

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant

Technology appraisal committee D [07th September 2022]

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Company: Takeda

For public Contains redacted markings

Background on cytomegalovirus (CMV) infection

Causes

- CMV is a common viral pathogen (of the herpesviridae family); prevalent in 60% to 70% of adult population
- Immunosuppressive chemotherapy after SOT or HSCT reduces protection from CMV and increases risk of latent CMV infection being reactivated, or CMV infection from donor being transferred

Epidemiology

- In 2019–2020, there were over 4,700 SOT procedures and 1,726 HSCT procedures in the UK
- Company estimate ■ people post-transplant have a CMV infection refractory or resistant to first-line treatment per year in UK so eligible for maribavir

Symptoms and prognosis

- Symptoms are mainly asymptomatic or mild but when host immunity is weakened or suppressed, latent CMV can reactivate
- High fever, liver dysfunction, or deterioration in graft function indicate clinically significant disease
- Patients are at risk of worse outcomes without treatment or if CMV is resistant or refractory to treatment

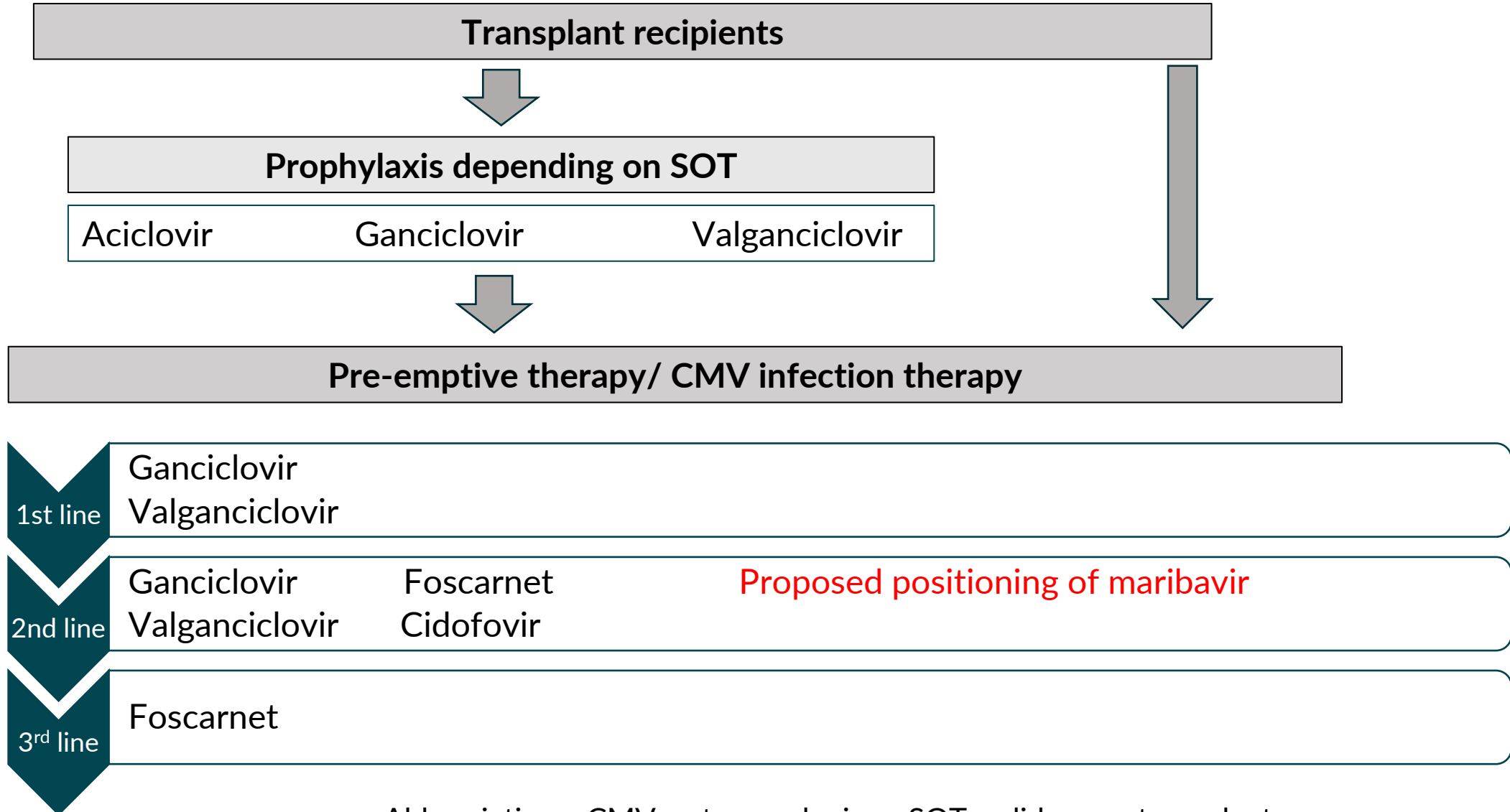
Diagnosis and classification

- CMV infection: CMV viral particles; infection is asymptomatic
- CMV disease: CMV syndrome or tissue invasive disease; infection is symptomatic
- CMV syndrome: For SOT- fever ($>38^{\circ}\text{C}$) for at least 2 days in 4-day period, CMV detected in blood and either neutropenia or thrombocytopenia; For HSCT - combination of fever and bone marrow suppression
- CMV tissue invasive disease: CMV detection or CMV syndrome, with end-organ disease

Abbreviations: CMV, cytomegalovirus; SOT, solid organ transplant; HSCT haematopoietic stem cell transplant

Treatment pathway Positioning of maribavir for solid organ transplants

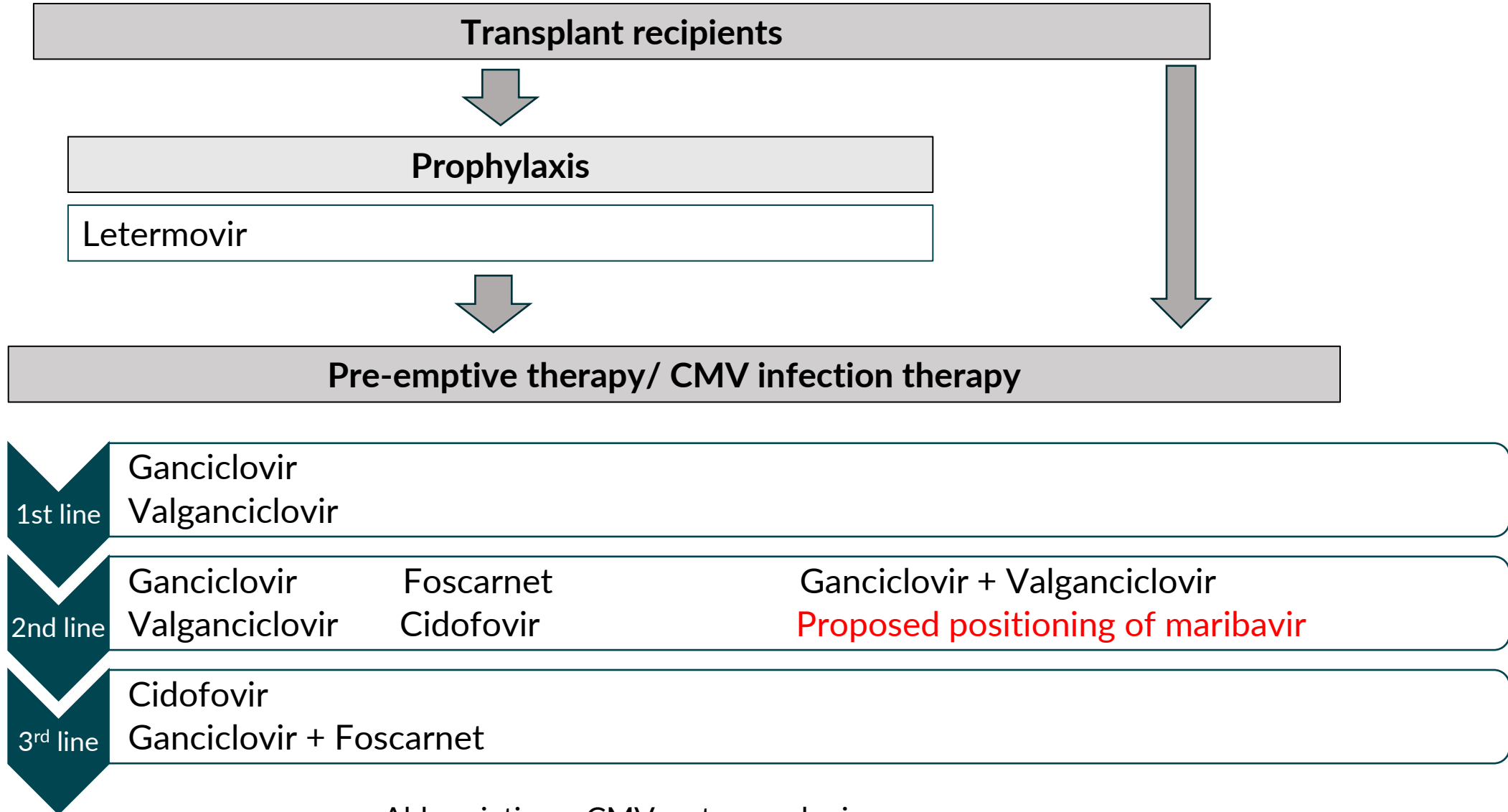
Figure 1: Treatment pathway for the population having solid organ transplants



Treatment pathway

Positioning of maribavir for haematopoietic stem cell transplants

Figure 2: Treatment pathway for the population having haematopoietic stem cell transplants



Patient perspectives

Submissions from Anthony Nolan and Leukaemia Care

- Refractory or resistant post-transplant CMV infections have serious effects on a patient's quality of life, can delay their post-transplant recovery and result in extended in-patient stays.
- The experience of refractory or resistant post-transplant CMV infections, and its associated effects, can have a significant psychological impact for both patients' recovery and their families.
- All current treatments have toxicity, which are significant in terms of the quality of life impact upon patients.
- The costs of treating someone affected by a refractory or resistant post-transplant CMV infection can be significant.
- Patients favour a treatment that can be administered orally; there is the potential for this to have both quality of life and cost saving benefits

"All I want is a normal life – not tied to a hospital"

"very little quality of life, no social life, unable to work and lost the bit of independence I had built up after leaving hospital after the transplant. I was very depressed and anxious"

"a massive step backwards in my recovery"

Abbreviations: CMV, cytomegalovirus

Clinical perspectives

Submissions from UK Renal Pharmacy Group; British Association for the Study of the Liver and British Liver Transplant Group and British Society of Gastroenterology

- Maribavir does not affect renal function so it has a strong advantage over other drugs for treating CMV resistant disease
- Long term IV treatment can have a prolonged in-patient hospital stay. Some people can be trained to self-administer foscarnet and can be discharged home with IV self-administration devices
- Treatment varies slightly with type of solid organ transplant but current usual second line agent is IV foscarnet although IV cidofovir can also be used. Treatment usually requires weekly dose adjustment. Average treatment duration is approx. 8 to 10 weeks adjusted to CMV viral load response
- Maribavir is an oral agent which can have significant patient and organisational benefit – including staff time saved training/observing patients to self-administer, aseptic services costs to make up and fill devices. There is also an environmental benefit from saving on plastic administration lines, plastic infusion bags/devices

“patients with impaired renal function have limited treatment options at the outset for CMV resistant disease”

“An oral preparation is more desirable than foscarnet which can be poorly tolerated”

Equality considerations

- Company noted two groups who may be more likely to receive a less than optimal match:
 1. People from minority ethnic family backgrounds are more likely to need a transplant
 - i. The best match will be from a donor of similar ethnic background and people from these backgrounds can wait longer for a suitable organ donor
 - ii. People from these communities represent 7% of all deceased donors in 2019–20 compared with 32% on the waiting list.
 2. Older people have fewer treatment options due to toxicity
- In both cases, a less than optimal match may cause higher levels of immunosuppression and an increased risk of CMV and graft rejection
- Post-transplant maintenance needs to be optimised to avoid graft rejection
- Anthony Nolan and Leukaemia research noted that maribavir is only being recommended for those over 12, this means some will not be able to benefit from the availability of this treatment. This is outside of expected marketing authorisation and therefore the remit for discussion











Innovation

Company consider

- There is an unmet need for people with post-transplant CMV infection and/or disease that is refractory or resistant to CMV treatment and prevention of transplant loss due to CMV infection reduces economic burden
- There are several benefits which company state are not captured in the model
 - All anti-CMV treatments used in UK clinical practice are used off-label and need several administrations a day, close monitoring and hospitalisation for treatment
 - Maribavir will not require hospitalisation so burden of treatment administration and monitoring will reduce
 - Maribavir has a favourable safety profile
 - Maribavir is less susceptible to mutations of the viral DNA polymerase that contribute to anti-viral resistance from using the other anti-CMV agents

Key issues

Table 1 Key issues

Issue	Resolved?	ICER impact
Imbalance in time since transplant in clinical trial	No for discussion	
Trial conduct leading to uncertainty	No for discussion	
Use of OTUS data	No for discussion	
Structural assumptions and overestimate of recurrences in model	No for discussion	
Estimation of costs	No for discussion	
Modelling of mortality in Stage 1 Markov	No for discussion	
Assumption of time since transplant in the model	Partially for discussion	
Modelling of disease complications	Partially for discussion	
Modelling of graft failure	Partially for discussion	
Modelling of utilities	Partially for discussion	
Modelling of mortality in Stage 2 Markov model	Yes	N/A



Small impact



Large impact



Unknown impact

Maribavir (Livtencity, Takeda)

Table 2 Technology details

Marketing authorisation*	<ul style="list-style-type: none"> • Maribavir does not currently have marketing authorisation in the UK • EMA and MHRA approval expected in November 2022 • Company's proposed indication: "for treatment of people aged 12 years and over with post-transplant CMV infection and/or disease who are resistant and/or refractory to prior therapy including ganciclovir, valganciclovir, cidofovir or foscarnet"
Mechanism of action	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Oral administration <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • List price per 56 x 200 mg pack: £ [REDACTED] List price per 8-week cycle: [REDACTED] Company has proposed a simple PAS discount

Abbreviations 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

Decision problem

Table 3 Population, comparators and outcomes from the scope

	Final scope	Company	ERG comments
Population	People with cytomegalovirus infection that is refractory or resistant to treatments after haematopoietic stem cell transplantation or solid organ transplant	Not applicable	SOLSTICE population in line with scope and included people broadly representative of population in UK but it had variable time since transplant which could impact on outcomes
Comparators	<ul style="list-style-type: none"> • Ganciclovir • Valganciclovir • Foscarnet • Cidofovir • Ganciclovir with foscarnet • Ganciclovir with hyperimmune globulins • Cytotoxic lymphocytes 	Cytotoxic lymphocytes and hyperimmune globulins not used in UK clinical practice	ERG clinical experts confirmed these are not relevant comparators Foscarnet considered key comparator but ganciclovir, valganciclovir and cidofovir may be relevant for some patients
Outcomes	CMV infection symptom improvement or reduction; Length of hospital stay; Mortality; Tissue invasive disease; Transplant graft function; Viral load Adverse effects of treatment; Health-related quality of life	Not applicable	Company presented data for all outcomes but there is limited data for tissue invasive disease, transplant graft function or death in SOLSTICE Key outcomes in model are viraemia clearance and clinically relevant recurrence

Abbreviations CMV, cytomegalovirus

Clinical effectiveness

Key clinical trial

Table 4 Clinical trial design and outcomes

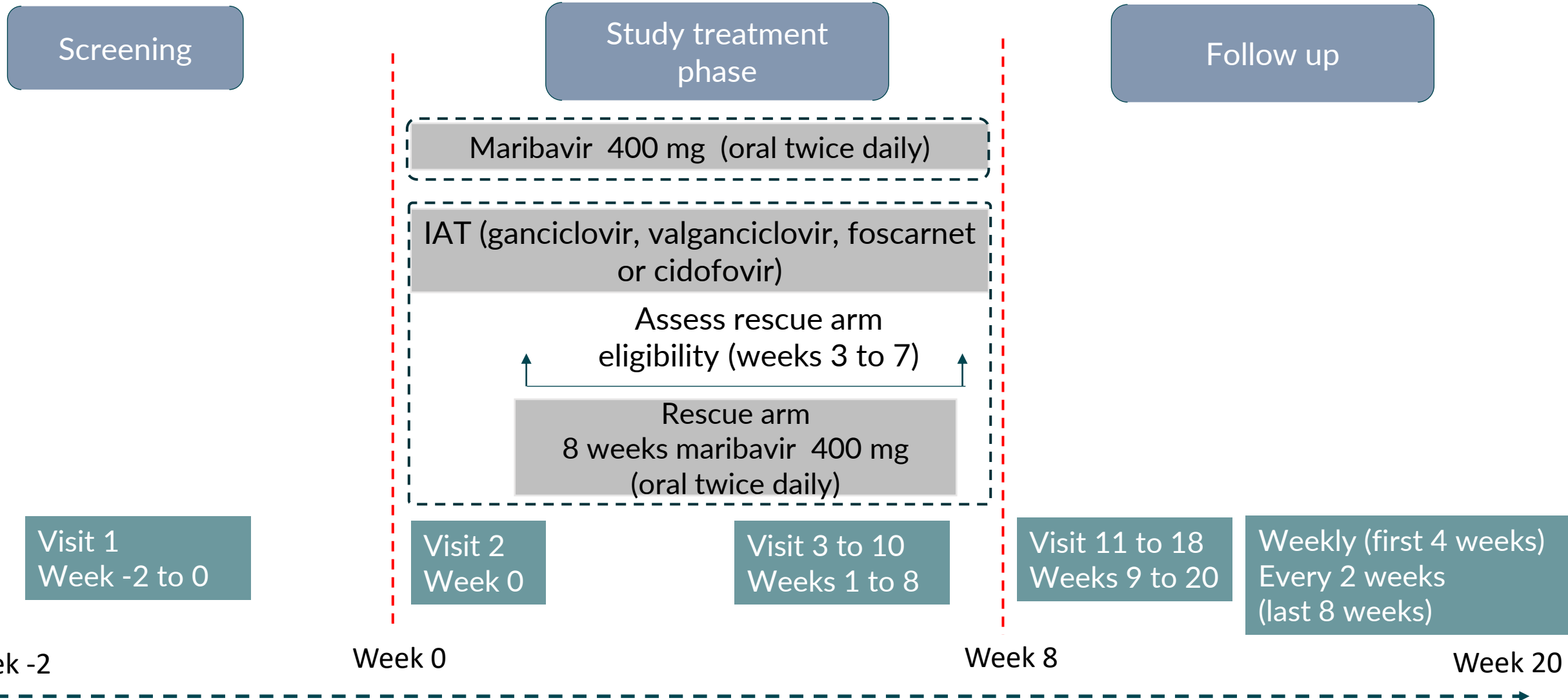
	SOLSTICE (TAK-620-303)
Design	Phase 3 multicentre, randomised, open-label, active-controlled study
Population	Post-transplant CMV infection and disease in patients with CMV that is resistant/refractory* to ganciclovir, valganciclovir, cidofovir or foscarnet
Intervention	Maribavir 400 mg (2× 200 mg oral tablets) BID for 8 weeks
Comparator(s)	IAT (ganciclovir [IV], valganciclovir [oral], foscarnet [IV], or cidofovir [IV]) Choice was at investigators' discretion (mono or combination therapy ≤2 drugs) with any IAT
Primary outcome	CMV viraemia clearance at week 8, based on the 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 and Australia
Used in model?	SOLSTICE was the primary source of clinical evidence in the 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

Clinical trial study design

Figure 3: SOLSTICE study design



SOLSTICE baseline characteristics

Table 5 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]



Are the differences in baseline characteristics in either maribavir and IAT arms representative of clinical practice?

Abbreviations: CMV, cytomegalovirus; IAT, investigator assigned treatment; SOT, solid organ transplant;

SOLSTICE results – CMV clearance

Clearance significantly higher in maribavir arm at 8 weeks

Table 6: CMV clearance at 4, 8 and 20 weeks

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

^{\$}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.

SOLSTICE results – CMV recurrence

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

Table 7: Recurrence of CMV viraemia at week 8 and 20

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

*Unadjusted difference in proportion (maribavir – IAT), calculated by the company

** defined as recurrence among responders after week 8 that had alternative anti-CMV treatment

SOLSTICE results – mortality

There was no statistically significant difference in all-cause mortality between treatment arms but more deaths were reported for HSCT than SOT and there was a small difference in favour of maribavir for SOT and IAT for HSCT

Table 8: Mortality by treatment group

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

SOLSTICE results – key subgroup analyses used in model

Table 9: 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			

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;



Key issue: Numerical imbalance in time since transplant in SOLSTICE

Background

- TST is a key prognostic factor for recurrence. Some imbalance in SOLSTICE (months): IAT = ■; maribavir = ■

Table 10: Company single covariate logistic regressions of recurrence needing treatment (SOLSTICE)

Covariate	Adjusted odds ratio (95% CI)	P-value
Model 1		
Treatment (maribavir vs IAT)	■	■
Time since transplant (months)	■	■
Model 2		
Treatment (maribavir vs IAT)	■	■
Transplant type (HSCT vs SOT)	■	■
Model 3		
Treatment (maribavir vs IAT)	■	■
Time since clearance (months)	■	■

Company

- Doesn't adjust effectiveness data in model
- Based on regression, treatment specific recurrence probabilities appropriate and not influenced by differences in TST
- Model allows for dependence of time in non-clinically significant CMV and probability of recurrence

ERG comments:

- Regression analyses are not robust evidence of a treatment effect of maribavir on recurrence
- Agree unlikely baseline TST influence recurrence in full trial population, but greater concern with HSCT population
- Recognise numerical difference in unadjusted recurrences needing treatment and significant uncertainty of results
- Reiterate there is no clinical rationale given for a treatment specific difference in recurrence
- ERG model assumes recurrence is independent of treatment received and dependent on time in clearance

NICE

Abbreviations: HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant; IAT, investigator-assigned anti-CMV treatment; TST, time since transplant

Key issue: Trial conduct and design leading to uncertainty (1)



Background

ERG noted 3 areas of uncertainty in trial conduct:

1. Large number having IAT had anti-CMV treatment despite confirmed resistance to IAT chosen
2. Clinically relevant recurrence open to bias from open label design and treatment at investigator discretion
3. Missing data for clearance and clinically relevant recurrence - could lead to conservative estimates of events

1. Company response to proportions having anti-CMV treatment

- Majority with IAT and resistance at baseline had acute or chronic renal dysfunction - may have ganciclovir/valganciclovir due to renal toxicity with other treatments
- Sensitivity analysis excluding IAT in those resistant at baseline showed statistically significant improvement in clearance with maribavir
- Clinical advice to company confirmed repeat use of ganciclovir/valganciclovir is appropriate

ERG critique

- High proportion of IAT given IAT to which they had confirmed resistance so efficacy of maribavir may be overestimated
- Company's sensitivity analysis excluding those resistant at baseline is less pronounced than primary analysis
- Unclear if this level of renal impairment among patients resistant to ganciclovir and valganciclovir is reflective of the patient population in clinical practice

Clinical expert response

- Large proportion of SOLSTICE were assigned to CMV treatment for which they were resistant. In clinical practice foscarnet is often tried for this group so important to identify efficacy in this cohort

Key issue: Trial conduct and design leading to uncertainty (2)



2. Company response to subjective assessment of clinically relevant recurrence

- Assume that trialists used the protocol definition for requirement of initial therapy
- Clarified clinically relevant recurrence is one requiring treatment with anti-CMV therapy

ERG critique

- Reiterates subjectivity contributes to uncertainty due to potential bias. This cannot be resolved by additional data but uncertainty should be taken into account in considering cost effectiveness results.

3. Company response to handling missing data

- Company provided sensitivity analyses using assumptions to handle missing data including:
 - a) All with clearance at study discontinuation
 - b) Last observation carried forward (those with clearance at any timepoint up to 8 weeks)
 - c) Clearance despite alternative anti-CMV therapy (not censoring those who had rescue changed to alternative anti-CMV treatment)

ERG critique

- All analyses are likely to overestimate clearance rates and effect will be more pronounced in IAT arm
- Proportions of missing data are unclear for subset informing analysis of clinically relevant recurrence
- Company did not comment on how missing data for recurrence was dealt with in TE response



Does the conduct and design of SOLSTICE lead to uncertainty around trial results?

Cost effectiveness

Company's model overview

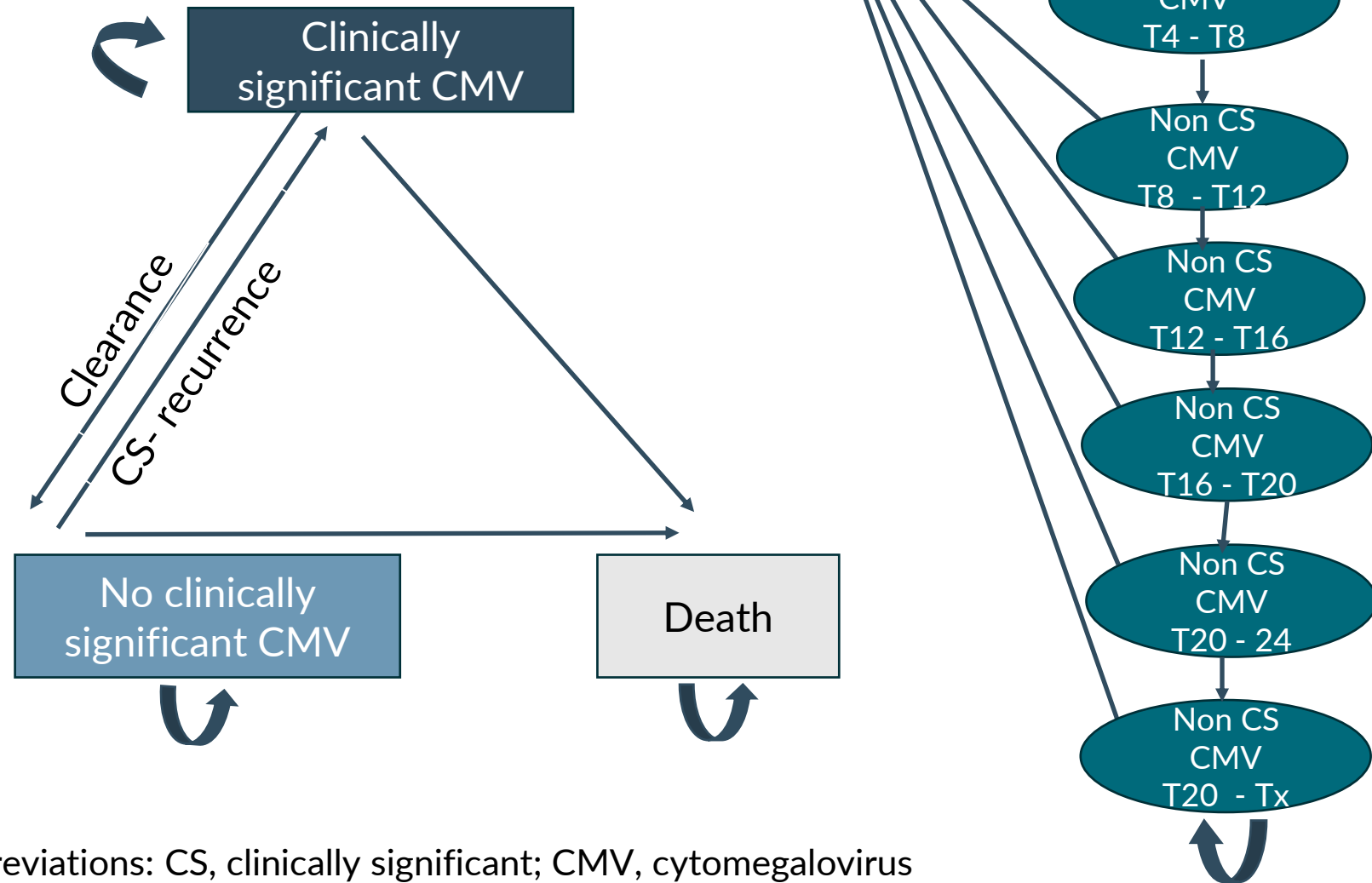
Company's base case model structure

Stage 1 Markov model (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

Figure 4: Model structure (stage 1)



Abbreviations: CS, clinically significant; CMV, cytomegalovirus

*Tn-Tn reflect time in weeks people spent in non CS-CMV health state

How company incorporated evidence into model

Table 11 Input and evidence sources

Input	Base case assumption
Population	CMV refractory or resistant to treatment after HSCT or SOT Mean time after transplant before categorised as R/R taken from study; time since transplant in days
Time horizon	Lifetime horizon; 4-week cycles for first 3 years, then 1-year cycles
Intervention and comparator efficacy	Clearance at 8 weeks taken from SOLSTICE Recurrence weeks 12 to 20 from SOLSTICE; week 20 onwards from OTUS
Adverse events	TEAEs that had an incidence of $\geq 10\%$ in SOLSTICE
Utilities	Stage 1 utility; Stage 2 disutility; AE disutility; Graft loss disutility
Disease complications	Risk of graft loss in CS-CMV and non CS-CMV
Costs	Drug; monitoring frequency; administration (i.e., IV or oral); Health state resource use (hospitalisation) and AE incidence
Mortality rates	Stage 1: transplant (week 0-8) and CMV status mortality from SOLSTICE Stage 2: transplant specific mortality estimates from Martin et al 2013 for HSCT and organ donation annual activity report for SOT

Abbreviations: AE, adverse event; CS, clinically significant; CMV, cytomegalovirus; HSCT, haematopoietic stem cell transplant; IV, intravenous; SOT, solid organ transplant; R/R, refractory or resistant; TEAE, treatment emergent adverse events

Use of OTUS to inform recurrence in company model

- Company provided data from OTUS, a real-world evidence retrospective analysis of people with r/r CMV in response to TE. Primary objective was to evaluate and describe clinical outcomes with current management patterns of CMV
- Results were separated for SOT and HSCT cohorts:
 - SOT included 115 patients, 58 were European that had an SOT between January 2014 and September 2021
 - HSCT included 121 patients, 39 were European that had an allogeneic HSCT from January 2017 to October 2021
- ERG consider OTUS provided a larger sample size and a much longer follow up period for IAT than SOLSTICE, and outcome data is likely to be more generalisable to UK clinical practice
- ERG considers SOLSTICE and OTUS populations are not comparable for following reasons:
 - 1) Study design (randomised controlled trial vs retrospective observational study)
 - 2) Mean TST at baseline was shorter in OTUS than SOLSTICE, suggesting in OTUS people were at higher risk of recurrences
 - 3) There were differences in proportion of type of transplanted organs for SOT

Abbreviations: CMV cytomegalovirus; r/r, refractory /resistant; SOT, solid organ transplant
HSCT, haematopoietic stem cell transplant; TE, technical engagement; TST. time since transplant



Key issue: Use of OTUS data

Background

- ERG recommended model be based on OTUS with maribavir relative treatment effect from SOLSTICE
- Company used OTUS data to model subsequent CMV events after first events modelled with SOLSTICE data which assumes populations, clearance and recurrences in both studies are interchangeable

Company

- No update to base case, present scenarios using OTUS data
- Clearance: use probability of [REDACTED] at 8 weeks (OTUS) and applied unadjusted OR for clearance ([REDACTED]) (SOLSTICE) to estimate probability of clearance maribavir relative to OTUS standard of care ([REDACTED])
- Recurrence: time varying probability of recurrence from (OTUS) and applied unadjusted OR [REDACTED] (SOLSTICE)
- Mortality and median/mean TST from OTUS

ERG

- Data from OTUS and SOLSTICE not interchangeable, company base case inappropriate
- [REDACTED]% estimate does not include HSCT clearances (company state not available). Estimate may be higher if HSCT included in weighted total
- ERG present results using data from OTUS, where:
 - Stage 1 Markov model is 39.2 weeks (20 weeks when SOLSTICE data used)
 - Mean TST is used
 - Clearance data is as per company scenario with adjustment for 8-week mortality removed



Is OTUS or SOLSTICE data most representative of clinical practice?

Abbreviations: CMV, cytomegalovirus; HSCT, haematopoietic stem cell transplant; TST, time since transplant



Key issue: Structural assumptions and overestimation of recurrence in model (1)

Background (ERG concerns)

1. Model included multiple recurrences after a second event, and assumed rate of third and further recurrences were the same as those for second recurrences observed in OTUS
2. Unclear about justification for 78 week duration of stage 1 Markov. Company based this on occurrence of CMV events at 4th recurrence (SOT) and 6th recurrence (HSCT), but inconsistent with use of OTUS data (point 1)
Prefer to model 1st and 2nd recurrence only with duration of stage 1 model reflecting timeframe for these = 39.3 weeks in OTUS (or 20 weeks if SOLSTICE data used)

Company justification and ERG critique

- Cited evidence demonstrating up to 6 recurrences
 - **ERG:** evidence is not robust. Additional recurrences are possible, but no evidence to justify same rate as 2nd recurrence. In OTUS rate much lower after 2nd recurrence so benefit of maribavir overestimated
- Company base case results in an average of [REDACTED] recurrences in IAT arm and OTUS shows an average of [REDACTED]
 - **ERG:** Model is over 1.5 years, but OTUS data over more than 3 years, so recurrences are overestimated in model

ERG

- Stage 1 model updated for duration of 1st and 2nd recurrences only



Has the company appropriately modelled recurrences or should the model be restricted to 2 recurrences?

Key issue: Structural assumptions and overestimation of recurrence in model (2)



Background

Clinical benefit of maribavir modelled via:

1. Higher probability of clearance for maribavir patients at week 8 (56% vs 24% for IAT, SOLSTICE)
2. Lower probability of recurrence for maribavir patients in the 12 weeks following clearance (based on SOLSTICE), meaning a higher proportion of maribavir patients are in the clearance state at week 24 in the model, when rates of recurrence become independent of treatment.

ERG comments

- Company did not explain why maribavir patients that achieved clearance for same amount of time as those having IAT (during first 12 weeks) have an added benefit of having a lower probability of recurrence despite being in clearance state for the same period of time.
- SOLSTICE shows a numerical advantage to maribavir in number of patients with sustained clearance from week 8 to week 20, compared to IAT patients.
 - But data not robust enough to confirm maintenance of clearance with maribavir for longer than with IATs
 - Company has provided no clinical rationale for this
- ERG model probability of maintaining clearance in the model was independent of the treatment received by patients, and only dependent on time spent in clearance



Should recurrence be independent of treatment received and driven by time in clearance?

Key issue: Estimation of costs (1)

Administration for IV drugs in IAT arm



- **ERG:** Concerned administration costs for IV drugs in IAT arm were overestimated
 - Considered company's use of the "first administration cost" inappropriate and company should use reference cost for "following IV treatments" in a cycle
- **Company:** "first administration cost" most suitable
- Company did not address concerns about use of first administration costs so **ERG** carried out 2 scenario analyses:
 - "First administration cost" used for first admission and "following IV treatments" used for subsequent administrations in treatment cycle
 - Daily administration costs for IV treatments estimated on hourly cost of a critical care nurse
- **Company:** Clarified its use of "first administration cost" based on TA591 (letermovir for preventing CMV)
 - Does not consider either of ERG's scenarios appropriate
- **ERG:** maintains view that subsequent cycles should be associated with a lower cost and consider that both scenario analyses still are relevant. These are included in the ERG's model.

Key issue: Estimation of costs (2)

CS-CMV and non CS-CMV health state cost



- **ERG:** During clarification company explained SOLSTICE indicate a proportion in non CMV and CMV state are likely to be hospitalised ([REDACTED]).
- Company applied higher unit hospitalisation costs to CS-CMV health state compared to non CS-CMV state
- **Company:** Used “non elective long stay costs for major infectious diseases **with** interventions” to estimate costs for hospitalisations for CS-CMV but used “non-elective long stay costs for major infectious diseases **without** interventions” for non CS-CMV
- **ERG** unclear why hospitalisation costs with or without clinically significant CMV would differ beyond CMV-related treatment acquisition and administration costs
 - Scenario to investigate with equal unit cost applied in both health states
- **Company:** Consider scenario is inappropriate as CMV patients would need additional care and incur greater costs (beyond treatment costs)
- **ERG** remains uncertain on company’s approach and advise more details are provided regarding additional costs needed by CMV patients



Would hospitalisation costs for those with CS-CMV differ to non CS-CMV beyond CMV treatment acquisition and administration costs?

Abbreviations: CS, clinically significant; CMV, cytomegalovirus; HSCT, haematopoietic stem cell transplant

NICE IAT, investigator assigned anti-CMV treatment; SOT, solid organ transplant



Key issue: Modelling of mortality in stage 1 Markov (1)

ERG concerns about company's modelling

- Company use SOLSTICE data to model different survival based on CMV presence, but difference is not significant

Figure 5 Kaplan-Meier plot of time to all-cause mortality

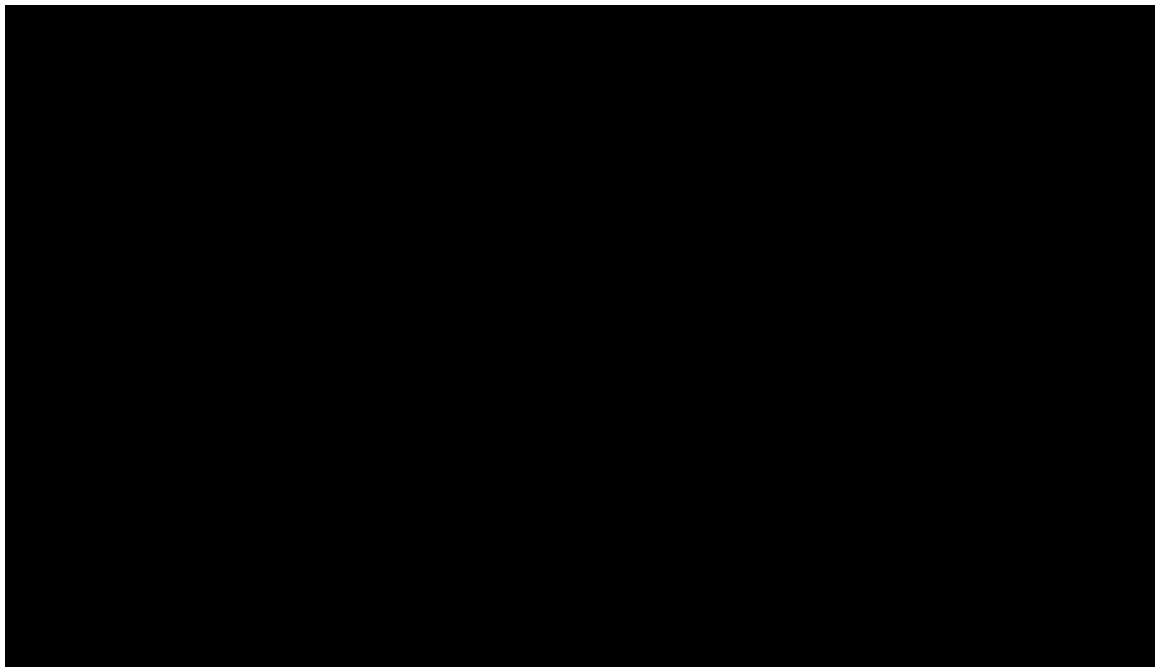
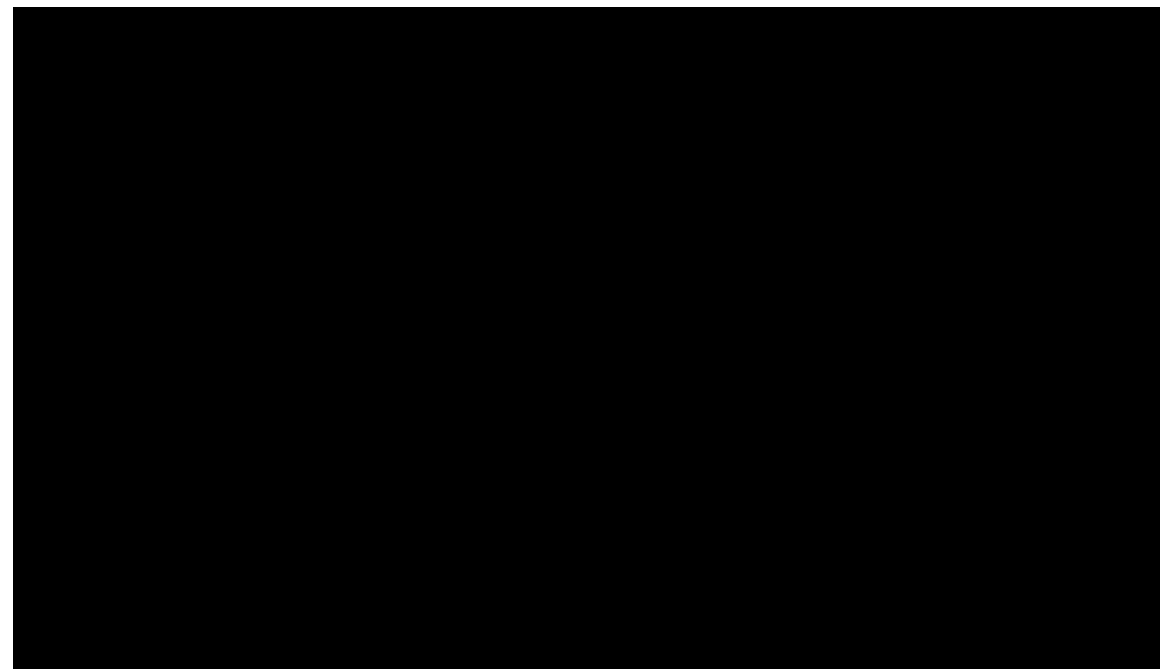


Figure 6 Kaplan-Meier plot of time to all-cause mortality adjusted for crossover by IPCW method


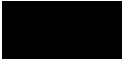
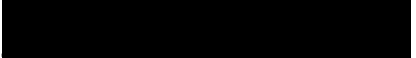
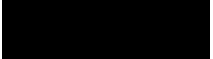


Abbreviations: CMV, cytomegalovirus; IPCW, inverse probability of censoring weights

Key issue: Modelling of mortality in stage 1 Markov (2)


Company's updated modelling after TE

Provided HR to adjust for crossover:

- IPCW adjusted HR 

- RPSFTM adjusted HR 

- Company used cross-over adjusted IPCW HRs to justify difference in CMV-related mortality, but used unadjusted SOLSTICE data in base case model
- Scenario based on OTUS used Hakimi *et al.* 2017 (SOT) and Camargo *et al.* 2018 (HSCT) to inform relative mortality risks for non CS-CMV and CS-CMV health states

ERG concerns about company's modelling

- SOLSTICE CMV-related mortality data are not robust enough to be included in the model
 - Adjusted 95% CIs suggest there was no statistically significant difference of survival in treatment arms
 - Could not validate use of adjusted survival data without understanding how adjustment was carried out
 - Company had not provided additional information on choice of method to adjust for crossover
- OTUS scenario analysis:
 - Overestimates CMV-related mortality
 - Data beyond 20 weeks is available, but not used by the company
 - Hakimi, Camargo and OTUS data all show risk of death decreases over time as time since transplant elapses

 Should CS-CMV status be used to determine mortality (as per company base case)?
Should OTUS data be used instead?

Abbreviations: CMV, cytomegalovirus; CS, clinically significant; CI, confidence interval; HR hazard ratio; TE, technical engagement; NICE IPCW, inverse probability of censoring weights; HSCT, haematopoietic stem cell transplant; SOT, solid organ transplant

Key issue: Assumption of time since transplant at baseline



Background

- ERG was originally unclear about company's assumption of mean time since transplant at baseline
- Suggested company model mean TST from SOLSTICE at baseline to capture cost effectiveness of maribavir

Company

- Clarified mean TST in the model is based on median TST in SOLSTICE (median TST at baseline was [REDACTED] days for SOT and [REDACTED] days for HSCT)

ERG critique

- Noted difference between mean and median TST at baseline in SOLSTICE (mean TST for SOT of [REDACTED] days and [REDACTED] days for HSCT)
- Uses mean value in its model

Clinical expert response

- Clinical outcomes vary as time from transplant elapses
- Symptoms from primary disease may occur at 20 days but rare 50 days after transplant
- In SOT prophylaxis is offered for at least 3 months after transplant in vulnerable groups



Should the mean values from SOLSTICE be used to model time since transplant?

Abbreviations: CMV, cytomegalovirus; HSCT, haematopoietic stem cell transplant; SOT, solid organ transplant;

Key issue: Modelling of disease complications



Leukemia

- Company base case did not include leukaemia recurrences
- **ERG** recommended scenario analysis that included recurrences of underlying disease for HSCT (based on scenario used in TA591- letermovir for preventing CMV)
- ERG updated model to include recurrence costs for 6 months and leukaemia relapse-related mortality. ICER increased
- Company had concerns around double counting of mortality, but ERG disagrees as these only include mortality without recurrent or progressive disease after HSCT

Chronic graft versus host disease

- Company base case did not include GvHD events. Experts indicate that HSCT patients with GvHD have a higher risk of death and ERG suggested a scenario on this
- **Company:**
 - A causal relationship in the literature isn't well established hence not included in base case
 - Provided scenario but did not appear to include higher mortality for GvHD patients
 - Data on GvHD from OTUS will become available in due course



Should higher mortality for GvHD be included in the model?

Abbreviations: CMV, cytomegalovirus; GvHD, graft versus host disease; HSCT, haematopoietic stem cell transplant; SOT, solid organ transplant;



Key issue: Modelling of graft failure

Background

- At TE company updated model to use graft failure estimates from Hakimi et al
- ERG agreed with company updates but recommended company use OTUS graft failure data in model

Company

- Report graft loss in OTUS occurred in xx (■■■■%) of SOT patients compared to ■■■% (estimated number of graft loss events in the company's model in the IAT arm taken from literature)
- Model uses estimates from Hakimi: 5.12% chance of graft failure at 6 months (or after) after transplant for people with a CMV episode, compared to 1.69% for patients without CMV over 1 year
- ■■■■ than that in OTUS which has longer follow up
- Impact on costs and quality of life in the model is small

ERG

- Agrees that impact on the model is limited



Should OTUS data or published literature be used to estimate graft failure in the model?

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

Key issue: Estimation of utilities



Company's updated model after TE

- Used multiple imputation to assess missing EQ5D-5L data
 - Used Missing at Random assumption
 - Updated model with 8-week utility values and multiple imputation included as conservative approach
- Applied method used in TA591 Ara and Brazier (2011) to estimate age adjustments in utility decline
 - Minimal impact on model between Ara et al (2010 and Ara and Brazier (2011) so maintained base case
 - Clarified week 8 time point is most likely to have greatest differentiation between health states

ERG comments

- In general considers issues around estimating quality of life are resolved
- Recommends using weeks 12, 16 and 20 as well as week 8 data points in MI model
- Utility values for stage 2 Markov might underestimate quality of life of non CS-CMV SOT but overestimate quality of life for non CS-CMV HSCT patients due to inconsistency between stage 1 and 2 values

Table 12 utility values for stage 2 Markov in company base case











Health state	Utility values	
	SOT	HSCT
Stage 1: CS-CMV		
Stage 1: Non CS-CMV		
Stage 2: Alive	0.81	0.71



Are the utility values appropriate?

Key issues

Table 13 Key issues

Issue	Resolved?	ICER impact
Imbalance in time since transplant in clinical trial (ERG change 1)	No for discussion	
Trial conduct leading to uncertainty	No for discussion	
Use of OTUS data (ERG scenario)	No for discussion	
Structural assumptions and overestimate of recurrences in model (ERG change 1 and b)	No for discussion	
Estimation of costs (ERG change 4, 5 and 6)	No for discussion	
Modelling of mortality in Stage 1 Markov	No for discussion	
Assumption of time since transplant in the model (ERG change a)	Partially for discussion	
Modelling of disease complications (ERG change 2 and 3)	Partially for discussion	
Modelling of graft failure (no ERG change)	Partially for discussion	
Modelling of utilities (no ERG change)	Partially for discussion	
Modelling of mortality in Stage 2 Markov model (no disagreement)	Yes	N/A



Small impact



Large impact



Unknown impact

Cost effectiveness results

All ICERs are reported in PART 2 slides because of confidential agreements

ERG changes to model:

- a) Using mean TST
- b) Limiting the stage 1 Markov to 20 weeks (SOLSTICE data) or 39.2 weeks (OTUS data)
 1. Assuming that the probability of maintaining clearance is independent of the treatment received by patients (using the probability associated with IAT)
 2. Including leukaemia recurrence in the model and correcting the cost for treatment to reflect 6 months of survival
 3. Including GvHD in model
 4. Using SB14Z cost code for the first administration of a treatment cycle and SB15Z for all subsequent administrations in that cycle
 5. Estimating the IV administration costs based on the PSSRU hourly cost of a critical care nurse and adding the cost of 15 minutes of hospital pharmacist time
 6. Applying an equal unit hospitalisation cost to both CMV and non-CMV patients

Thank you.