Slides for public observers

Lead team presentation

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

1st Appraisal Committee meeting
Background & Clinical Effectiveness
Committee D, 12 June 2017

Lead team: Malcolm Oswald, Bernard Khoo, Paula Parvulescu

Company: Merck Sharp & Dohme

Chair: Gary McVeigh

Evidence review group: CRD and CHE Technology Assessment Group

NICE team: Aimely Lee, Christian Griffiths, Helen Knight

Key clinical issues (1)

- Are the PN001 trial results generalisable to clinical practice?
  - What proportion of patients would be expected to have treatment beyond 100 days? (Mean duration 69.4 days in trial)
  - Is a delay in initiating prophylaxis post HSCT likely to occur? (Mean delay in trial of [redacted])
  - What proportion of patients would receive cyclosporin A (CsA)? (51.7% in trial)
  - What proportion of patients would receive alemtuzumab? (4% in trial)
- Should the Full Analysis Set (FAS; company base case) or the All Subjects as Treated (ASaT) be used to evaluate efficacy?

Key clinical issues (2)

- The FAS population excluded people with detectable CMV on day 1. In clinical practice, would people with detectable CMV DNA have letermovir prophylaxis?
- Patients with missing data or who prematurely discontinued from study had their treatments considered as ‘Failures’. Is this an appropriate way of handling missing data?
- Is there any mortality benefit from letermovir?
  - All-cause mortality benefit was not significant at week 48. The difference was 3.8%. Is this plausible after considering uncertainties and differences between trial and clinical practice?
  - Mortality benefit associated with avoiding CMV reactivation is uncertain but people who got a CMV infection in the letermovir arm had ~50% lower mortality rate than those in placebo

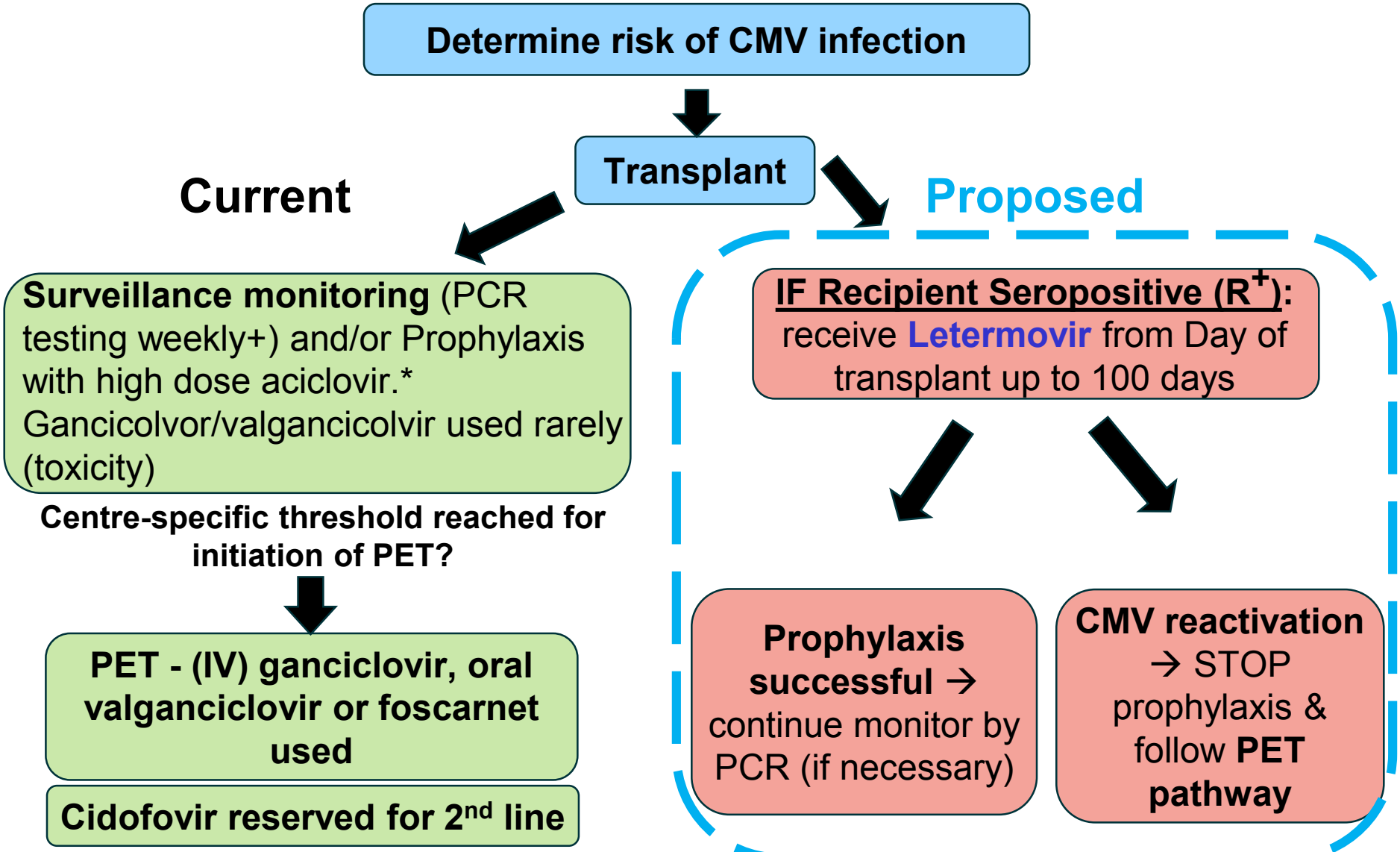
Disease background

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

Letermovir (Prevymis)

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

Treatment pathway – CMV in allogeneic HSCT



* Clinical experts stated that aciclovir used in NHS but has poor effectiveness

Abbreviations: PET = pre-emptive therapy

Patient experts comments
Anthony Nolan

- CMV reactivation affects quality of life and causes patients to return to hospital without the protection against infection associated with a transplant unit
- No authorised treatments available for CMV prophylaxis directly following HSCT
  - Letermovir could provide substantial benefit to patients and families
- Current treatments have serious side effects that causes severe problems. Patients stated: *“A kinder treatment is definitely needed; after going through chemo and total body irradiation the treatment for CMV was by far the worst part”*
- “8 of 13 (62%) patients surveyed said that CMV reactivation had a 'negative' or 'very negative' effect on their mental health and well-being”
- Oral option welcomed by patients, allowing management at home in conjunction with visits to blood test clinic

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

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

NHS England comments

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

Decision problem: Deviations from final scope

	Final scope	Company submission and rationale
Comparators	• Aciclovir • Valaciclovir • No preventative treatment	Included a placebo group. Did not consider aciclovir and valaciclovir because: - no relevant/robust UK evidence supporting their use for this indication and population - lack of observed efficacy with aciclovir and both aciclovir and valaciclovir associated with neurotoxicity
Outcomes	• CMV infection rate • Reduction of hospital in-patient days • Time to onset of clinically significant CMV infection • Time to initiation of PET for CMV viraemia • Time to all-cause mortality • Overall survival • Adverse effects of treatment • Health-related quality of life	Outcomes reflect but do not exactly match: • Clinically-significant CMV infection • ocumented CMV viraemia Time to onset of clinically-significant CMV infection • CMV disease • Initiation of PET for documented CMV viraemia • Time to initiation of PET for d • All-cause mortality • Opportunistic infections • Acute and/or chronic GvHD • Re-hospitalisations • Adverse events • Health-related quality of life

- ***Is the company decision problem appropriate for decision-making?***

Clinical evidence: PN001 Trial

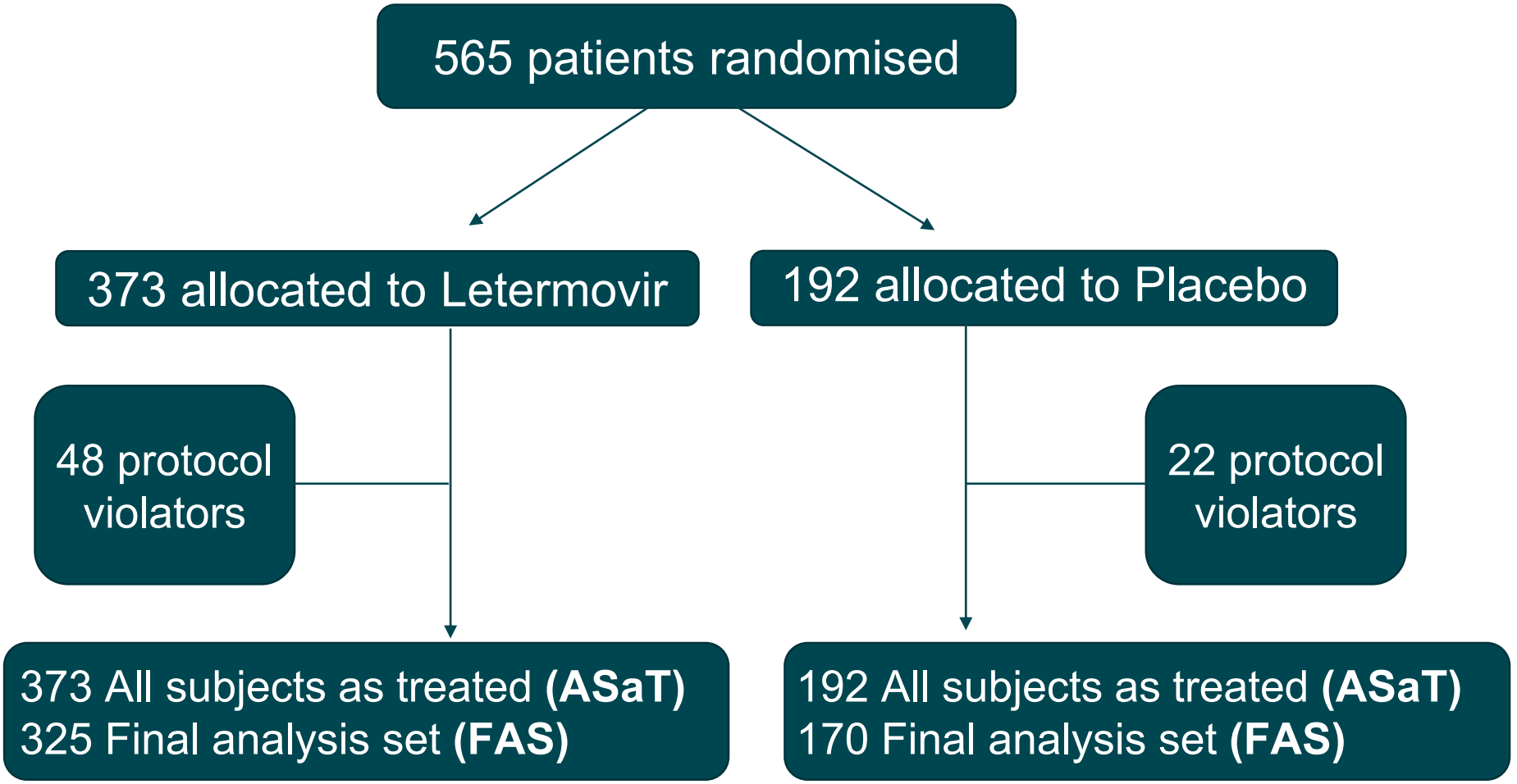
Study type	Phase III, International, multicentre, randomised, double-blind, placebo-controlled trial
Population	Adult CMV-seropositive recipients of an allogeneic HSCT (n=570)
Intervention	Oral or IV letermovir 480 mg once-daily (OD, n=376), adjusted to 240 mg OD if co-administered with CsA)
Comparator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

Source: table 5 (page 27-29) of the company submission; * Clinically-significant CMV infection is defined as the initiation of PET based on documented CMV viraemia (~151 copies/ml) or onset of CMV end-organ disease

ERG critique: Trial design limitations

- Treatment period was up to 100 days (14 weeks) potentially underestimating the efficacy and duration of letermovir – Some people may require longer treatment in clinical practice (e.g. high risk of reactivation)
- Follow-up period for primary end-point was limited to 24 weeks and mortality was only an exploratory analysis
- Clinically-significant CMV infection leading to the initiation of PET is defined differently in trial than in UK practice (viral load threshold of 300 copies/ml in trial) potentially overestimating CMV infection rate and underestimating the potential efficacy of letermovir

PN001 consort diagram



- ***Is the FAS or ASaT more appropriate for decision-making?***

- Protocol violators = patients who tested positive for CMV DNA on Day 1

PN001 (ASaT) – baseline characteristics

	Letermovir (n=373) n (%)	Placebo (n=192) n (%)
Age (yr), median (range)	53.0 (18.0 - 75.0)	54.0 (19.0 - 78.0)
Male	211 (56.6)	116 (60.4)
Weight (kg), median (range)	76.2 (35.1 - 141.5)	74.4 (40.9 - 113.1)
- High risk of CMV reactivation **- Low risk of CMV reactivation**	121 (32.4) 252 (67.6)	54 (28.1) 138 (71.9)
- Cyclosporin A use **- Tacrolimus use**	193 (51.7) 160 (42.9)	100 (52.1) 79 (41.1)
Antithymocyte globulin (ATG) use	140 (37.5)	58 (30.2)
Alemtuzumab use	12 (3.2)	11 (5.7)
Source: table 9 (page 44-46) of the company submission		

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

ERG critique: Baseline characteristics

- Only 12 patients from UK enrolled in the trial
- Average age: ~51 years in trial vs. ~45 years in NHS practice and include more matched unrelated patients than in the trial
- No detectable CMV DNA at baseline – appropriate reflection of clinical practice?
- Prevalence of CsA use: 51.7% of patients on letermovir (ASaT population) in trial vs. 90% in NHS practice
- Prevalence of alemtuzumab use: 4% in trial vs. ~85% in some UK centres → trial likely to underestimate CMV reactivation rates and overestimate incidence of GvHD
- Unclear for how long patients received concomitant CsA and/or alemtuzumab in trial

Efficacy results:

Clinically significant CMV infection by week 24

	Letermovir (n=325)	Placebo (n=170)	Difference* (95% CI)
FAS population, n (%)			
Primary endpoint: % failed prophylaxis by wk24[a] **(Non-completer=Failure; NC=F)**[b]	122 (37.5)	103 (60.6)	-23.5 (-32.5, -14.6); p<0.0001
% failed prophylaxis by wk24 **(Data As Observed; DAO)**	[redacted]	[redacted]	[redacted]
Discontinued before Week 24	56 (17.2)	27 (15.9)	-
Missing outcome	9 (2.8)	5 (2.9)	-
ASaT population, n (%)			
Primary endpoint: % failed prophylaxis by wk24[a] **(NC=F)**[b]	[redacted]	[redacted]	[redacted]
% failed prophylaxis by wk24 **(DAO)**	[redacted]	[redacted]	-
Discontinued before Week 24	[redacted]	[redacted]	-
Missing outcome	[redacted]	[redacted]	-

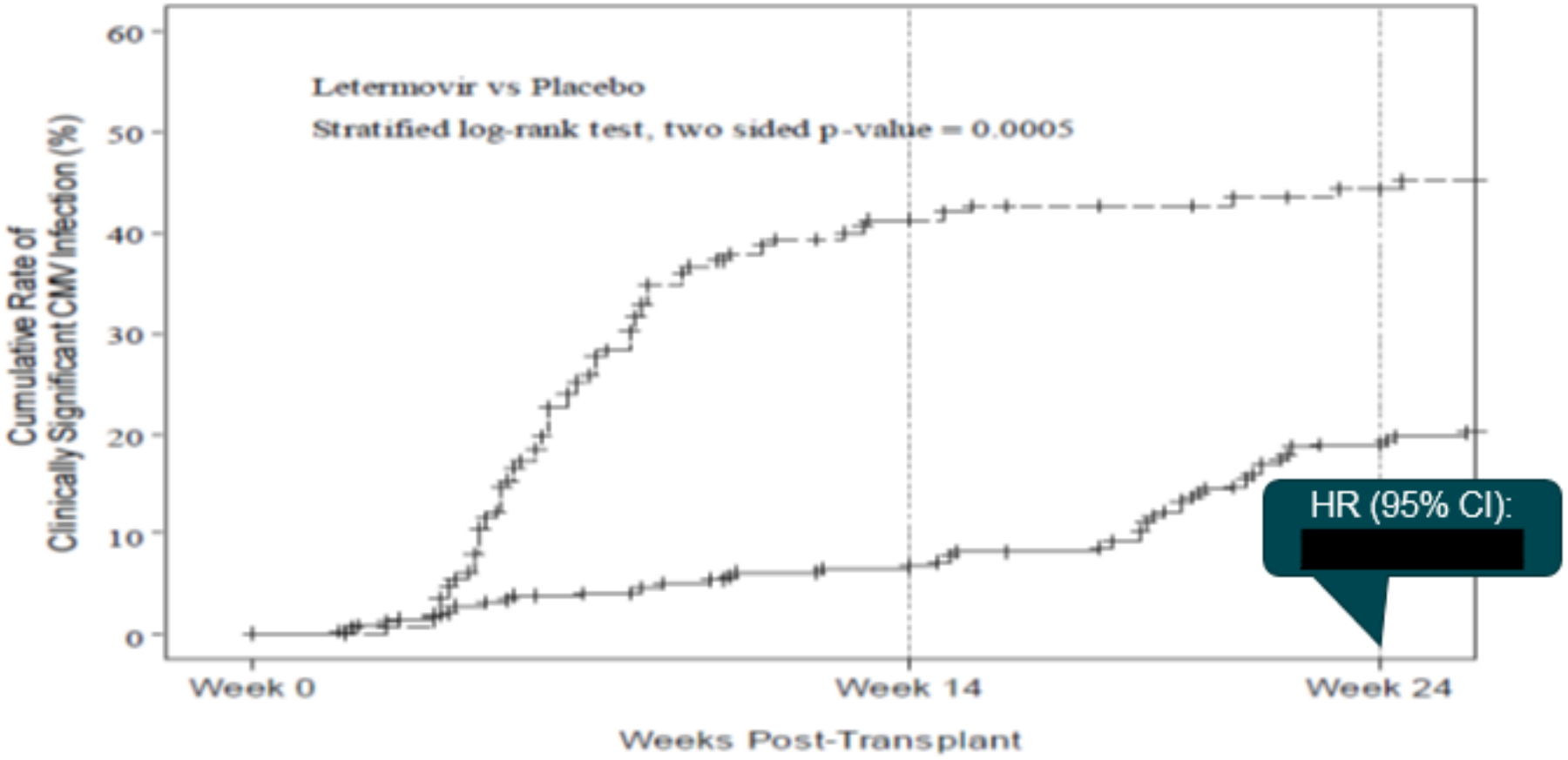
Source: table 11 of the company submission and tables 7 and 9 of the clarification response document; [a]Clinically significant; [b] Non-completer-failure refer to those who discontinued from the study early and assumed that prophylaxis has failed; [c] Based on documented CMV viraemia; *Stratum-adjusted treatment difference (95% CI) (letermovir-placebo), One sided p value

Efficacy results (FAS):
Initiation of PET for documented viraemia by week 24

Parameter	Letermovir (n=325), n(%)	Placebo (n=170), n(%)	Difference* (95% CI)
FAS population			
Initiation of PET (**NC=F**)	119 (36.6)	101 (59.4)	-23.3 (-32.3, -14.3), p<0.0001
Initiation of PET (**DAO**)	52 (16.0)**	68 (40.0)**	-30.6 (-40.2, -21.0), p<0.0001
Discontinued before Week 24	57 (17.5)	28 (16.5)	-
Missing outcome	10 (3.1)	5 (2.9)	-
ASaT population			
Initiation of PET (**NC=F**)	[redacted]	[redacted]	[redacted]
Initiation of PET (**DAO**)	[redacted]	[redacted]	
Discontinued before Week 24	[redacted]	[redacted]	
Missing outcome	[redacted]	[redacted]	

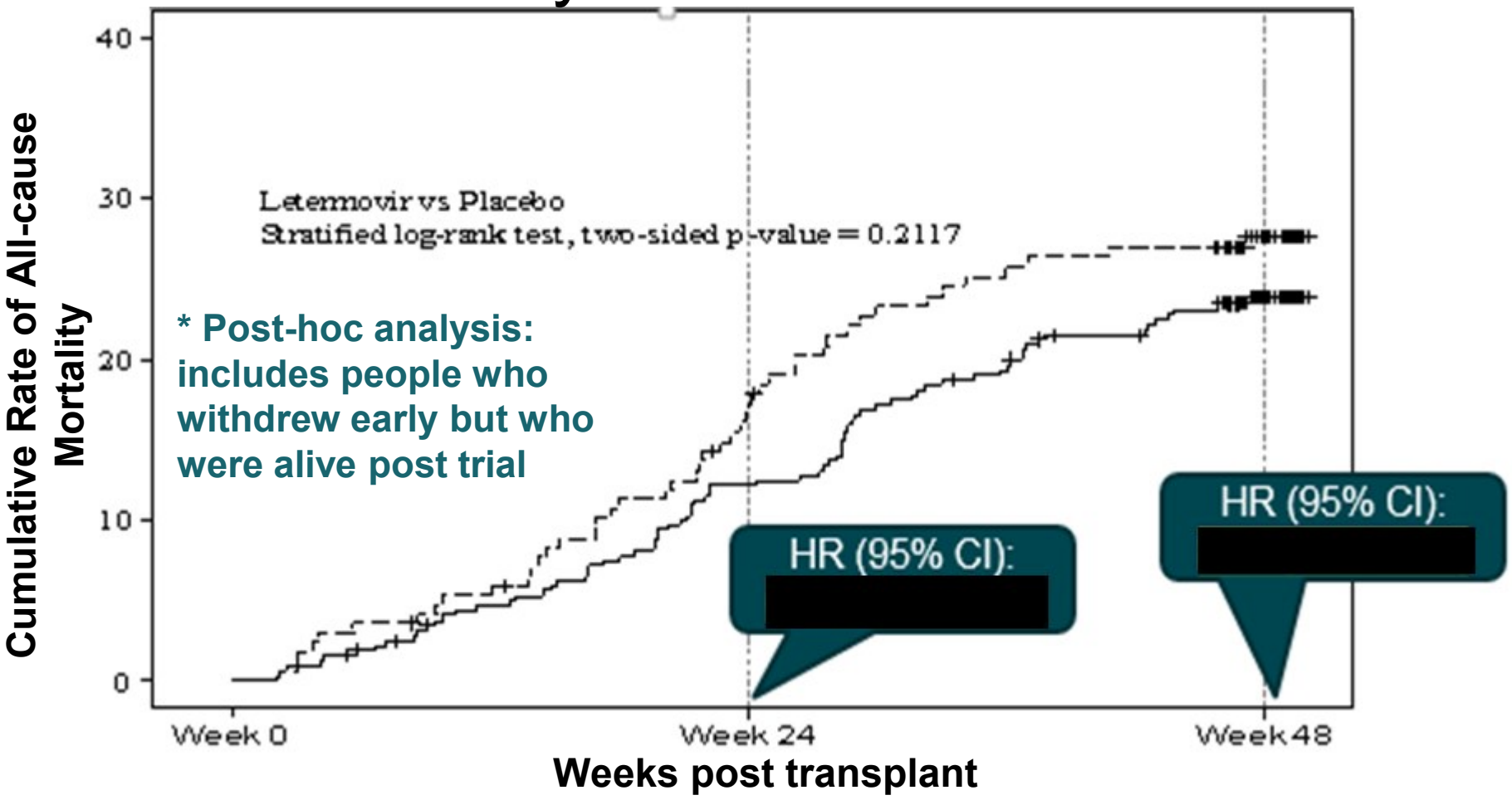
Source: table 10 in the ERG report; *Stratum-adjusted treatment difference (95% CI) (letermovir-placebo), One sided p value; ** Percentage based on intention-to-treat

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



[redacted]

Efficacy results (FAS): Time to all-cause mortality at week 24 and 48*



No. at risk: KM estimates (%)

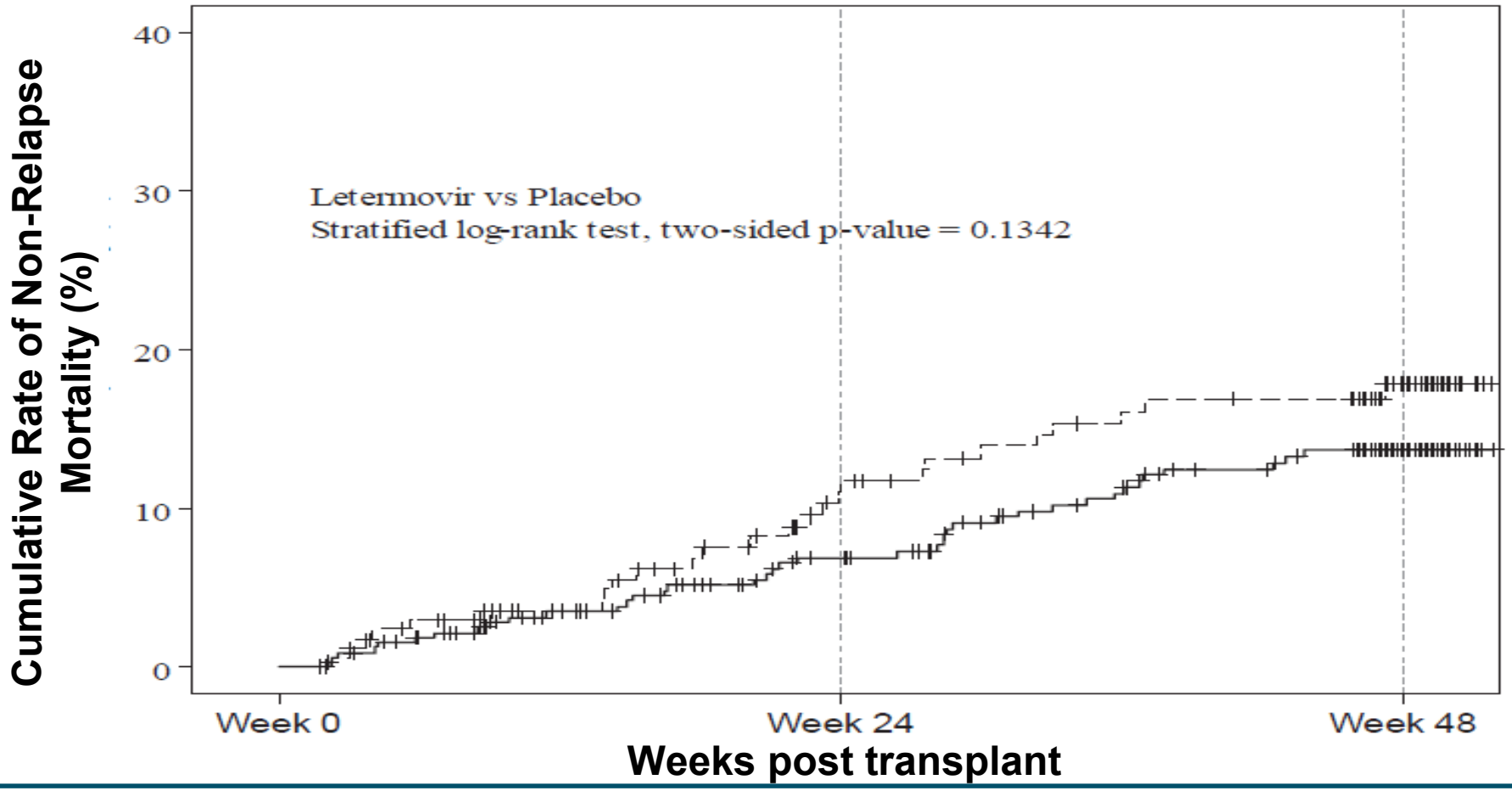
• Letermovir vs Placebo:	12.1 vs 17.2	23.8 vs 27.6
• Difference:	5.1%	3.8%

Efficacy results (FAS): Ad-hoc analysis
All-cause mortality risk - stratified by prior CMV infection

- People on letermovir that had clinically-significant CMV infection through week 24 had lower mortality rate to week 48;
  - similar mortality rates were seen in both treatment groups with people without clinically-significant CMV infection to week 24
- Company states that the decrease in all-cause mortality in the letermovir group is likely due to prevention of CMV viraemia post-transplant

Week 48	**Incidence of all-cause mortality**	
Clinically significant CMV infection	9/57 [**15.8%**])	22/71 [**31.0%**])
No Clinically significant CMV infection	52/268 [19.4%]	18/99 [18.2%]

Efficacy results (FAS): Time to non-relapse mortality through week 48 (1)



No. at risk: KM estimates (%)

- **Letermovir vs Placebo:** [redacted] vs [redacted] [redacted] vs [redacted]
- **Difference:** [redacted]% [redacted]%

Efficacy results (FAS): Time to non-relapse mortality through week 48 (2)

- This outcome and analysis reported in the clinical study report was not considered scientifically sound by the EMA assessors and were omitted from the EPAR
- EPAR's reasoning: the definition of CMV-related mortality was "death to any reason in subjects who met the primary endpoint"
  - In most cases the cause of death was unrelated to CMV infection or CMV DNAemia
  - Incidence of CMV infection was also highly skewed between study groups → unacceptable bias

Health-related Quality of Life results in PN001:
EQ-5D Index and FACT-BMT total score

- [redacted]

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

Source: table 15 (page 60) in the ERG report

Exploratory endpoints (FAS):
GvHD, re-hospitalisation & opportunistic infections

- GvHD, re-hospitalisation, re-hospitalisation for CMV infection, and documented CMV viraemia through week 14 and 24 were all numerically lower in letermovir group compared with placebo group

- Documented CMV viraemia greatly favoured letermovir through week 14 and 24 (letermovir vs placebo; % [95% CI]): 31.7 (26.7, 37.1) vs. 69.4 (61.9, 76.2) and 57.2 (51.7, 62.7) vs. 72.9 (65.6, 79.5), respectively

- Bacterial/fungal infections through week 14 and 24 were numerically slightly higher in letermovir group compared with placebo group

- No statistical tests for the significance of these differences were presented by the company

Subgroup analyses

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

Results showed that:

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

Overall safety profile (ASaT)

Treatment phase

- The most commonly reported AEs (frequency comparable between the 2 treatment groups
  - graft-versus-host disease (GvHD), nausea, vomiting, diarrhoea, pyrexia and rash
  - no drug-related deaths in either treatment group.
  - cardiac disorder; hyperkalaemia; ear and labyrinth disorder; and dyspnoea more common on letermovir vs placebo
  - CMV infection: 8.3% letermovir vs. 45.8% placebo; -37.5% difference (95% CI: -45.1%, -30.0%)
  - SAEs reported were similar in both groups (44.2% letermovir vs. 46.9% placebo; diff -2.6%, 95%CI -11.3% - 6.0%)

AEs through to week 24 and week 48 post-transplant

- AE profile to wk48 similar for both groups, and consistent with wk 24
- Overall the AE results are difficult to interpret because of underlying disease and the toxicities associated with various PET regimens

ERG critique: Trial results (1)

Efficacy:

- Evidence on the effectiveness of letermovir is limited by the fixed maximum treatment duration of 100 days and lack of follow-up of clinically significant CMV infection beyond week 24

- A delay (median 9 days, ASaT; [redacted], FAS) in between HSCT and start of prophylaxis in trial potentially underestimates the efficacy of and treatment duration expected for letermovir prophylaxis in clinical practice

- Magnitude of all-cause mortality benefit from letermovir is uncertain because of limited follow-up duration and heterogeneous population; mortality benefit associated with avoiding CMV reactivation is not known
  - 48 week post-hoc analysis provides a more complete data set

- The decrease in all-cause mortality in the letermovir group with prior CMV infection does not indicate that letermovir completely prevents CMV reactivation - it suggest that letermovir prevents additional CMV-related mortality

ERG critique: Trial results (2)

HrQoL:

- Trial showed no significant treatment benefit on HRQoL; only a small possible utility benefit on GvHD, rehospitalisation, and opportunistic infections but these were not formally tested

Adverse effects

- AE results difficult to interpret because of the patients' underlying conditions and treatments and the toxicities associated with various PET regimens

Key clinical issues (1)

- Are the PN001 trial results generalisable to clinical practice?
  - What proportion of patients would be expected to have treatment beyond 100 days? (Mean duration 69.4 days in trial)
  - Is a delay in initiating prophylaxis post HSCT likely to occur? (Mean delay in trial of [redacted])
  - What proportion of patients would receive cyclosporin A (CsA)? (51.7% in trial)
  - What proportion of patients would receive alemtuzumab? (4% in trial)
- Should the Full Analysis Set (FAS; company base case) or the All Subjects as Treated (ASaT) be used to evaluate efficacy?

Key clinical issues (2)

- The FAS population excluded people with detectable CMV on day 1. In clinical practice, would people with detectable CMV DNA have letermovir prophylaxis?
- Patients with missing data or who prematurely discontinued from study had their treatments considered as ‘Failures’. Is this an appropriate way of handling missing data?
- Is there any mortality benefit from letermovir?
  - All-cause mortality benefit was not significant at week 48. The difference was 3.8%. Is this plausible after considering uncertainties and differences between trial and clinical practice?
  - Mortality benefit associated with avoiding CMV reactivation is uncertain but people who got a CMV infection in the letermovir arm had ~50% lower mortality rate than those in placebo

Public observer slides

Lead team presentation

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

1st Appraisal Committee meeting

Cost effectiveness

Committee D, 12 June 2017

Lead team: Malcolm Oswald, Bernard Khoo, Paula Parvulescu

Company: Merck Sharp & Dohme

Chair: Gary McVeigh

Evidence review group: CRD and CHE Technology Assessment Group

NICE team: Aimely Lee, Christian Griffiths, Helen Knight

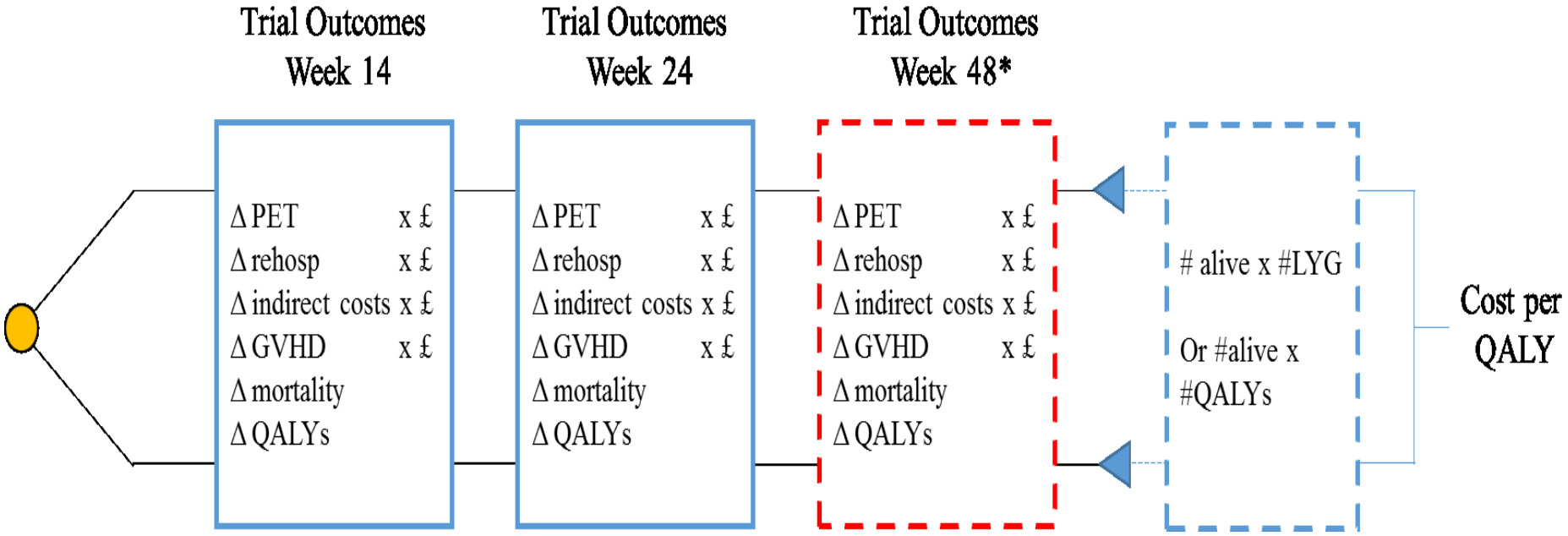
Key cost-effectiveness issues (1)

- In the company model, there are no health states to capture differences in QALYs in the 2 treatment groups and no link between the rate of CMV events and mortality. Is this approach appropriate?
- Are the clinical data used to populate the model appropriate?
  - 24 week data used instead of 48 week data
  - No imputation of missing data
- All-cause mortality differences are the primary drivers of QALY benefits and even decreasing it by 1% pushes the ICER over £30,000 per QALY gained
  - Company assumed the mortality rate in year 2 was equal to year 3. Is this plausible?
  - ERG modelled a survival benefit of 3.8% from letermovir – is this plausible after considering all uncertainties and differences between trial and clinical practice?

Key cost-effectiveness issues (2)

- Are the company's assumptions plausible?
  - 95% of patients to receive concomitant cyclosporin A (51% in the trial)
  - 95% of patients to receive IV letermovir (27% in the trial)
  - 25% of patients to receive foscarnet (ERG suggest 15%)
  - No administration costs for oral therapy
- Any significant health benefits not captured or equality issues to be taken into account?
- What is the most plausible ICER?

Company model
Two phases: Decision-tree and Markov model



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

- Lifetime analysis based on week 24 outcomes
- Markov model length: 1 year (with half cycle corrections)
- Utilities and costs discounted at 3.5%
- NHS and personal and social services (PSS) perspective

ERG critique: Structure of the model

- **Over simplified modelling approach → company model lacks explicit health states to capture differences in QALYs**
  - No link between the occurrence of CMV events and the accrual of QALYs or the rate of CMV events and mortality, which is the key driver of cost-effectiveness
  - Direct impact of a CMV event and other clinical events e.g. GvHD on QoL are therefore not fully explored in the model

- **A major cost category associated with having received a HSCT has been omitted**
  - Ongoing care and management costs
  - Costs associated with a relapse in the underlying condition

Modelling clinical outcomes (1): Decision-tree phase

- Mean duration of therapy was 69.4 days (ASaT population)
- Cumulative probabilities of 6 different clinical events from PN001 (week 24 DAO outcomes from FAS population) were included in the model

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

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

Modelling clinical outcomes (2): Markov model phase

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

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

HMRN = Haematological Malignancy Research Network

ERG critique: Clinical data inputs

- **Clinical inputs based on 24 week data instead of 48 week data**
  - Inappropriate and inadequately justified by the company
- **Data-as-observed approach used to account for missing data**
  - Incomplete follow ups are not adjusted
  - More complete data available following FDA request with just 3.2% patients lost to follow up vs. 13.5% in main analysis
- **Uncertainty in mortality benefits and data used to calculate standardised mortality ratio (SMR)**
  - All-cause mortality in year 2 assumed equal to year 3 – plausible?
    - HMRN reports 19% vs 2.7% in the company model for 2 years post-HSCT
  - Wingard data used to calculate SMR covers 1980 to 2003 and >40% of the data set are from paediatric population – relevant to current practice?
- **Considerable uncertainty in duration of letermovir prophylaxis**
  - Unlikely to be delays in starting letermovir in practice and plausible that some people require >100 days prophylaxis → ERG considers the FAS data (people with no CMV DNA on Day 1; mean 72 treatment days + [redacted] days treatment delay) to be most reflective of current practice

Assumptions used in the company model (base case)

95% concomitant CsA use
95% of people start with oral letermovir
Average duration of PET = 21 days
2 PCR tests per week applied to both arms of the model
Prescribing pattern of PETs: 37.5% ganciclovir, 37.5% valganciclovir and 25% foscarnet
CMV disease equal to the total cost of PET
RR of mortality at 2 years from Wingard et al (2011) is equal to the RR at 1 year
RR of mortality for CML, CLL etc, assumed = to severe aplastic anaemia
RR of mortality for myelofibrosis and PCM assumed equal to MDS
Opportunistic infections treated in the outpatient setting
Methylprednisolone IV administration for GvHD takes place in the outpatient setting
No administration costs for oral letermovir therapy

ERG critique: Costs and resource use assumptions

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

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

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

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

- Utility expected for survivors 1 year post-transplant was either 0.82 from an acute myeloid leukemia population who underwent a HSCT (Leunis et al., 2014 based on EQ-5D-5L) or the age-specific general population utility (Ara et al., 2011), whichever was lowest
- At clarification stage, company provided a scenario analysis where a long-term disutility following SCT (0.0114) was applied to the general population utilities
- Disutilities associated with AE were not included in the model – assumed to be captured in EQ-5D utility

ERG critique: Utilities

- **Company model does not fully capture the long-term utility decrement associated with people having undergone SCT:**
  - Utility values reported in Leunis et al is based on EQ-5D-5L instead of EQ-5D-3L (NICE's preferred measure)
  - The disutility applied in the company analysis (0.0114) is based on a mix of EQ-5D-5L and EQ-5D-3L values
    - The ERG considers this an inconsistent approach and is inconsistent with the value reported in Leunis et al. based on EQ-5D VA scores of 0.046
- **Disutilities associated with GvHD**
  - The ERG considers this should be included in the base-case analysis (only a scenario analysis was provided by the company)
- **ERG disagrees that disutilities associated with AEs are captured by the trial utility values**
  - Strong likelihood that disutility due to PET AEs have not been included because HRQoL data is not collected for patients when documented CMV viraemia leading to initiation of PET occurs

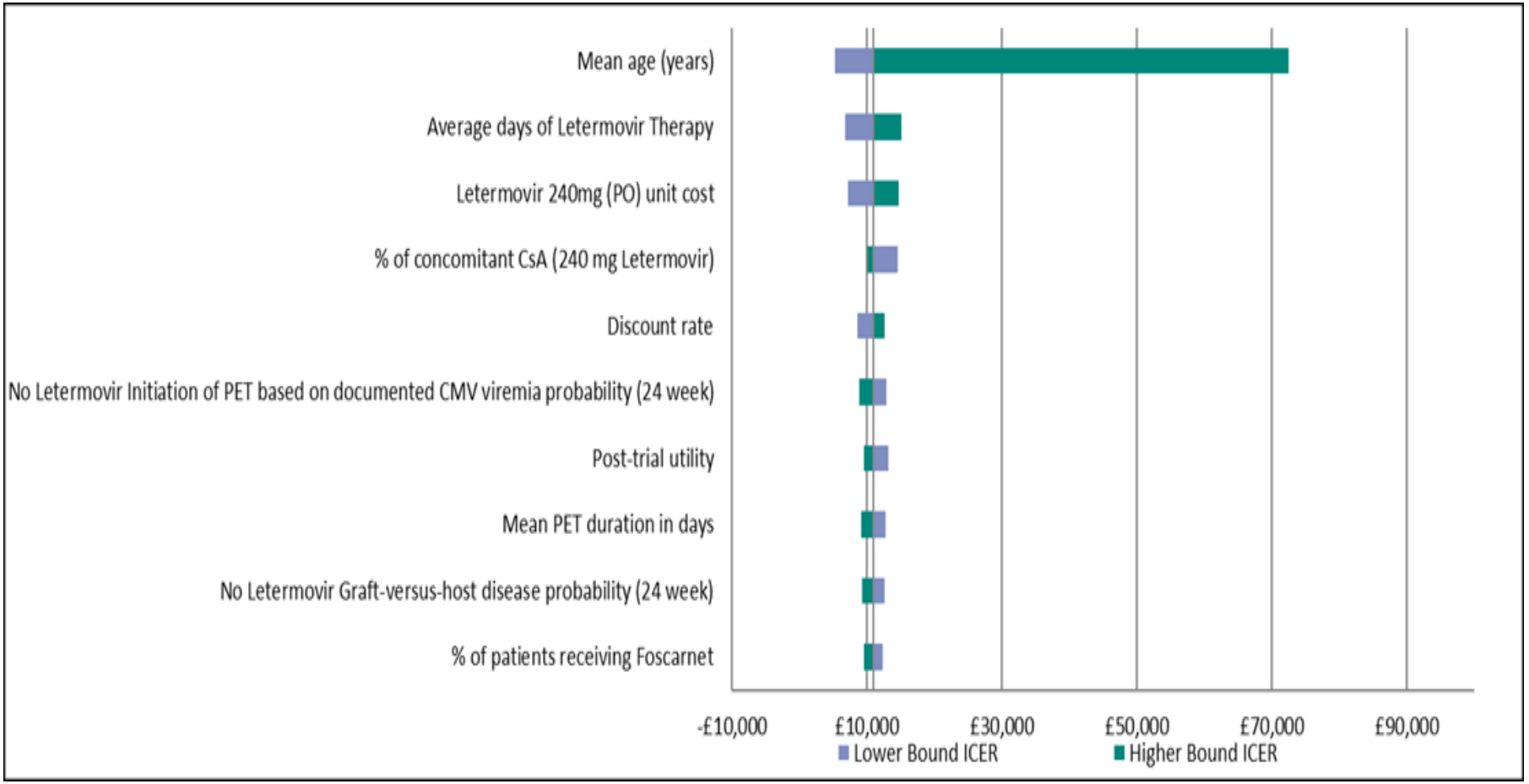
Company base case model results (with PAS)

Deterministic base case ICER

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

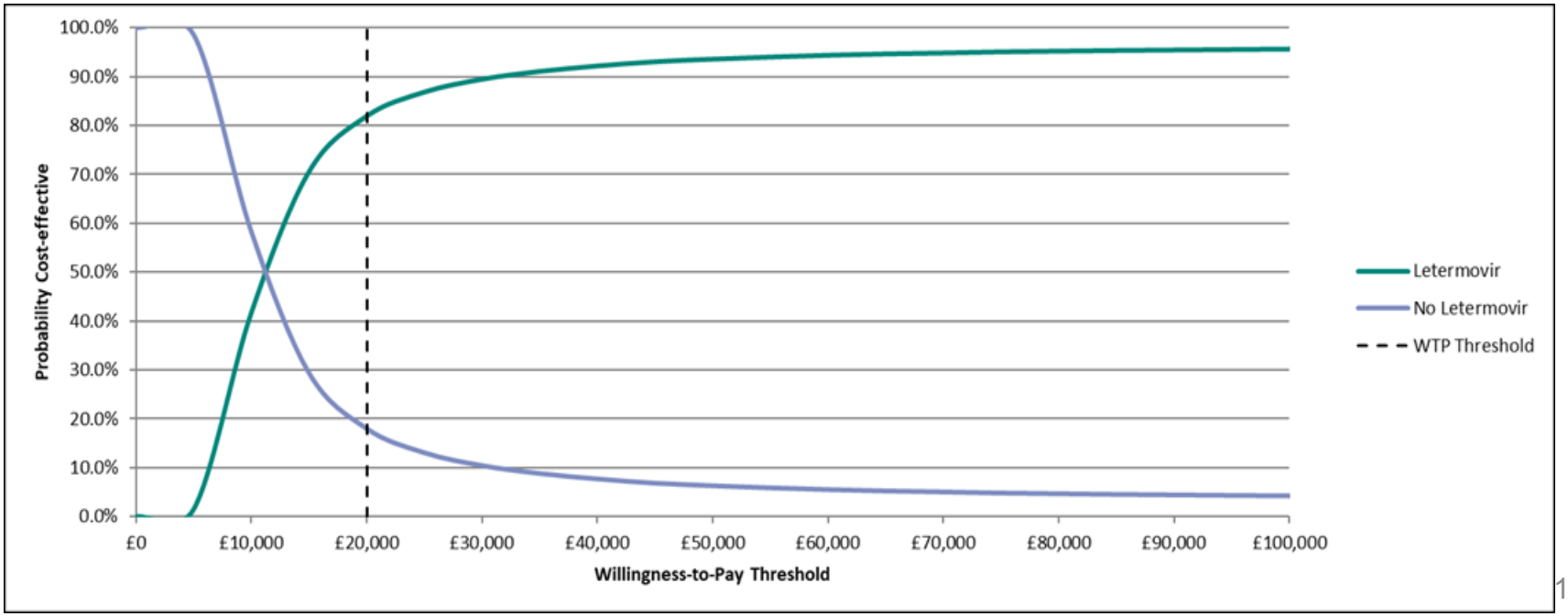
Deterministic sensitivity analyses

- Base-case ICER is most sensitive to the age parameter



Probabilistic sensitivity analyses (with PAS)

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



Company scenario analyses (with PAS) (1)

Model input	Parameter	ICER
Base case		**£10,904**
Average days of letermovir therapy	81	**£13,679**
Average days of letermovir therapy	100	**£18,226**
% of patients receiving oral letermovir therapy	73%	**£12,432**
% of patients receiving oral letermovir therapy	100%	**£10,556**
Average days of letermovir IV therapy	28	**£11,285**
% of patients receiving 240mg Letermovir	51.9%	**£17,471**
Average days of PET	59	**Letermovir dominant**
Beyond trial mortality in year 1 and 2 based on probability between week 24 and 48	11.5%	**£13,629***
cGvHD disutility	0.090	**£10,871**
% of concomitant CsA (240 mg letermovir) % of IV letermovir Average days of pre-emptive therapy	51.9% 27% 59	**£14,962**
Lifetime horizon based on week 24 data	At 5 years	**£21,723**
	At 20 years	**£11,132**
Lifetime horizon based on week 48 data	At 5 years	**£22,662**
	At 20 years	**£12,135**
	Lifetime	**£11,897**
Source: table 53-54 in company submission; *Model run based on week 48 data		

Company scenario analyses (with PAS) (2)

Scenarios/Model input	ICER
Base-case	**£10,904**
Long-term disutility (0.0114) post HSCT included	**£10,959**
Follow-up cost year 1 and 2 post SCT	**£12,322**
Relapse post SCT assuming 6 month, 1 or 2 year survival	**£11,041 – 11,387**
Additional costs and disutility included for acute and chronic GVHD	**£10,866**
All clinical inputs using DAO analysis and ASaT population	**£11,888**
All clinical inputs using DAO analysis and FAS population	**£11,966**
All clinical inputs using NC=F approach for missing data	**£12,204**
Using 48 week clinical data – DAO_ASaT population	**£11,168**
Using 48 week clinical data – DAO_FAS population	**£13,069**
Using revised mortality data elicited by the FDA – DAO_ASaT population	**£10,687**
Using revised mortality data elicited by the FDA – DAO_FAS population	**£15,071**

Source: table 37-39, 41-44 in the company clarification response; table 42 in the ERG report

ERG exploratory analyses

ERG alternative base case: Summary of changes

The following amendments were made to the company's base case:

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

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

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

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

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

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

Scenario analysis on the ERG's preferred base case

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

1. **Duration of therapy**
   - 45% of patients receiving letermovir prophylaxis at 100 days were assumed to continue therapy for a fixed period 2, 4 and 6 weeks post 100 days
2. **Alternative approaches to handling missing data**
   - Non Completer =Failure
   - Missing-not-at random (MNAR)
3. **Mortality at 48 weeks**
   - Alternative values for the mortality benefit associated with letermovir were considered

Results of ERG scenario analyses (with PAS)

Scenario	ICER (£/QALY)
ERG preferred base-case analysis	**27,536**
Assumed maximum duration of therapy	
100 days + 2 wks	**29,776**
100 days + 4 wks	**31,909**
100 days + 6 wks	**34,255**
Approach for handling missing data	
failure (Non Completer =F)	**30,179**
standard care arm (Missing-not-at-random)	**30,567**
Mortality difference	
+2.8%	**34,471**
+3.3%	**30,570**
+4.3%	**25,110**
+4.8%	**23,124**

Source: tables 51-53 in the ERG report

Key cost-effectiveness issues (1)

- In the company model, there are no health states to capture differences in QALYs in the two treatment groups and no link between the rate of CMV events and mortality. Is the company's modelling approach appropriate?
- Are the clinical data used to populate the model appropriate?
  - 24 week data used instead of 48 week data
  - No imputation of missing data
- All-cause mortality differences are the primary drivers of QALY benefits and even decreasing it by 1% pushes the ICER over £30,000 per QALY
  - Company assumed that mortality rate in year 2 was equal to year 3. Is this plausible?
  - ERG modelled a survival benefit of 3.8% from letermovir – is this plausible after considering all uncertainties and differences between trial and clinical practice?

Key cost-effectiveness issues (2)

- Are the company's assumptions plausible?
  - 95% of patients to receive concomitant cyclosporin A (51% in the trial)
  - 5% of patients to receive IV letermovir (27% in the trial)
  - 25% of patients to receive foscarnet (ERG suggest 15%)
  - No administration costs for oral therapy
- Any significant health benefits not captured or equality issues to be taken into account?
- What is the most plausible ICER?