference case. Note that the costs to the NHS were included, but PSS costs have not been considered due to the unavailability of data to incorporate this into the model.	Section B.3.5 pg. 104-124
Time horizon	Lifetime analysis based on week 24 outcomes.	In accordance with the NICE reference case.	Section 3.2.2.2 pg. 86
Discount rates	Beyond one year, the costs and benefits were discounted at 3.5% per annum.	In accordance with the NICE reference case.	Section 3.2.2.2 pg. 87

the PN001 trial population were recruited. The ERG therefore considers that the patient's characteristics reported in the HMRN data to be at least as plausible as those in the PN001 trial.

5.2.4 Interventions and comparators

5.2.4.1 Interventions

The cost-effectiveness model compared the use of letermovir prophylaxis against SoC (no treatment). The recommended dosage of letermovir is one 480 mg dose per day, or alternatively 240 mg when taken concomitantly with ciclosporin A (CsA), which significantly increases the bioavailability of letermovir. Letermovir is available as both as an oral formulation and as a solution for intravenous (IV) infusion (240 mg and 480 mg). The oral and IV formulations may be used interchangeably at the discretion of the physician, with no dose adjustment necessary. The expected proportion of patients using each dose and formulation was based on clinical opinion, see Section 5.2.9 for further discussion and comment.

Modelled initiation and duration of treatment was based on mean duration of therapy observed in the ASaT population of the PN001 trial (69.4 days) which permitted initiation of treatment between day 0 (day of HSCT) and 28 days post-transplant. Maximum duration of therapy permitted in the PN001 trial was set at 100 days. This broadly matches the SmPC, though importantly, the SmPC does not mandate any futility rules and instead states:

> *"Prolonged letermovir prophylaxis beyond 100 days post-transplant may be of benefit in some patients at high risk for late CMV reactivation (see section 5.1). Use of letermovir prophylaxis for greater than 100 days requires a careful assessment of the benefit-risk balance."* Pg. 2 of SmPC

ERG comment

The ERG's primary concern with respect to the intervention is the duration of therapy which the ERG consider may be considerably longer than the mean of 69.4 days reported in the ASaT trial population of the PN001 study.

Firstly, reflecting the licence and the clinical experience gained as part the PN001, the ERG deem it likely that clinicians will be more confident to initiate letermovir prophylaxis immediately post-HSCT, as PN001 demonstrated no deleterious interaction with engraftment success. This means that it is unlikely that the mean delay between HSCT and initiation of prophylaxis of [redacted] days would be expected in practice, therefore patients will receive treatment earlier and for longer than in the trial.

5.2.4.2 Comparators

The NICE final scope listed aciclovir and valaciclovir as well as 'no preventative treatment' as comparators; however, the NICE scope noted that neither active drug had current marketing authorisation for the relevant indication. The CS included only 'no prophylaxis against CMV reactivation', i.e. no active comparators were included. The reasons given for this in the CS were: neither drug currently has a marketing authorisation in the UK for this indication; there is no relevant UK evidence supporting use of either treatment for CMV prophylaxis in this patient population (based on a systematic literature review (SLR)), and the overall evidence base is not considered to be robust by professional bodies [2].

ERG comment

As stated in Section 3.3, the ERG concurs with this reasoning, and does not consider aciclovir and valaciclovir to be relevant comparators for letermovir in this appraisal.

5.2.5 Perspective and time horizon

The economic model adopted a National Health Service (NHS) perspective in accordance with the NICE reference case.

The NICE reference case indicates that the time horizon used for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs and benefits between the technologies being compared. The time horizon used in the economic model, was 101 years; equivalent to a lifetime horizon. The ERG considers this more than adequate to capture any differences between letermovir and standard care.

5.2.6 Discounting

The costs and benefits in the model were discounted at an annual rate of 3.5%, as per the NICE reference case.

5.2.7 Treatment effectiveness and extrapolation

As described in Section 5.2.1 the economic model presented by the company comprises a decision tree up to week 24 (48 in scenario analysis) and a Markov model covering the remaining time horizon of the model. The clinical parameters used in the two distinct parts of the model differ.

Decision tree phase

The decision tree phase of the model utilises six different clinical outcomes with each outcome indicating the occurrence of a clinical event. The six clinical events included in the economic model are as follows:

Table 7: Grade 3/4 adverse events in the model (CS, Table 47, p 124)

Adverse events, % of patients	Letermovir	standard care
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
CS, company submission		

Because the PN001 study collected utility data on patients irrespective of whether they had experienced an AE, disutilities associated with AE were not included in the model as it was assumed that the trial based utilities already incorporated the impact of AE's. Adverse event rates therefore impacted only on costs included. See Section 0 or details of the costs applied.

ERG comment

The ERG has a few concerns regarding the data use and approach to modelling AEs in the company economic model. Firstly it is not clear why the company chose not to include AEs associated with treatment, as even if differences in HRQoL are included in the trial utilities used in the economic modelling, the costs are not. With respect to this, the ERG notes that there are few differences in the AE's rates for patients receiving letermovir, see Section 4.3. Secondly, the rates of adverse events applied for patients experiencing CMV infection appear to be based on AEs incurred throughout the whole trial period by all patients, and therefore do not reflect AEs incurred only by patients who have experienced a CMV infection or end-organ disease. Thirdly, because the HRQoL data was not collected after CMV infection or end-organ disease, the trial based utilities do not include the impact of these AEs on HRQoL. The ERG does not consider the issues raised important, as the impact of alternative assumptions regarding AEs is likely to be negligible and therefore the ERG presents no further exploratory analysis to address this weakness in the company's approach.

5.2.8 Health related quality of life

The company conducted a systematic literature review to identify the literature on health-related quality of life (HRQoL). The searches used were described and the inclusion/exclusion criteria used in the study selection were presented in Appendix H. While a number of studies were identified as having potentially useful information, none of the studies examined HRQoL in patients with CMV disease (see Table 30 in Appendix H. Therefore, the HRQoL values collected in the trial, using the EQ-5D-3L, were used within the decision tree phase of the model. The HRQoL values used in the Markov model phase were derived from published literature.

5.2.8.1 Trial utilities

In PN001, the EQ-5D questionnaire was administered at the time points of weeks 0, 14 and 24, during the primary study period, and at the conclusion of the follow-up period (week 48) to estimate the treatment-specific utility weights. HRQoL was also measured if early discontinuation or infection occurred.

The baseline utilities used in the company's model were derived from the baseline utilities observed in the PN001 trial. The baseline utility value for letermovir was [redacted] and for SoC was [redacted]. A weighted average of these two values ([redacted]) was applied to both arms within the model.

In order to calculate the utilities at Week 14, 24 and 48, the mean change from baseline values, as presented in the 48 week CSR, were combined with the baseline utility values to derive the utility values for each time point and are presented in **Table 8** below.

Table 8: Utility time point weights (Table 37 in CS, pg. 103)

Timepoint	Letermovir	Standard of care
Week 14	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Week 48	[redacted]	[redacted]

ERG Comment

The ERG has two concerns regarding the utility values used in the company's analysis; the capacity of the data collected in the trial to capture HRQoL differences, and the methods of analysis used.

Group differences

The approach taken by the company to modelling the differences in the HRQoL of patients receiving letermovir or standard care assumes that the values obtained in the trial reflect any differences in the HRQoL of these two patient groups. The CS, however, states that in PN001, once a patient had documented CMV viraemia, they were excluded from the analysis and HRQoL data were not collected after this point. Therefore, it is likely that the disutility associated with CMV infection and the resulting ill-health has not been captured in the trial utilities. Given that this is likely to be a primary benefit of letermovir treatment, the ERG feel that this should be accounted for in the estimation of QALYs, however, the magnitude of these benefits is likely to be very small and as such the ERG do not undertake further analysis exploring this issue.

Methods of analysis

The utilities used in the company base-case model appear to be based on unadjusted differences in the EQ-5D data collected in the trial. The ERG, however, notes that the magnitude of the differences

Table 9: General (UK) population utility values (Table 38 of CS, pg. 103)

Age	Utility value EQ-5D (95% CI)
60 to ≤ 65	0.8072 (0.793, 0.821)
65 to ≤ 70	0.8041 (0.790, 0.817)
70 to ≤ 75	0.7790 (0.766, 0.791)
75 to ≤ 80	0.7533 (0.739, 0.767)
80 to ≤ 85	0.6985 (0.677, 0.719)
>85	0.65497 (0.624, 0.675)
CI=confidence interval; EQ-5D=EuroQol-5 Dimension	

These values, as described in Ara and Brazier (2011) [17] are age stratified general population health statuses, where the population has a previous health condition.

ERG Comment

The ERG considers the general approach of the company to modelling post-trial HRQoL to be appropriate, including the adjustments for age, but has some concerns regarding the appropriateness of the post-trial utility value of 0.82 sourced from. Leunis *et al* [16] Firstly, this utility value is based on the EQ-5D-5L which currently does not align with NICE's preferred method of eliciting utilities[21] EQ-5D-3L. Further it has been noted in a recently published study,[22] that EQ-5D-5L estimates tend to be higher than those generated using the EQ-5D-3L instrument, due to the smaller differences in values between the health states in the value set. Secondly, the ERG notes that this implies a utility value higher than that of the general public based on the EQ-5D-3L, which would appear to be inconsistent with the fact these patients have survived a very serious illness. This also is inconsistent with results in the Leunis study which reports results, using the EQ-VAS, that show that survivors of AML have lower HRQoL than age and sex matched members of the general public. Reflecting these concerns the ERG requested that the company present a scenario analysis where a utility decrement from the long-term effects of HSCT has been incorporated: see Section **Error! Reference source not found.** for further details. The ERG, however, does not consider that this analysis fully captures the long-term utility decrement associated with having undergone SCT as it mixes EQ-5D-5L and EQ-5D-3L values. It also suggests a decrement much smaller than estimated in Leunis based on the EQ-VAS. The ERG explores this issue further in Section 6.

5.2.8.3 Adverse event disutilities

The CS states that the company explored the recent technology appraisals for ALL and AML [23, 24] for impacts of AEs on HRQoL, however this search did not uncover any studies with this information provided. The company noted that as the EQ-5D data collected in the trial was at particular time

To identify the cost and resource-use data to be used, the company carried out a systematic review of healthcare resource utilisation and cost studies. As discussed in Section **Error! Reference source not found.**, the review appears to have been appropriately undertaken.

5.2.9.1 Drug acquisition and administration costs

In the CS base-case model, the cost per day was calculated for letermovir, taking into account the drug cost, administration cost and concomitant dosing adjustments. The unit costs per day were calculated accounting for both route of administration (oral or IV), and the dose administered (240mg and 480mg). Oral administration of therapy was assumed to be associated with no administration costs while IV administration was assumed to incur a unit cost sourced from NHS Reference costs: Deliver Simple Parenteral Chemotherapy at First Attendance. The total unit costs per day of treatment associated with each route of administration and dose are presented in **Table 10** below and include the company's proposed PAS, which equates to a [redacted] % discount on the list price of letermovir.

Table 10: Letermovir cost breakdown (Table 31 in CS, pg. 92)

Letermovir	**Oral**		**IV Infusion**	
	240mg (concomitant with CsA)	**480mg**	**240mg (concomitant with CsA)**	**480mg**
List Price	[redacted]	[redacted]	[redacted]	[redacted]
PAS Price	[redacted]	[redacted]	[redacted]	[redacted]
CsA=ciclosporin A; IV=intravenous; PAS=patient access scheme				

The proportion of the patient receiving concomitant ciclosporin A (CsA) was assumed to be 95%, the vast majority of patients were therefore assumed to require a 240mg, rather than a 480mg, dose of letermovir. The proportion of patients receiving concomitant CsA was based on expert opinion which suggested more widespread use of CsA as an immunosuppressive agent than was observed in the PN001 trial, in which 42% of patients were treated with tacrolimus, which does not require a dose reduction of letermovir. To explore the uncertainty regarding this assumption, the CS also presented a scenario analysis where the proportion of patients concomitantly using CsA was varied from 71% to 100%.

With the base case analysis the company assumes that 5% of patients will receive initial IV infusion, this reflects the administration route observed in the 12 UK patients in the PN001 trial (100% PO; MSD, Data on file) and the assumption that a proportion of patients would not be able to tolerate oral administration initially, due to gastrointestinal complications and would receive letermovir initially via IV infusion. Patients who initial receive IV are not assumed to continue to receive IV infusion

throughout the duration of letermovir prophylaxis, but assumed to revert to receiving oral letermovir after [redacted] days. The duration of [redacted] days was based on the mean duration of IV letermovir within the PN001 trial.

When the drug costs, administration costs, mode of administration and concomitant dosing adjustments were taken into account, the company estimated that the letermovir cost per day was [redacted].

ERG Comment

The ERG considers that, for the most part, the assumptions used to estimate the letermovir cost per day are appropriate including the assumptions made regarding the proportion of patients receiving concomitant CsA. Clinical advice received by the ERG confirmed that tacrolimus is rarely used in the UK and that the vast majority of patients would receive concomitant CsA throughout the maximum 100 day treatment period. However, the ERG has concerns regarding the proportion of patients assumed to receive IV letermovir. The ERG also thinks it inappropriate that no administration costs have been include for oral letermovir therapy.

The ERG considers that the proportion observed in the trial (27%) receiving IV letermovir is more likely to be representative of UK practice than the assumption of 95% made in the company base-case. Firstly, the company's justification based on the UK trial participants is at odds with the value used; 100% of UK patients received oral therapy. Secondly, the use of IV therapy is primarily driven by the ability of patients to tolerate an oral administration rather than clinician or patient preference. It is therefore unclear why the proportion would vary with location unless patients differed in their ability to tolerate oral therapy by region. The ERG therefore considers it more reasonable to assume that the proportion of patients unable to initially tolerate oral administration will align with the PN001 trial. A scenario based on this assumption is presented in Section 6.

With respect to the administration costs associated oral treatments (both letermovir and valganciclovir), the ERG considers that some administration costs should be included to reflect the resource required give patients instructions on how and when to take the tablets as well dispensing costs to cover pharmacists' time. Inclusion of administration costs for oral therapy is also consistent with Committees' preferred assumptions in several previous appraisals of oral cancer therapies; TA395, TA406, TA 422 and TA500. The ERG, therefore presents a scenario based on applying an administration cost for patients receiving oral letermovir Section 6.

5.2.9.2 CMV disease monitoring costs

The company's base-case analysis includes twice-weekly CMV viral load monitoring for both the letermovir and SoC arms of the model. The model also allows for a scenario where CMV viral load monitoring was incorporated on a weekly basis. The cost of the PCR test was estimated to be £32.62, this estimate was derived from Nottingham University Hospital. For modelling purposes, whether patients received monitoring was based on their survival. An average proportion of patients in each arm being monitored was estimated based on survival rates half-way through the model's time period.

ERG Comment

As noted in Section 3.5.7 of the CS, there is a degree of variation in clinical practice with respect to PCR testing, with the majority of centres undertaking PCR once a week, and smaller proportion of centres undertaking twice weekly testing. Further, the ERG's clinical advisor noted that in centres undertaking twice weekly monitoring, this would not continue for the entire duration of patients' post-transplant care, with monitoring being reduced to weekly when patients leave hospital. It is therefore likely that the company have slightly overestimated the monitoring required. Altering the frequency of testing, however, has minimal impact on the ICER and this issue is not explored further.

5.2.9.3 Pre-emptive therapy costs

When the CMV viral load monitoring detects CMV viraemia or clinically-significant CMV infection, patients begin pre-emptive therapy (PET). The rates of initiation of PET for the letermovir and SoC arms of the model for the 14 week and 24 week outcomes were derived from the PN001 trial, see Section 0 for further details.

The company's model includes three PET CMV antivirals: ganciclovir, valganciclovir and foscarnet. Cidofovir was a PET received by patients in the PN001 trial but was not included in the company's model for this submission, due to its lack of use in NHS clinical practice. Ganciclovir and foscarnet are both administered intravenously and therefore the model includes a drug administration cost for these therapies of £236.19 per infusion (the same administration cost as applied for IV letermovir). Because ganciclovir and foscarnet require multiple infusions per day (ganciclovir requires an infusion twice daily; foscarnet requires an infusion thrice daily) these costs was multiplied by the number of infusions required per day for the two treatments. The drug costs, administration costs and proportions of patients receiving each treatment used in the model are presented in **Table 11**. The CS assumes that patients receive PET for a mean duration of 21 days.

Table 11: Pre-emptive therapy therapies (based on Table 43 and Table 44 of CS, pg. 117-8)

Pre-emptive therapy therapies	Dosing	Source	% of patients receiving this treatment in the company's model	Drug cost	Drug administration cost
Valganciclovir	900mg (PO) twice daily	eMC SmPC Valcyte (valganciclovir) [26]	37.5%	£28.84	N/A
Ganciclovir	5mg/kg infusion once every 12 hours (twice daily)	eMC SmPC Cymevene (ganciclovir) [27]	37.5%	£45.60	£472.38*
Foscarnet	60mg/kg infusion once every 8 hours (thrice daily)	eMC SmPC Foscavir (foscarnet) [28]	25%	£275.42	£708.57*
PO=per oral; eMC=electronic Medicines Compendium; SmPC=Summary of Product Characteristics *Based on patient weight of 76.6kg obtained from PN001 week CSR (ref 29)					

The CS includes additional hospital stay costs for patients receiving foscarnet, which is assumed to require an inpatient stay; valganciclovir and ganciclovir are both assumed to be outpatient treatments. Costs are applied are assumed to be equal to £305.72 per day based on a weighted average of elective and non-elective excess bed days, obtained from the NHS Reference Costs 2015/16 [29].

Taking the drug costs, drug administration costs and additional inpatient and outpatient days required due to PET, the total cost of pre-emptive therapy included in the CS was estimated at £11,077.

ERG Comment

The ERG are satisfied with the arguments for cidofovir to have been excluded from the company's model. As stated in the CS, cidofovir had its European marketing authorisation withdrawn in 2014 [30], and there is no list price available from the BNF. In addition, it is likely that a very small number of patients, if any, would receive this drug in clinical practice (the company's clinical advisor suggested 5%; the ERG's clinical advisors both noted that this would be a third-line PET treatment).

The CS assumption that patients receive PET for a mean duration of 21 days is lower than that observed in the PN001 trial (mean duration was 60.4 days in the letermovir arm and 58.5 days in the SoC arm) and was based on correspondence with the company's clinical expert. This is a conservative assumption, as increasing the duration of PET has the effect of reducing the ICER for letermovir. The ERG's clinical advisors considered the assumed mean duration of 21 days to be reasonable and in line with UK practice.

The ERG has a number of concerns regarding the proportion of patients receiving foscarnet and the administration costs associated with each kind of PET.

1. GvHD

The rates at which these events occur were based on the clinical inputs derived from the PN001 trial, see Section **Error! Reference source not found.** for further details.

CMV end-organ disease

CMV end-organ disease was assumed to be associated with the same total cost as pre-emptive therapy (i.e. £11,077), as per the British guidelines on CMV management [11]. The company consider this to be an underestimate; they expect patients would be treated with more intensive medicines and would incur more serious conditions such as renal damage and cytopaenia, which would require additional resources.

CMV-related re-hospitalisation

The company's model also includes the cost associated with extra days in hospital due to pre-emptive therapy/CMV disease. The inpatient cost was assumed to be the same as that assumed for PET costs detailed above. The average number of extra inpatient days required was assumed to be 13.9 days in the model. This was based on Jain *et al.* (2014) [31] which assessed the costs associated with CMV. The company stated that no additional costs associated with treatments/procedures were included apart from this excess bed day cost, and therefore, this may be an underestimate of the true cost. Using these estimates, the company calculated that the CMV-related rehospitalisation cost was £4,250.

Opportunistic infection

The company estimated the cost of opportunistic infection based on a published study [32] and NHS reference costs. The three most common opportunistic infections, as per Krüger *et al*. were included. The proportion of patients contracting each infection, along with the associated costs, are presented in **Table 12**.

Table 12: Costs associated with Opportunistic infection (adapted from table 39, pg. 105-109 in CS)

Variable	Parameter	Reference
% of patients with FUO	63.7%	Krüger *et al* (1999) [32]
% of patients with pneumonia	18.7%	Krüger *et al* (1999) [32]
% of patients with septicaemia	17.6%	Krüger *et al* (1999) [32]
FUO cost	£1,020	NHS reference costs WJ07A-D
Pneumonia cost	£1,905	NHS reference costs DZ11KI-V
Septicaemia cost	£2,164	NHS reference costs WJ06A-J
Total cost of opportunistic infection	£1,387	

12. Mean duration of therapy assumed to be 83 days;
13. Inclusion of medium-term care costs for survivors of HSCT and (ERG)survivor disutility;
14. Revisions to assumptions regarding GvHD costs and QALYs;
15. Inclusion of relapse disease based on HMRN rate of relapse;
16. Revisions to administration cost for letermovir and PET and IV letermovir use;
17. Foscarnet use assumed to be 15%;
18. Mortality data in the Markov phase of the model based on date from HMRN and relative risk from Martin et al.

Under the ERG's alternative set of assumptions, the deterministic ICER for letermovir prophylaxis versus standard care is £27,536 per QALY.

Table 13: ERG preferred base-case analysis

Technologies	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's base case (including PAS)					
SoC	28,805	6.73	-	-	-
Letermovir	33,819	7.19	5,014	0.46	10,904
ERG preferred base-case analysis					
SoC	29,250	5.35	-	-	-
Letermovir	37,683	5.65	8,433	0.31	27,536
ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; SoC=standard of care					

6.5 Scenario analysis on the ERG preferred base-case

This section presents additional scenario analyses considering uncertainty surrounding three assumptions/inputs used in the model. These concern the duration of letermovir therapy, the approach used to model missing data, and mortality at 48 weeks.

6.5.1 Duration of therapy

As noted above, there is some uncertainty as to whether all patients receiving letermovir prophylaxis will discontinue therapy at 100 days post-transplant as was mandated in the clinical trial given the lack of any futility rules in the SmPC. To explore this uncertainty the ERG reruns a number of scenarios presented in Section 6.3.1 on the ERG's base-case model. These scenarios assumed that those patients receiving letermovir prophylaxis at 100 days continue therapy for a fixed period 2, 4 and 6 weeks post 100 days. As above, no adjust is made to account for the fact extending duration of therapy will likely improve effectiveness. These ICERs therefore are likely to overestimate the true ICER. **Error! Reference source not found.**