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 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 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 (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%/ 15.1% 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 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.

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 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 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 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.

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 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 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 Table 14.

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 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 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 ([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 26** 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 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

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 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 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 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 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 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. Table 50