Maribavir for treating refractory or resistant cytomegalovirus infection after transplant

Part 1 Slides for public observers – No confidential information

Technology appraisal committee D [02 November 2022]

Chair: Stephen Smith

Evidence assessment group: BMJ-TAG

Technical team: Janet Boadu, Michelle Green, Linda Landells

Company: Takeda

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Recap from ACM1

Not recommended, within its anticipated marketing authorisation for treating CMV infection that is refractory or resistant to treatment including ganciclovir, valganciclovir, cidofovir or foscarnet in adults who have had a HSCT or SOT as ICERs above the range considered cost-effective	
Equalities issues	None identified
Innovation	All benefits captured by the model
Outstanding uncertainties	The following sources of uncertainty were identified by the committee: • Uncertainty around the main clinical evidence because of the way the trial was done • Uncertainty in the assumptions for mortality in the stage 1 model • Other issues with the assumptions made in the model were identified (section 3.16 of the ACD) but these have been addressed by the company

Committee concluded there was uncertainty about the main clinical evidence and the most likely cost-effectiveness estimates are above the range that NICE considers an acceptable use of NHS resources

Abbreviations: ACD, appraisal consultation document; CMV, cytomegalovirus; HSCT haematopoietic stem cell transplant; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year; SOT, solid organ transplant

Maribavir (Livtencity, Takeda)

Table 1 Technology details

Marketing authorisation*	• CHMP positive opinion was granted on 15th September 2022 • "Maribavir is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT)" • EMA and MHRA approval expected in November 2022
Mechanism of action	• Maribavir attaches to the UL97 encoded kinase stopping phosphotransferase and making it less susceptible to mutations of the viral DNA polymerase and enabling activity against strains with viral DNA polymerase mutations
Administration	• Oral administration • 400 mg twice a day, (200 mg x 2 tablets in the morning and 200 mg x 2 in the evening) with or without food for 8 weeks
Price	• List price per 56 x 200 mg pack: [redacted]; List price per 8-week cycle: [redacted] • Company has proposed a simple PAS discount (increased during ACD consultation)

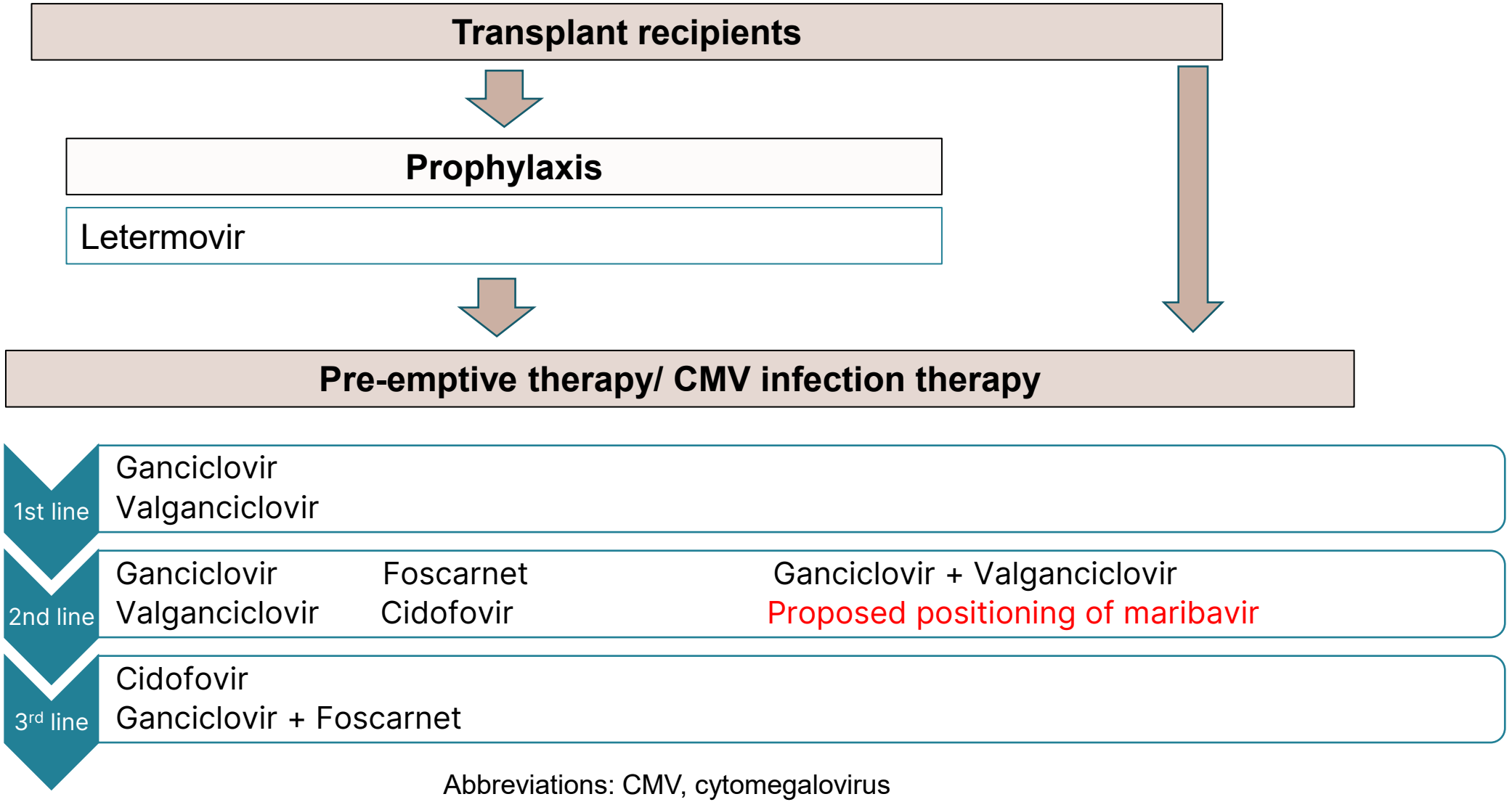
Abbreviations: CHMP, Committee for Medicinal Products for Human Use; CMV, cytomegalovirus; EMA, European Medicines Agency; MHRA, Medicines and Healthcare Products Regulatory Authority; PAS, patient access scheme

* Marketing Authorisation as expected at time of committee meeting

Treatment pathway

Positioning of maribavir for haematopoietic stem cell transplants

Figure 1: Treatment pathway for the population having haematopoietic stem cell transplants

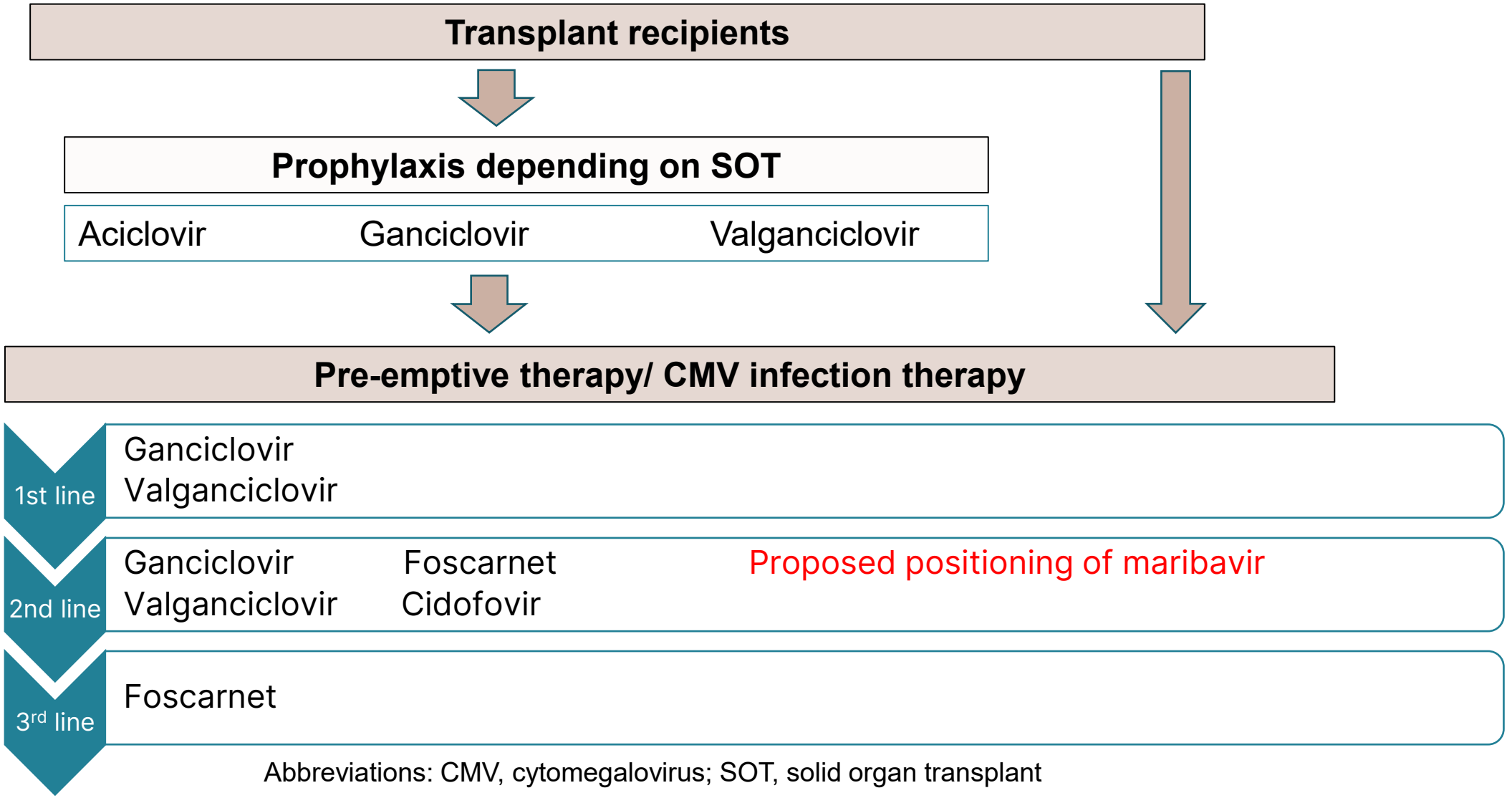


Abbreviations: CMV, cytomegalovirus

Treatment pathway

Positioning of maribavir for solid organ transplants

Figure 2: Treatment pathway for the population having solid organ transplants



Abbreviations: CMV, cytomegalovirus; SOT, solid organ transplant

Key issues from ACM1

Table 2 Key issues

Issue	Resolved?	ICER impact
Imbalance in time since transplant in clinical trial	Partially resolved - difficult to resolve	Unknown
Trial conduct leading to uncertainty	Partially resolved - difficult to resolve	Unknown
Use of OTUS data	Partially resolved - for discussion	Small
Structural assumptions and overestimate of recurrences in model	Resolved (in company revised base case)	
Estimation of costs		
Modelling of mortality in Stage 1 Markov	Company base case assumptions differ from committee conclusions at ACM1	Large
Assumption of time since transplant in the model	Resolved (in company revised base case)	
Modelling of disease complications	Partially resolved - for discussion	Small
Modelling of graft failure	Resolved (in company revised base case)	
Modelling of utilities		
Modelling of mortality in Stage 2 Markov model		

Clinical effectiveness recap

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Key clinical trial

ACD section 3.2 "[*The committee] concluded that some aspects of the conduct and design of SOLSTICE could bias the results*"

RECAP

Table 3 Clinical trial design and outcomes

	SOLSTICE (TAK-620-303)
Design	Phase 3 multicentre, randomised, open-label, active-controlled study
Population	Post-transplant CMV infection and disease in patients with CMV resistant/refractory* to ganciclovir, valganciclovir, cidofovir or foscarnet
Intervention	Maribavir 400 mg (2× 200 mg oral tablets) BID for 8 weeks
Comparator(s)	IAT (ganciclovir [IV], valganciclovir [oral], foscarnet [IV], or cidofovir [IV]) Choice at investigators' discretion (mono or combination therapy ≤2 drugs) with any IAT
Primary outcome	CMV viraemia clearance at week 8, based on full trial population
Key secondary outcomes	CMV viraemia clearance and CMV infection symptom control at Week 8 with benefit maintained through to Week 16
Locations	Canada, US, UK, Belgium, Germany, Denmark, Spain, France, Croatia, Italy, Singapore, Australia
Used in model?	SOLSTICE was the primary source of clinical evidence used to derive relative efficacy in model

Abbreviations: BID, twice daily; CMV, cytomegalovirus; IAT, Investigator assigned anti-CMV treatment; IV, intravenous

*Refractory defined as documented failure to achieve >1 log10 decrease in CMV DNA level in whole blood or plasma after treatment of 14 days or more with IV ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir

SOLSTICE baseline characteristics

Table 4 Baseline characteristics for intervention and comparator

Characteristic	IAT (N=117)	Maribavir 400 mg BID (N=235)
Age (years), median (range)	54.0 (19, 77)	57.0 (19, 79)
Male sex, n (%)	65 (55.6)	148 (63.0)
SOT, n (%)	69 (59.0)	142 (60.4)
Patients with or without CMV mutations known to confer resistance to ganciclovir, foscarnet, and/or cidofovir, n (%)		
Refractory CMV infection with resistance	69 (59.0)	121 (51.5)
Refractory CMV infection without resistance	34 (29.1)	96 (40.9)
Missing resistance results	14 (12.0)	18 (7.7)
Time since transplant		
HSCT Mean, days (SD)	[redacted]	[redacted]
HSCT Median, days	[redacted]	[redacted]
SOT Mean, days (SD)	[redacted]	[redacted]
SOT Median, days	[redacted]	[redacted]

ACD section 3.3 "*the length of time since transplant at randomisation in the SOT subgroup and the imbalance between treatment arms in the HSCT population would likely have a large impact on the generalisability of the SOLSTICE results to clinical practice*"

NICE Abbreviations: CMV, cytomegalovirus; IAT, investigator assigned treatment; SOT, solid organ transplant; HSCT haematopoietic stem cell transplant

SOLSTICE results – CMV clearance

ACD section 3.4 "*[the committee] concluded that that SOLSTICE suggests an advantage for maribavir achieving clearance. But because of uncertainties in the SOLSTICE data, it could not be sure that the data was robust enough to confirm the size of this benefit*"

Table 5: CMV clearance at 4, 8 and 20 weeks

	IAT (n=117)		Maribavir (n=235)				
	n/N	%	n/N	%	Adjusted[$] Diff. % (95% CI)	Unadjusted Diff. % (95% CI)	p
Clearance at 4 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clearance at 8 weeks (primary outcome)	28/117	23.9	131/235	55.7	32.8 (22.8 to 42.7)	[redacted]*	<0.001
Clearance at 8 weeks based on no clearance at 4 weeks	[redacted]	[redacted]	[redacted]	[redacted]	NR	[redacted]	NR
Clearance at 20 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[$]adjusted for the stratification factors transplant type (SOT vs. HSCT) and baseline plasma CMV DNA viral load (low vs. pooled intermediate/high), *Unadjusted difference in proportion (maribavir – IAT) and the corresponding 95% CI is computed by the normal approximation method by the company.**Unadjusted difference in proportion (maribavir – IAT) calculated by the ERG.

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; Diff, difference; IAT, Investigator-assigned anti-CMV treatment; NR, not reported

SOLSTICE results – mortality

ACD section 3.10 "*[the committee] recognised there was a lot of uncertainty in the assumptions for mortality in the stage 1 model, but that SOLSTICE had not shown a survival benefit. It considered that mortality should not differ for people based on treatment, so there should be no life year gain with maribavir in the model. It concluded that risk of mortality in the stage 1 model should be the same for the maribavir and IAT groups.*"

Table 6: Mortality by treatment group

	IAT n= 117		Maribavir n=235			
	n/N	%	n/N	%	HR (95% CI)	P value
Mortality at week 8	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
All-cause Mortality at week 20*$	13/117	11.1	27/235	11.5	[redacted]	[redacted]
Mortality at week 20	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Mortality at week 20 in HSCT patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Mortality at week 20 in SOT patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR

Unadjusted difference in proportion (maribavir – IAT), calculated by the company
*All-cause mortality included all deaths reported regardless of receipt of anti-CMV treatment or rescue therapy
$ Included 4 people who died after 20 weeks but were followed up due to ongoing serious adverse events
** This value is likely to be incorrect, but corrected value not provided by company

Abbreviations: CI, confidence interval; IAT, Investigator-assigned anti-CMV treatment; HR, hazard ratio; NR, not reported; HSCT, haematopoietic stem cell transplant; SOT, solid organ transplant

Cost effectiveness recap

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Company's model overview

Company's base case model structure

Stage 1 Markov model (at ACM1) (3 state) covers 78 week period
Includes tunnel states to estimate transitions between CS-CMV and the non CS-CMV states:

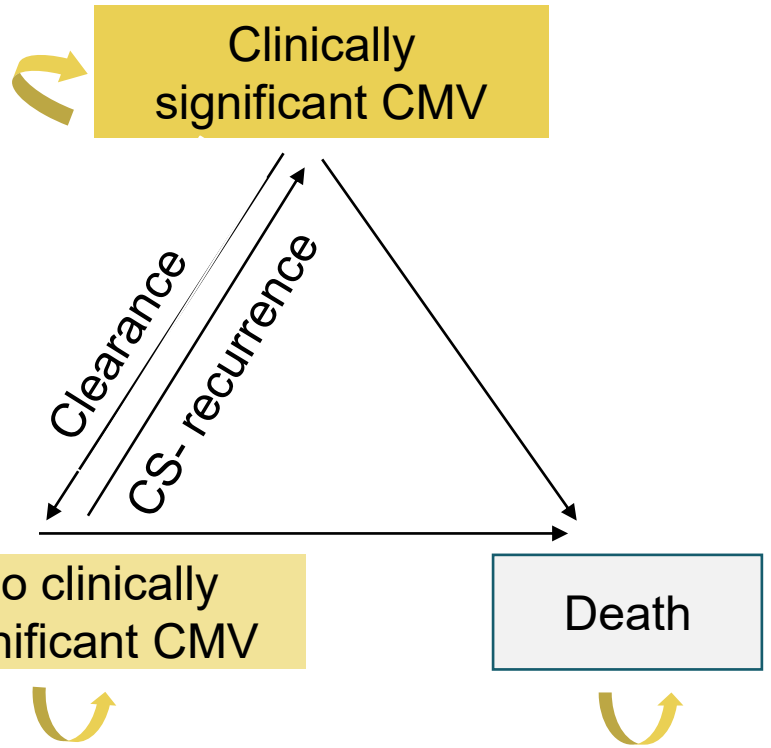
- probability of remaining in the first clearance state for the initial 12 weeks - SOLSTICE data
- probability of remaining in the clearance state 12 weeks after initial clearance in the model - OTUS data
- After 2nd+ recurrence/clearance probability of remaining in clearance beyond 4 weeks – OTUS data

Stage 2 Markov model (2 state) include alive or dead from 78 weeks for rest of lifetime

Updated model post ACM1

- Stage 1 covered 78 weeks, now covers 39.2 weeks
- Maximum of 2 CMV recurrences
- Stage 1 uses OTUS data, with relative treatment effect of maribavir from SOLSTICE

Figure 3 Model structure (stage 1)*



ACD section 3.5 "*[the committee] concluded that the overall model structure and health states used by the company in both stages of the model were appropriate, but that it had some concerns about the duration of stage 1 of the model* "

*Tunnel states were included in the model
Abbreviations: CS, clinically significant; CMV, cytomegalovirus

Response to consultation

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ACD consultation responses (1)

Consultation comments

Comments received from:

- Company (Takeda UK Ltd)
- British Transplantation Society
- UK Renal Pharmacy Group
- Anthony Nolan
- No web comments

Key themes (excluding modelling assumptions updated by company) have been summarised over the next 2 slides

An effective oral agent (ACD Section 3.1)

- Maribavir is preferable to treatments that require both hospitalization and IV administration

Benefits not captured by QALYs (ACD Section 3.18)

- The physical, psychological and economic impact on quality of life due to treatment of CMV for people who have experienced refractory or resistant CMV infection post-stem cell transplant not fully recognised

Abbreviations: ACD, appraisal consultation document; CMV, cytomegalovirus

ACD consultation responses (2)

Maribavir, after foscarnet treatment failure or early cessation, is only viable alternative treatment option for renal patients (ACD Section 3.1)

- Foscarnet is nephrotoxic and is very poorly tolerated in renal transplant patients or immunocompromised patients with renal dysfunction in clinical practice
- Cidofovir for many renal patients is contra-indicated and not a treatment option

Inclusion of disease complications (ACD Section 3.12)

- Agree with the committee to include disease complications in the modelling to consider transplant graft loss as a consequence of CMV treatment from foscarnet

Lower toxicity of maribavir than other CMV treatments (ACD Section 3.1)

- Ganciclovir and valganciclovir are marrow toxic and can cause cytopenia and neutropenia and may increase other autoimmune issues including GvHD

SOLSTICE shows that maribavir improved clearance compared with IAT (ACD Section 3.4)

- Uncertainties the committee identified represent the reality of clinical practice
- The highly significant advantage of maribavir over alternative therapies has been demonstrated in a patient group comparable to those managed in transplant units around the UK

Are any updates to the guidance needed based on these comments?

Abbreviations: ACD, appraisal consultation document; CMV, cytomegalovirus; GvHD, graft versus host disease

Committee preferred assumptions and ACD responses (1)

Table 7 Committee preferred assumptions and company responses to these

ACD Conclusion	Change to ACM1 base case?	Updated information or analyses
Maribavir price too high to be cost-effective	**Yes**	Update in PAS
Data source in the stage 1 Markov model	**Partial**	• Used OTUS to populate the stage 1 Markov model, with SOLSTICE for relative treatment effect of maribavir • Removed adjustment of OTUS data for mortality at 8 weeks • Clearance rates from OTUS based on SOT patients only. No HSCT data provided • Mortality data from week 20 to 39 in OTUS not used and assume value from week 20 applies to week 39
Risk of recurrence	**Yes**	Risk of recurrence treatment independent (same values used in both the maribavir and IAT arms of the model)
Modelling of CMV recurrence	**Yes**	• Restricted stage 1 Markov model to 39.2 weeks and 2 CMV recurrences in absence of robust data • No additional scenarios provided by company

Abbreviations: CMV, cytomegalovirus; IAT, Investigator-assigned anti-CMV treatment

Committee preferred assumptions and conclusions (2)

Table 7 (continued) Committee preferred assumptions and conclusions from the first meeting

Key themes in ACD response	Change to ACM1 base case?	Updated information or analyses
Modelling of survival	**No**	Maintained a mortality benefit for maribavir in the stage 1 Markov
Time since transplant at entry to the model	**Yes**	Used mean time since transplant at model entry
Modelling of disease complications	**Partial**	Included disease complications in the model to model recurrences of leukaemia, GvHD and graft failure
Subsequent IV IAT administration costs	**Yes**	Subsequent IV administration cost cheaper than first administration for IAT treatments (NHS reference costs)
Hospitalisation costs	**Yes**	Used higher hospitalisation costs for people with clinically significant CMV than people hospitalised without clinically significant CMV

Abbreviations: CMV, cytomegalovirus; GvHD, graft versus host disease; IAT, Investigator-assigned anti-CMV treatment; IV, intravenous

Unresolved: Modelling of mortality in stage 1 Markov (1/3)

Background (at ACM1)

- Company used SOLSTICE data to model different survival based on CMV presence
- ERG noted adjusted 95% CIs suggest no statistically significant difference of survival in treatment arms and could not validate use of adjusted survival data as company had not provided additional information on choice of method to adjust for crossover

ACD: committee considered mortality should not differ for people based on treatment, so there should be no life year gain with maribavir in the model. Committee concluded that risk of mortality in the stage 1 model should be the same for maribavir and IAT groups

Figure 4 Kaplan Meier plot of OS by clearance status at week 8

Company response to ACD

- Disagree with committee that there should be no life year gain in the model and maintain previous view
- Maintain SOLSTICE provides clear evidence of a difference in survival associated with response to CMV treatment
- Plot shows statically significant difference in hazard rate of death between CMV clearance at week 8 (in either treatment group) compared with no CMV clearance

Abbreviations: CMV, cytomegalovirus; CI, confidence interval; IAT, investigator assigned anti-CMV treatment

Unresolved: Modelling of mortality in stage 1 Markov (2/3)

Company response to ACD

- 12-month extension study: TAK620-5004 (retrospective study among transplant recipients from maribavir arm in SOLSTICE), primary objective was all-cause mortality at 12 months and median overall survival, (overall population, HSCT and SOT cohorts)
- Final analysis: [redacted] patients ([redacted] ([redacted]%) SOT; [redacted] ([redacted]%) HSCT); overall mortality [redacted]% at 12 months

Figure 5 1-year mortality estimates and CIs

Abbreviations: CI, confidence interval; HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant

Unresolved: Modelling of mortality in stage 1 Markov (3/3)

Table 8 Probability of all-cause mortality in ERG's scenarios

	Company's base case		No benefit assumed (mortality data pooled from OTUS)		CMV patients assumed to have twice the probability of death as nCMV patients	
Input	SOT	HSCT	SOT	HSCT	SOT	HSCT
nCMV (weeks 8 to 20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CMV (weeks 8 to 20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nCMV (week 20 onwards)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CMV (week 20 onwards)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG comments:

- Disagree with company's implementation of mortality in model:
  - Company didn't provide analysis looking at significance of CMV vs nCMV mortality data from OTUS
    Company didn't clarify if KM data from OTUS used in analysis only included patients without CMV
- ERG produced a scenario analysis as per the committee's preferred view of no survival associated with nCMV and note the model key driver is the assumption of a mortality benefit associated with nCMV (Table 8)
- Maintains view that assuming a survival benefit for nCMV is a more clinically plausible approach

Is the survival benefit being modelled plausible?

NICE Abbreviations: CMV, cytomegalovirus; nCMV; no cytomegalovirus; HSCT, hematopoietic stem cell transplant; KM, Kaplan Meier; SOT, solid organ transplant

Partially resolved: Use of OTUS data

Model updated using OTUS, with maribavir relative effect from SOLSTICE

SUPERSEEDED

Background (at ACM1)

- Company used OTUS to model subsequent CMV events after 1st events modelled from SOLSTICE
- ERG preferred model based on OTUS with maribavir relative treatment effect from SOLSTICE

ACM: committee concluded using OTUS data as far as possible with relative treatment effect of maribavir from SOLSTICE is more robust for modelling outcomes in the state Markov model, and data from OTUS should not be adjusted for mortality at 8 weeks

Company response to ACD

- Acknowledge committee's concerns and incorporate OTUS data in revised analyses
- But note uncertainty of integrating 2 data sources in model. Maintain SOLSTICE is most reliable to estimate treatment effect of maribavir vs standard care

ERG comments

- Company approach not fully in line with committee's preferences
- Company don't use mortality data from week 20 to 39 from OTUS and assume value from week 20 applies
- Company's [redacted] estimate for probability of clearance does not include HSCT patients and likely underestimates clearances for HSCT population in both arms (ERG scenario shows limited impact on ICER)
- Company haven't provided source of data containing the [redacted] clearance events for the SOT population

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Has the OTUS data been used appropriately?

Abbreviations: CMV, cytomegalovirus; HSCT, haematopoietic stem cell transplant

Partially resolved: Modelling of disease complications (1/2)

Company provided analyses including disease complications in the model aligned with committee preference

Background (at ACM1)

- Company base case didn't include leukaemia recurrences or GvHD events, provided scenario including GvHD
- ERG updated model to include recurrence costs for 6 months and leukaemia relapse-related mortality
- ERG preferred inclusion of GvHD and included the company's scenario in its base case

ACM: committee concluded that disease complications should be included in the model, and accepted the ERG's approach to modelling recurrences of leukaemia, GvHD and graft failure

Company response to ACD

- Leukaemia: incorporated leukaemia recurrences into revised analyses
- GvHD: Accepts committee preference and amended scenario to account for TST
  - Updated scenario estimates probabilities based on KM plot from Hahn et al (2008) from around time of mean TST from OTUS of [redacted] days for HSCT; at this time point approx. 25% of patients having GvHD at day 40 and 30% at day 100 (latest follow-up point)
  - Calculated 4-week probability of 3.2% using the two time points

NICE Abbreviations: CMV, cytomegalovirus; GvHD, graft versus host disease; HSCT, haematopoietic stem cell transplant; KM, Kaplan Meier; TST, time since transplant

Partially resolved: Modelling of disease complications (2/2)

Company provided analyses including disease complications in the model aligned with committee preference

ERG comments

- Agrees that the company's approach is in line with the committee's preference for leukaemia recurrence and graft failure
- Disagrees with company's estimation of the probability of GvHD:
  - Inappropriate for company to apply the Cantoni et al. HR, to estimate the proportion of patients with GvHD without CMV, as baseline estimate of GvHD included patients with and without CMV
- The company didn't include impact of GvHD on survival as requested by the committee which would increase the ICER

Table 9 4-weekly probability of GvHD

	4-weekly probability of GvHD	
	CMV	nCMV
Company base case and ERG scenario	6.8%	3.2%
ERG scenario (from Cantoni)	7.5%	7.5%

Is GvHD modelled appropriately?

NICE Abbreviations: CMV, cytomegalovirus; GvHD, graft versus host disease; HSCT, haematopoietic stem cell transplant; HR, hazard ratio; KM, kaplan meier; nCMV, no cytomegalovirus; TST, time since transplant

Summary of base case assumptions (1)

The company and ERG base case assumptions are aligned and consistent with committee preferences

Table 10 Committee preferred assumptions and company and ERG base cases

Assumption	Committee preference	Company aligned with committee?	ERG aligned with committee?
Model outcomes in the stage 1 Markov model	• OTUS data used to populate stage 1 Markov model, with SOLSTICE data used to determine relative treatment effect of maribavir • OTUS data not adjusted for mortality at 8 weeks	Yes (but ERG didn't see HSCT data)	Yes (but ERG didn't see HSCT data)
Risk of recurrence	Treatment independent	Yes	Yes
Modelling of CMV recurrence	Stage 1 Markov model restricted to 39.2 weeks and 2 CMV recurrences with longer duration and additional recurrences considered	Yes (but no scenarios with longer stage 1 model provided)	Yes (but no scenarios with longer stage 1 model provided)
Modelling of survival	Risk of mortality in stage 1 model the same for the maribavir and IAT groups	No	No

Abbreviations: CMV, cytomegalovirus; HSCT, haematopoietic stem cell transplant

Summary of base case assumptions (2)

The company and ERG base case assumptions are aligned and consistent with committee preferences

Table 10 (continued) Committee preferred assumptions and company and ERG base cases

Assumption	Committee preference	Company base case	ERG base case
Time since transplant at entry to the model	Mean TST at model entry	Yes	Yes
Modelling of disease complications	Included in model using ERG's approach to model recurrences of leukaemia, GvHD and graft failure	Yes (but ERG can't validate GvHD fully as company did not address GvHD mortality)	Yes (but ERG can't validate GvHD fully, but present scenarios without GvHD mortality)
Subsequent IV IAT administration costs	Subsequent IV administration of IAT treatments incurs lower NHS reference cost than 1st administration	Yes	Yes
Hospitalisation costs	Costs for people with CS-CMV higher for people with non CS-CMV	Yes	Yes

Abbreviations: CMV, cytomegalovirus; CS, clinically significant; GvHD, graft versus host disease; IAT, investigator-assigned anti-CMV treatment; IV, intravenous; TST, time since transplant

Cost effectiveness results – overview

- Cost-effectiveness results will be presented in part 2 because of confidential comparator discounts.

Table 11 Company and ERG modelling assumptions

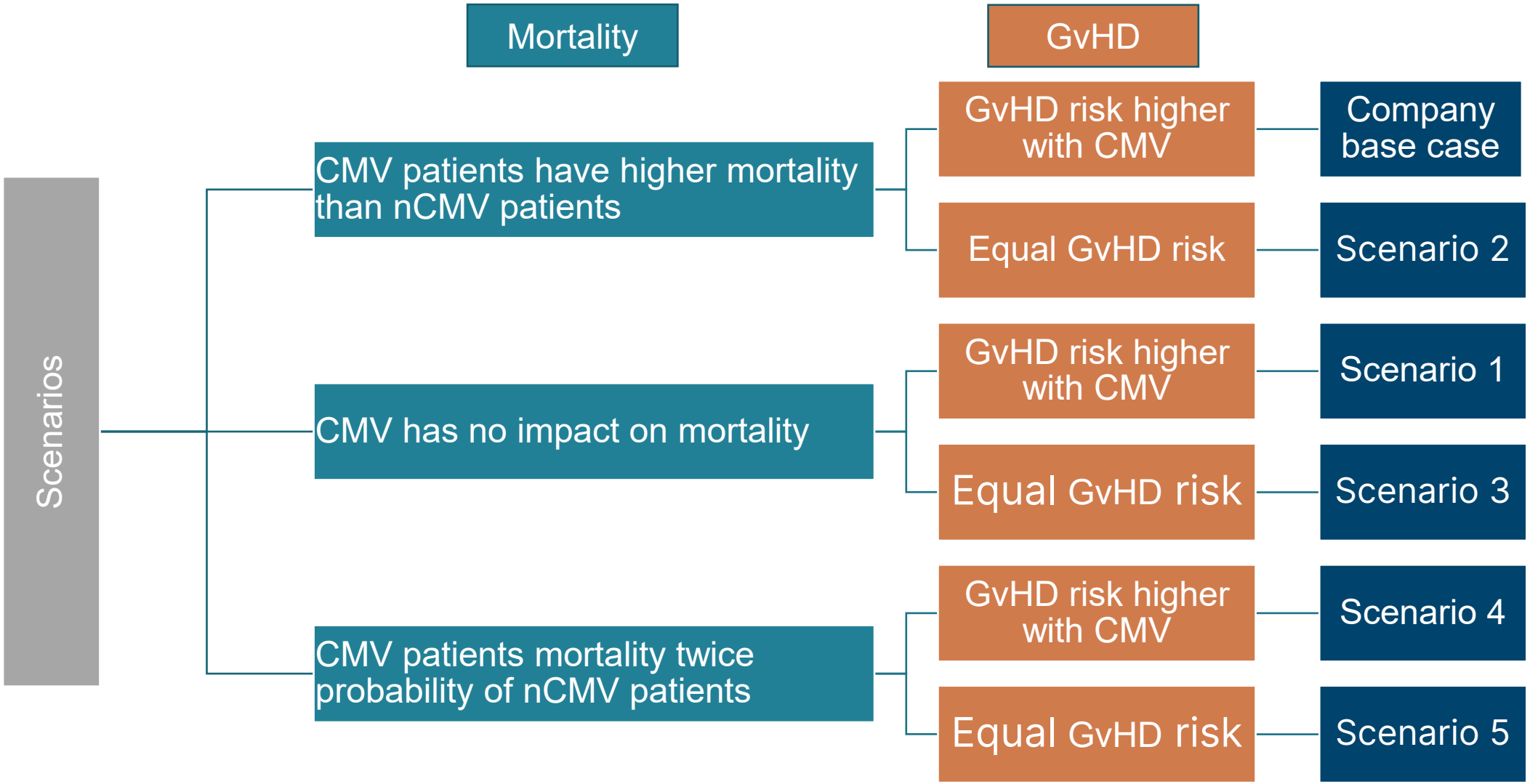
Assumption	Company base case at ACM2	ERG scenarios
Data in stage 1 Markov model	OTUS data with treatment effect from SOLSTICE	
Risk of CMV recurrence	Treatment independent	
CMV recurrence model structure	Stage 1 = 39.2 weeks and maximum of 2 CMV recurrences	
Modelling of survival	Survival dependent on CMV status	Survival dependent on CMV status CMV has no impact on mortality CMV doubles risk of death
TST at model entry	Mean TST used	
Disease complications (GvHD)	Assume CMV increases the probability of GvHD	CMV increases the probability of GvHD CMV doesn't increase the probability of GvHD
Subsequent IV IAT administration costs	IAT subsequent IV administration lower cost than 1st administration	
Hospitalisation costs	Costs for people with CS-CMV higher for people with non CS-CMV	

- Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be around £20,000 per QALY gained (ACD, section 3.16)

Abbreviations: CMV, cytomegalovirus; CS, clinically significant; GvHD, graft versus host disease; IAT, investigator-assigned anti-CMV treatment; IV, intravenous; ICER, incremental-cost effectiveness ratio; QALY, quality-adjusted life year; TST, time since transplant

Committee decision points

Figure 6 Decision tree for company and ERG scenarios



ERG provided a scenario with alternative CMV clearance rate in HSCT population, but impact on ICER is limited

Abbreviations: CMV, cytomegalovirus, nCMV, non cytomegalovirus; GvHD, graft versus host disease; HSCT, haematopoietic stem cell transplant

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SOLSTICE results – CMV recurrence

More people in maribavir arm had confirmed CMV viraemia recurrence compared with IAT although statistical significance was not reported

Table 12: Recurrence of CMV viraemia at week 8 and 20

	IAT n= 117		Maribavir n=235			
	n/N	%	n/N	%	Unadjusted Diff. % *	P value
Recurrence in first 8 weeks	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Recurrence in follow-up period (week 8 to week 20)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Recurrence any time on study	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Clinically relevant recurrence** at week 20 among responders at week 8	[redacted]	35.7	[redacted]	26.0	[redacted]	[redacted]

*Unadjusted difference in proportion (maribavir – IAT), calculated by the company
** defined as recurrence among responders after week 8 that had alternative anti-CMV treatment

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; Diff, difference; IAT, Investigator-assigned anti-CMV treatment; NR, not reported

SOLSTICE results – key subgroup analyses used in model

Table 13: Endpoints by transplant type

Endpoint	IAT	Maribavir	
Confirmed CMV viraemia clearance at week 8, n (%)[a]			**Adjusted difference in proportion (95% CI); p-value**
HSCT	10 (20.8)	52 (55.9)	36.1 (21.1 to 51.2); [redacted]
SOT	18 (26.1)	79 (55.6)	30.5 (17.3 to 43.6); [redacted]
ITT population	(23.9)	(55.7)	32.8 (22.8 to 42.7); <0.001
Number of patients who died, n (%)[b]			**HR (95% CI)**
HSCT	[redacted]	[redacted]	[redacted]
SOT	[redacted]	[redacted]	[redacted]
ITT population	13 (11.1)	27 (11.5)	[redacted]

Percentages are based on the number of patients in the Randomised Set [a] Analysis was pre-specified [b] Post hoc analysis

*This value is likely to be incorrect, but corrected value not provided by company

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Abbreviations: CI, confidence interval; IAT, Investigator-assigned anti-CMV treatment; ITT, intention to treat; HR, hazard ratio; HSCT, haematopoietic stem cell transplant; SOT, solid organ transplant

Resolved: Risk of recurrence

Company updated base case aligned with committee preference that risk of recurrence should be treatment independent

Background (at ACM1)

- Company originally modelled different risks of CMV recurrence dependent on the treatment received
- ERG noted risk of CMV recurrence should depend on time spent in clearance rather than treatment received, and included this in updated model

ACD: committee concluded that the risk of recurrence should not be treatment specific, and risk of recurrence should be treatment independent (same values should be used in both the maribavir and IAT arms of the model)

Company response to ACD

- Accept the committee's preference in the absence of direct supporting evidence within SOLTSTICE
- Applied treatment independent recurrence probabilities despite believing evidence of an effect

ERG comments

- Agrees that the company's approach is in line with the committee's preference

NICE

Abbreviations: CMV, cytomegalovirus; IAT, investigator assigned anti-CMV treatment

Resolved: Duration of stage 1 Markov model and recurrences

Company updated base case aligned with committee preference to restrict stage 1 Markov model to 39.2 weeks and 2 CMV recurrences

Background (at ACM1)

- Company originally used 20-week data from SOLSTICE to model CMV recurrences up to 52 weeks (stage 1 Markov model had a duration of 52 weeks). Based on the OTUS data the company increased the duration of the stage 1 model to 78 weeks
- ERG modelled 1st and 2nd recurrence only with duration of stage 1 model reflecting timeframe for these (39.2 weeks in OTUS), and included this assumption in its base case

ACD: In absence of robust data, stage 1 Markov model should be restricted to 39.2 weeks and 2 CMV recurrences, and scenario analyses to explore the potential impact of further CMV recurrences, with a stage 1 duration of between 39.2 and 78 weeks

Company response to ACD

- Believe the OTUS data is a robust source for modelling recurrences over time
- Accept committee's preference and updated base case now has stage 1 model duration of 39.2 weeks, noting this is conservative
- Did not provide any scenarios with a longer stage 1 duration and more than 2 recurrences

ERG comments

- Agrees that the company's approach is in line with the committee's preference

Abbreviations: CMV, cytomegalovirus

Resolved: Assumption of time since transplant at baseline

The company updated its base case aligned with committee preference to use mean time since transplant

Background (at ACM1)

- Company originally used median TST from SOLSTICE to inform baseline characteristics of modelled population
- ERG preferred to use the mean TST to fully reflect the whole population

ACD: committee concluded that it was more appropriate to use the mean value in the absence of data on the distribution of TST

Company response to ACD

- Agree with the committee's preference to use mean TST and reflect this in their updated base case
- Acknowledge uncertainty in whether medium or mean TST should be used at model entry given the heterogeneous population

ERG comments

- Agrees that the company's approach is in line with the committee's preference

Abbreviations: TST, time since transplant

Resolved: IV administration costs

Company updated its base case aligned with committee preference to include different IV administration costs for first and subsequent administrations in model

Background (at ACM1)

- Company originally assumed daily IV administration cost used for IATs was equal to an NHS reference cost for complex chemotherapy at first attendance
- ERG preferred subsequent cycles should be associated with a lower cost; company's assumed 'daily IV cost should only apply to the first administration of IV IATs

ACD: committee concluded the model should include different IV administration costs for first and subsequent administrations

Company response to ACD

- After consultation, amended the administration cost to account for reduced cost of subsequent attendance

ERG comments

- Agrees that the company's approach is in line with the committee's preference

Abbreviations: CMV, cytomegalovirus; IAT, investigator assigned anti-CMV treatment; IV, intravenous

Resolved: Hospitalisation costs

The committee concluded that the company's approach was appropriate in that the hospitalisation costs for people with CS-CMV is likely to be higher than for people without CS-CMV

Background (at ACM1)

- Company applied a higher unit hospitalisation cost in model for CS-CMV than for non CS-CMV
- ERG preferred to apply an equal unit hospitalisation cost for CS-CMV and non CS-CMV

ACD: committee considered that people hospitalised with CS-CMV would need extra care and incur greater costs (beyond treatment costs) than people hospitalised without CS-CMV, therefore the company's approach was appropriate

Company response to ACD

- Agree with committee conclusion and maintained hospitalisation costs in updated base case

ERG comments

- Agrees that the company's approach is in line with the committee's preference

Abbreviations: CS, clinically significant; CMV, cytomegalovirus