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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

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Rider on responsibility for report

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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.

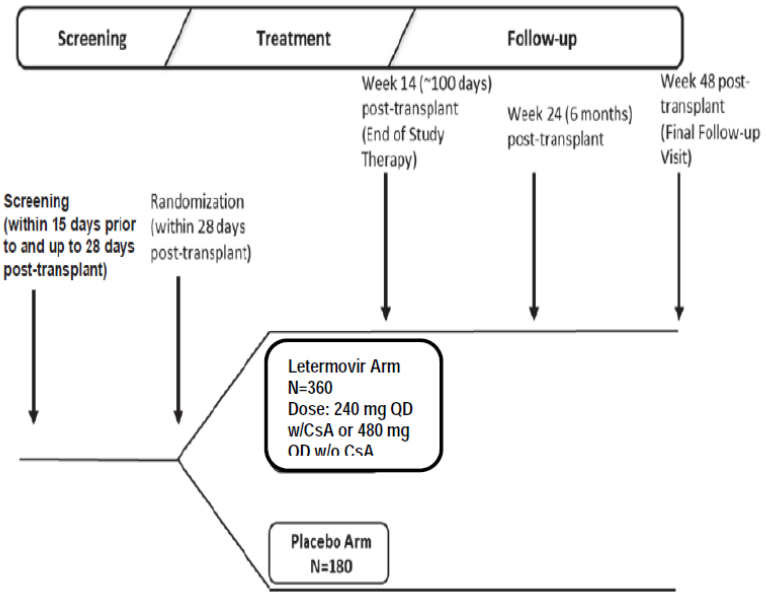
The clinical advisors to the ERG agreed with this categorisation of high and low risk, although noted that in vivo T-cell depletion with ATG or alemtuzumab will confer high risk, and could have been included.

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

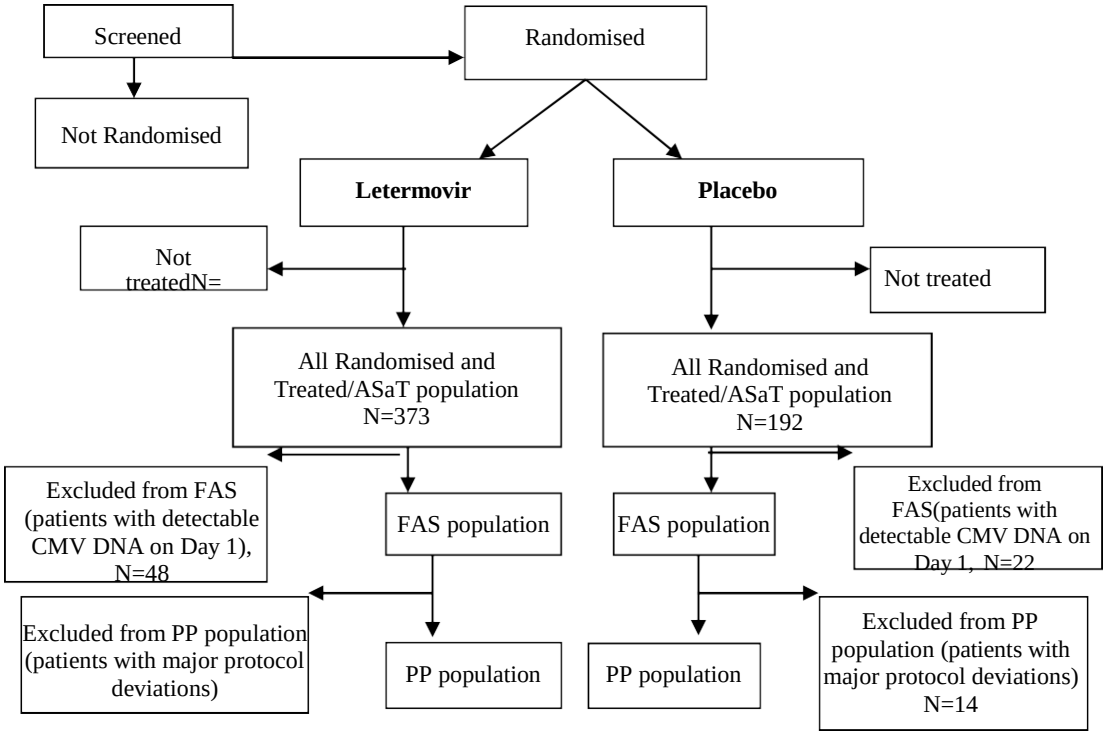
treatment is commenced; however, in practice this would not be expected in the absence of a period of preceding viraemia. As some patients may have stable low levels of CMV activation over a long period, PET is often delayed to allow a natural immune response and avoid exposure to toxic drugs.[11, 12]. 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
	n/N	% (95% CI)	n/N	% (95% CI)	% (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.

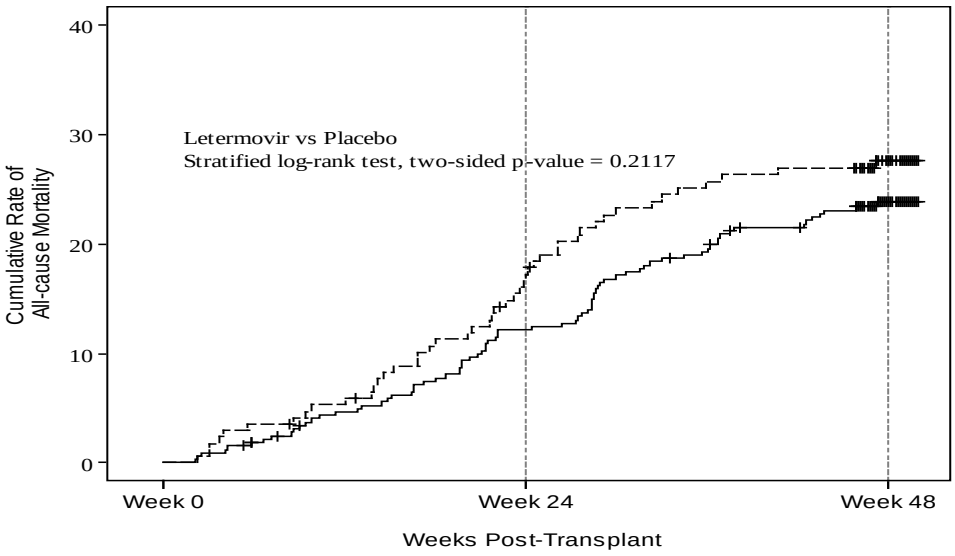
Table 14 Results for All-cause mortality through weeks 14, 24 and 48 (FAS population) (adapted from CS figures 5 and 6 and Response to clarification questions, Tables 15 and 16)

	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.

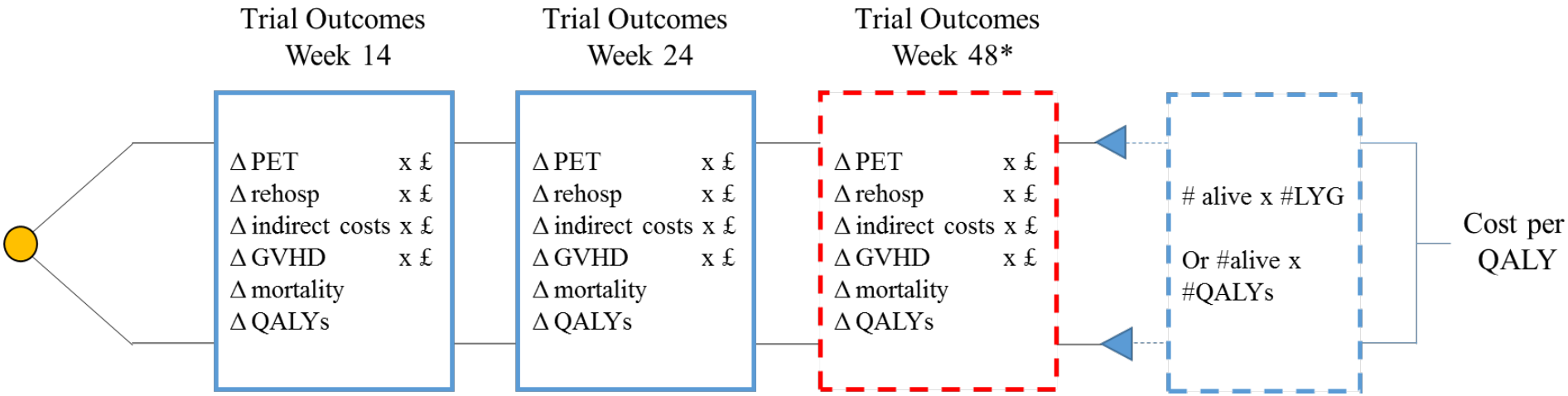
Mortality	Differences in mortality during the decision tree phase (up to 24 weeks) of the model were drawn from the PN001 study. Beyond 24 weeks of the trial no further survival gains from letermovir were assumed and long-term outcomes were extrapolated using mortality rates generated using natural history 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 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 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

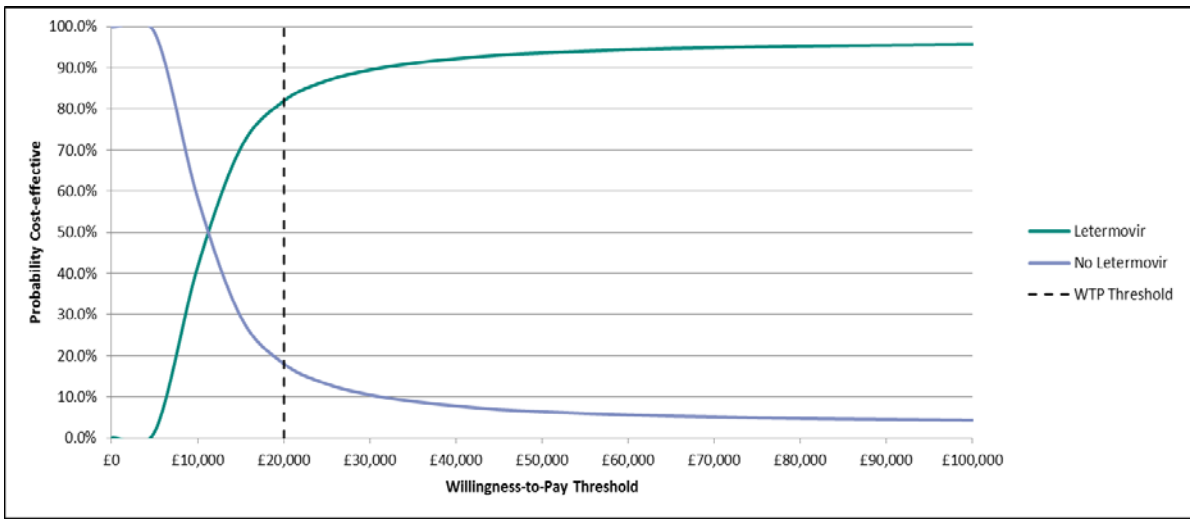
The average QALYs gained with letermovir compared with SoC were 0.46. The average incremental cost was £5,036, resulting in an average ICER of £10,913 per QALY gained. The results of the PSA were similar to those of the deterministic analysis (compare **Table 32** and **Table 33**).

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)

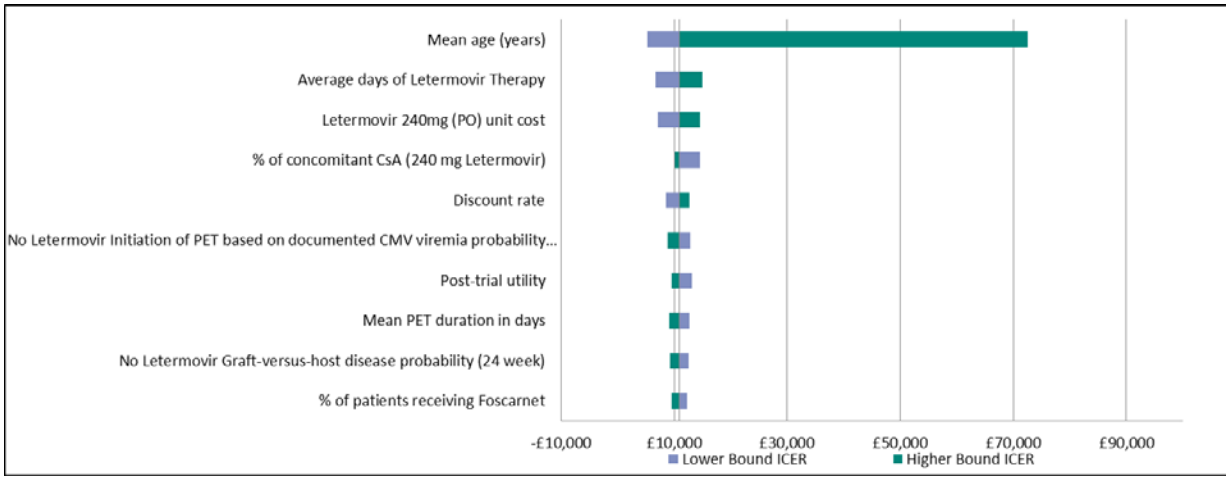


WTP=willingness-to-pay

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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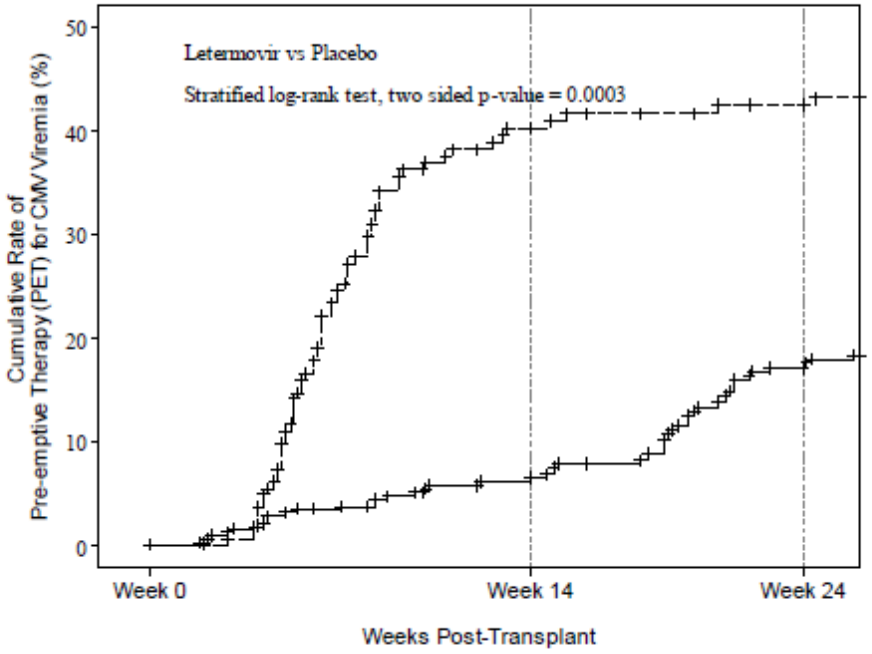
10 Appendices

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