12 October 2023
EMA/525117/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

PREVYMIS

International non-proprietary name: letermovir

Procedure No. EMEA/H/C/004536/II/0033/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ADME	adsorption, distribution, metabolism, and excretion
AE	adverse event
ANC	absolute neutrophil count
APaT	All Participants as Treated
AUC	area under the curve
BID	twice daily
CI	confidence interval
CMV	cytomegalovirus
CrCl	creatinine clearance
CsA	cyclosporin A
CSR	clinical study report
D+	donor seropositive
D-	donor seronegative
DDI	drug-drug interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
E-R	exposure-response
EU	European Union
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCSF	granulocyte colony-stimulating factor
GVHD	graft versus host disease
HSCT	hematopoietic stem cell transplant
IV	intravenous
LET	letermovir (MK-8228, PREVYMIS™)
LH	luteinizing hormone
PET	pre-emptive therapy

PK	pharmacokinetic
PopPK	population pharmacokinetic
PSUR	periodic safety update report
R+	recipient seropositive
R-	recipient seronegative
SAE	serious adverse event
SOC	system organ class
sSAP	supplemental statistical analysis plan
US	United States
VGCV	valganciclovir
WBC	white blood cell

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 7 March 2023 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Grouped application consisting of 1) Extension of indication to include treatment of prophylaxis of cytomegalovirus in kidney transplant recipients (KTR) for PREVYMIS, based on final results from study P002MK8228; this is a Phase III, randomized, double-blind, active comparator-controlled study to evaluate the efficacy and safety letermovir versus valganciclovir for the prevention of Human Cytomegalovirus (CMV) Disease in adult kidney transplant recipients. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes; 2) Update of section 4.2 of the SmPC in order to update duration of treatment recommendation based on final results from study P040MK8228; this is a Phase III randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of letermovir (LET) prophylaxis when extended from 100 days to 200 days post-transplant in cytomegalovirus (CMV) seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT).

The group of variations requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

PREVYMIS, was designated as an orphan medicinal product EU/3/11/849 on 15 April 2011. PREVYMIS was designated as an orphan medicinal product in the following indication: Prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) (P/0362/2019) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were

deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Filip Josephson Co-Rapporteur: Aaron Sosa Mejia

Timetable	Dates
Submission date	7 March 2023
Start of procedure	25 Mar 2023
CHMP Rapporteur Assessment Report	17 May 2023
PRAC Rapporteur Assessment Report	22 May 2023
CHMP Co-Rapporteur Critique	31 May 2023
PRAC Outcome	08 Jun 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 June 2023
Request for supplementary information	22 Jun 2023
Submission of responses	11 Aug 2023
Start of procedure	14 Aug 2023
CHMP Rapporteur Assessment Report	18 Sep 2023
CHMP members comments	02 Oct 2023
Updated CHMP Rapporteur Assessment Report	05 Oct 2023
Opinion	12 Oct 2023

2. Scientific discussion

2.1. Introduction

The data provided in this application are intended to support an indication for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor [D+/R-]. The MAH is also seeking a modification of the current approved posology to extend prophylaxis beyond 100 days post-HSCT. This may be of benefit in some patients at high risk for late CMV reactivation. The safety and efficacy of letermovir use for more than 200 days has not been studied in clinical trials.

2.1.1. Problem statement

Disease or condition

Cytomegalovirus is ubiquitous and generally acquired early in life, with the majority of the adult population being CMV-seropositive in most countries worldwide. Kidney transplant recipients and allogeneic HSCT recipients are immune-compromised, which increases the risk for CMV infection.

Among individuals with intact immune systems, reactivation of CMV infection is uncommon and is generally asymptomatic. However, CMV reactivation in immunocompromised patients, such as transplant recipients, can cause significant morbidity and mortality.

Epidemiology

In kidney transplant recipients the CMV disease incidence varies by serostatus with the highest incidence among CMV seronegative (R-) kidney recipients with a transplanted kidney from a CMV positive donor.

Aetiology and pathogenesis

CMV infection and disease is a serious or even fatal complication in immunocompromised patients, such as those undergoing transplantation. In HSCT recipients the risk of CMV infection is mostly due to reactivation of latent CMV infection. Hematopoietic stem cell transplant recipients with prior CMV infection (R+) are at highest risk for developing CMV reactivation and disease, especially during the first 100 days post-transplant (Özdemir 2007).

The risk for CMV infection is reduced after the first 100 days post-transplant as the immune system reconstitutes. However, there are certain HSCT populations who remain at high risk for CMV infection and/or disease beyond 100 days post-transplant due to delayed immune reconstitution, ongoing immunosuppression as a result of treatment for GVHD, or onset of new GVHD when immunosuppression is tapered.

Clinical presentation

In the absence of prophylaxis, CMV disease is the most common clinically significant viral infection experienced after transplant causing substantial morbidity and mortality in transplant recipients due to direct (eg, pneumonia, hepatitis, retinitis, encephalitis) (Boeckh et al 2011; Ljungman et al 2002; Boeckh 2011) and indirect (eg, increased risk of select opportunistic bacterial and invasive fungal infections, graft-versus-host disease (GVHD), delayed engraftment or graft failure/rejection, increased overall mortality) effects (Craddock et al 2001; Miller et al 1986; Ozdemir et al 2007; Martino et al 2001; Söderberg et al 1993; Larsson et al 2004; Marty et al 2011; Ariza-Heredia et al 2014; Ljungman et al 2016).

Management

The current standard of care in kidney transplant recipients is CMV prophylaxis with valganciclovir (VGCV), an orally bioavailable prodrug of ganciclovir. The cumulative rate of CMV disease with no prophylaxis in D+/R- kidney transplant recipients may be inferred to above 50% over 12 months, in the absence of prophylaxis.

VGCV has been shown to be efficacious in reducing the incidence of CMV disease both post solid organ as well as post HSCT. However, VGCV is poorly tolerated, primarily due to myelosuppression and persistent leukopenia and neutropenia. This is a particular problem post HSCT, to the extent that pre-emptive therapy rather than prophylaxis with VGCV is preferred in this setting.

2.1.2. About the product

Prevymis (letermovir) is an inhibitor of the viral DNA terminase complex, which plays a key role in cleavage and packaging of viral progeny DNA. Virological characterization and sequence analysis of resistant viruses indicate that the viral terminase complex is the target of this compound. Unlike currently marketed anti-CMV drugs, which act via inhibition of the viral DNA polymerase, terminase inhibitors interfere with viral DNA maturation and packaging of monomeric genome units. Consequently, cross-resistance is not expected between letermovir and currently approved medicines for the treatment of CMV infection. There is no known mammalian counterpart of the viral terminase complex.

The positive B/R of 100 days of letermovir prophylaxis post HSCT has previously been accepted by CHMP.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The initial approval of LET for the prophylaxis of CMV infection and disease after HSCT was supported by 28 Phase 1 studies, 2 Phase 2 studies, and a Phase 3 pivotal study (P001). Continued development of LET includes 4 studies consisting of 3 completed Phase 3 studies: P040 (evaluating extending LET administration from 100 days to 200 days post-transplant for CMV infection and/or disease prophylaxis in allogeneic HSCT recipients), P002 (evaluating the use of LET for CMV prophylaxis in kidney transplant recipients), and P042 (nonrandomized, single-arm, open-label study in adult Japanese kidney transplant recipients), and 1 ongoing Phase 2b study: P030 (a single-arm, open-label study in

paediatric recipients of an HSCT). Studies P002 and P040 are included in this submission.

In 2018, the Sponsor requested CHMP advice that carcinogenicity studies for LET are not warranted because the carcinogenic hazard for humans following administration of LET for up to 200 days is negligible. The CHMP indicated that the omission of a carcinogenicity study to support administration for up to 200 days could be agreed, provided that there are no signals for development of neoplasms detected during review of the final application dossier.

Prevymis is an orphan product in the approved indication of prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).

2.1.4. General comments on compliance with GCP

The MAH states that the clinical studies were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such studies including the archiving of essential documents. All studies were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed.

2.2. Non-clinical aspects

2.2.1. Introduction

Letermovir is a viral DNA terminase complex inhibitor, approved in the EU for the prophylaxis of CMV reactivation and disease in adult CMV R+ of an allogeneic haematopoietic stem cell transplant (HSCT). The duration of treatment is 100 days.

In this variation, the MAH proposes a prolonged treatment duration of up to 200 days post HCST, and to add a new indication: for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor [D+/R-] with a treatment duration of up to 200 days.

To support the use of letermovir for a longer treatment duration than 6 months, three new non-clinical studies, as outlined below, were conducted. In addition, a weight of evidence (WoE)-based carcinogenicity risk assessment was included. An update to SmPC section 5.3 was proposed.

Table 1: Toxicology program to support the continuous use of letermovir for longer than 6 months

Study Type/ Duration	Route	Species	Dose Levels (mg/kg)	Study No. (GLP Status)
Repeat-dose toxicity				
Exploratory 2-week TK	Oral (gavage)	Mouse CByB6F1-Tg(HRAS)2Jic (wt/wt)	50, 100, 300, 1000	TT #18-6068 (Non-GLP)
4-week DRF with TK	Oral (gavage)	Mouse CByB6F1-Tg(HRAS)2Jic (wt/wt)	0, 50, 150, 300	TT #19-6010 (GLP)
Carcinogenicity				

Study Type/ Duration	Route	Species	Dose Levels (mg/kg)	Study No. (GLP Status)
26-week Carcinogenicity	Oral (gavage)	Mouse CByB6F1-Tg(HRAS)2Jic (Hemizygous)	0, 2, 25, 150 (M); 0, 10, 100, 300 (F)	TT #20-9016 (GLP)

DRF=dose range-finding; F=female; GLP=Good Laboratory Practice; M=male; TK=toxicokinetic.

2.2.2. Pharmacology

New studies on antiviral drug resistance have been conducted, see section 2.3.4.

2.2.3. Pharmacokinetics

No new non-clinical pharmacokinetics studies have been conducted.

2.2.4. Toxicology

The new non-clinical studies and the weight of evidence (WoE)-based carcinogenicity risk assessment are presented and assessed below.

Repeat dose toxicity

Table 2: Summary of dose-finding studies with letermovir in CByB6F1-Tg(HRAS)2Jic (wt/wt) mice

Study ID/GLP/ Duration	Species/Sex/Number/ Group	Dose (mg/kg/day)/Route	NOAEL
TT #18-6068 Non GLP 2 weeks exploratory with TK	Mouse/CByBF1-Tg(HRAS)2Jic wt/wt 13/sex/group + satellites for TK	50, 100, 300, 1000 Oral (gavage) Vehicle: 0.5% (w/v) tylose in deionized water	N/A

Study objective

The purpose of this study was to determine the TK profile of letermovir when administered once daily by oral gavage to mice for 2 weeks, in support of dose selection for the one-month oral range-finding and TK study in rasH2 transgenic mice (wild-type). Assessment of tolerability was based on mortality, clinical observations, body weights, food consumption.

Noteworthy findings

Toxicokinetic:

Day 1:

Day	Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (ng/mL*hr)	C_{max} (ng/mL)	T_{max} (hr)
1	50	Female	62,800 ± 8300	21,700 ± 898	0.50 ± NC
		Male	172,000 ± 66,600	24,000 ± 1500	1.0 ± NC
	100	Female	69,300 ± 16,100	22,700 ± 2670	0.50 ± NC
		Male	152,000 ± 15,200	29,300 ± 638	1.0 ± NC
	300	Female	796,000 ± 69,400	51,900 ± 5440	1.0 ± NC
		Male	942,000 ± 144,000	75,900 ± 15,000	2.0 ± NC
	1000	Female	1,040,000 ± 152,000	80,500 ± 10,800	2.0 ± NC
		Male	1,800,000 ± 93,300	115,000 ± 2050	7.0 ± NC
NC=Not Calculated.					

Day 14:

Day	Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (ng/mL*hr)	C_{max} (ng/mL)	T_{max} (hr)
14	50	Female	55,100 ± 13,100	11,500 ± 3720	1.0 ± NC
		Male	81,100 ± 14,300	21,300 ± 4970	1.0 ± NC
	100	Female	66,700 ± 6170	17,000 ± 2160	1.0 ± NC
		Male	119,000 ± 31,400	26,700 ± 4400	1.0 ± NC
	300	Female	159,000 ± 14,400	28,700 ± 4380	1.0 ± NC
		Male	274,000 ± 84,300	23,500 ± 10,700	2.0 ± NC
NC=Not Calculated					

Mortality: There were test article-related unscheduled deaths in females and males dosed at 1000 mg/kg/day between Study Days 1 and 3. There were no gross changes that could be ascribed to an intubation accident in any mice that were found dead or sacrificed early. Due to these unscheduled deaths and clinical signs indicative of deteriorating physical condition, remaining high-dose animals were early sacrificed on Study Day 3.

Clinical observations: Eyes partially closed with white discharge and decreased activity, observed post-dose in 1 male at 1000 mg/kg/day before early sacrifice on Study Day 3, considered related to the poor condition of the animal.

Body weight: Test article-related effects on body weights included decreases in mean body weight gain in males at 300 mg/kg/day, when compared to other dose groups, and increases in frequency in individual body weight losses in females and males at 300 mg/kg/day.

Food consumption: There were no test article-related changes in food consumption.

Study ID/GLP/ Duration	**Species/Sex/Number/ Group**	**Dose (mg/kg/day)/Route**	**NOAEL**
TT #19-6010 GLP 4 weeks DRF with TK	Mouse/CByBF1-Tg(HRAS)2Jic wt/wt 10/sex/group + satellites for TK	0 (vehicle), 50, 150, 300 Oral (gavage) Vehicle: 0.5% (w/v) tylose in deionized water	300 mg/kg/day for females and 150 mg/kg/day for males.

Study objective

The purpose of this study was to determine the potential toxicity and TK profile of letermovir when administered once daily by oral gavage to rasH2 transgenic mice (wild-type) for approximately 1 month, in support of dose selection for the 6-month carcinogenicity study in rasH2 transgenic mice (hemizygous mice).

Noteworthy findings

Toxicokinetic:

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (ng/mL*hr)	C_{max} (ng/mL)	T_{max} (hr)
50	Female	51,200 ± 5700	14,800 ± 407	1.0 ± NC
	Male	68,500 ± 13,300	22,000 ± 2540	1.0 ± NC
	All	59,900 ± 7620	18,400 ± 1990	1.0 ± NC
150	Female	161,000 ± 22,800	31,100 ± 1830	1.0 ± NC
	Male	72,500 ± 9250	25,900 ± 3750	1.0 ± NC
	All	117,000 ± 23,300	28,500 ± 2190	1.0 ± NC
300	Female	190,000 ± 37,300	31,500 ± 4810	1.0 ± NC
	Male	168,000 ± 27,100	30,500 ± 5980	1.0 ± NC
	All	179,000 ± 20,900	31,000 ± 3440	1.0 ± NC
NC=Not Calculated.				

Mortality: There were no test article-related unscheduled deaths.

Clinical observations: There were no test article-related clinical observations.

Body weight/food consumption: Decreases in mean body weight gain in males at 300 mg/kg/day (-53% compared to concurrent controls).

Haematology: There were no test article-related effects.

Clinical chemistry: Test article-related very slightly increased mean alanine aminotransferase activity was present in females and males at 300 mg/kg/day (+53% to +83%, respectively, compared to the mean value from concurrent controls). In addition, two females at 150 mg/kg/day had alanine aminotransferase activity that was outside the range of values present in concurrent controls. There were very slightly decreased mean cholesterol and triglyceride concentrations in males at 300 mg/kg/day (-52% and -46%, respectively, compared to the mean values from concurrent controls), and very slightly decreased mean albumin concentrations in females at 300 mg/kg/day (-10% compared to the mean values from concurrent controls). These serum biochemical findings were not adverse because of the small magnitude of the changes.

Gross pathology:
Liver; increased size and/or discoloration/prominent pattern in both genders at ≥150 mg/kg/day, correlating with microscopic alterations.

Organ weight:
Liver; increased weight in males at 50 mg/kg/day and in both genders at ≥150 mg/kg/day, correlating with microscopic alterations.

Microscopic pathology:
Liver, centrilobular hypertrophy occurring with an increased incidence and severity in males at all doses and in females at ≥150 mg/kg/day.

Carcinogenicity

26-week Carcinogenicity Study of Letermovir by Oral Gavage in CByB6F1/Tg rasH2 Hemizygous Mice

In the 26-week carcinogenicity study in CByB6F1/Tg rasH2 hemizygous mice, the high dose was set at the MTD in both sexes; 150 mg/kg/day in males and 300 mg/kg/day in females. The low and intermediate doses (5 and 25 mg/kg/day in males, and 10 and 100 mg/kg/day in females) were expected to provide sufficient separation of systemic exposures to avoid overlap between dose levels.

Table 3: Summary of 26-week carcinogenicity study performed with letermovir in CByB6F1/Tg rasH2 hemizygous mice.

Study ID /GLP/ Duration	Species/No. of animals	Dose (mg/kg/day)/ Route	Major findings
TT #20-9016 GLP 26 Weeks	Mouse/CByB6F1-Tg(HRAS)2Jic hemizygous mice 25/sex/group + 15/sex in positive control group + sentinels and satellites for TK	Control 1 (vehicle), Control 2 (vehicle), Control 3 (water) and 10, 100, or 300 (females), or 5, 25 or 150 (males) Oral gavage Vehicle: 0.5% Tylose (w/v) in water	There were no apparent test item-related clinical signs during the study. Test item-related decreases in mean body weight (-13%) and mean body weight gain (-50%) were observed in males at 150 mg/kg/day as compared to vehicle controls (Group 1). Slight decreases in mean food consumption at 150 mg/kg/day in males generally corresponded to reductions in body weight.
		Positive control NMU at 75 mg/kg (intraperitoneal injection)	There were no changes in mean body weight, mean body weight gain, or food consumption at 5 and 25 mg/kg/day in males or at 10, 100, and 300 mg/kg/day in females.

NMU; N-Nitrosomethylurea

Mortality

There were no test-item-related unscheduled deaths. The statistically significant ($p \leq 0.05$) increase in unscheduled deaths only in males through the 150 mg/kg/day group was not related to the test article because 1) the incidences of these unscheduled deaths were low, and with no dose response, and 2) the causes of death in treated groups were of the type and incidence seen in untreated mice in this laboratory. There was no statistically significant increase in the unscheduled deaths of females through the 300 mg/kg/day group. The test article-related histomorphologic change noted in the high-dose female and male mice in these unscheduled deaths consisted of hypertrophy of liver that correlated with a gross finding of increased size or prominent lobular pattern of liver. The total unscheduled deaths are listed below.

Table 4: Total unscheduled deaths (incidence and percentage of animals found dead or unscheduled sacrificed; n = 25/sex/group)

Dose Group[a]	Number Dead (Percent)	
	Females	Males
Vehicle Control 1 (0 mg/kg/day)[b]	1 (4%)	0 (0%)
Vehicle Control 2 (0 mg/kg/day)[b]	1 (4%)	0 (0%)
Water Control 3 (0 mg/kg/day)[c]	2 (8%)	1 (4%)
Combined Controls	4 (5%)	1 (1%)
MK-8228 (dose level for females/males)		
10/5 mg/kg/day	0 (0%)	2 (8%)
100/25 mg/kg/day	3 (12%)	4 (16%)
300/150 mg/kg/day	2 (8%)	2 (8%)

[a] Dose volume was administered orally once daily.
[b] Vehicle control group with 0.5% Tylose (w/v) in Reverse Osmosis Deionized (RODI) Water.
[c] Reverse osmosis deionized water control.

One 25 mg/kg/day male (Animal No. 5501) was euthanized on Day 35 due to an apparent leg injury and one 25 mg/kg/day male (Animal No. 5013) was euthanized on Day 51 due to an apparent tail injury.

For the positive control article, N-nitrosomethylurea (NMU), there was a higher incidence of mortality in males (87%) and females (73%) primarily due to malignant lymphoma, an expected finding in positive controls in this model.

Non-neoplastic findings
Administration of letermovir was associated with minimal to moderate hepatocellular hypertrophy in females dosed at 300 mg/kg/day and males dosed at 150 mg/kg/day, as summarized in Table 5. The hepatocellular hypertrophy was characterized by increased size of the hepatocytes in the centrilobular to midzonal region of the hepatic lobule. This change correlated with the gross finding of increased size or prominent lobular pattern of the liver observed at necropsy.

Hyperplastic/neoplastic changes
Although there were no statistically significant trends in tumours after the multiplicity adjustment, the increased incidence of benign papilloma in the squamous mucosa of the non-glandular stomach (forestomach) of female mice at 300 mg/kg/day was considered MK-8228 related since this benign neoplastic change occurred concurrently with increased incidence of focal reactive hyperplasia in the squamous mucosa of the forestomach of mice. The hyperplasia, a likely preneoplastic change, was characterized by focally increased thickness of the stratified squamous epithelium lining the forestomach showing increased number of cells and hyperkeratosis (increased amounts of keratin) on the luminal surface, with occasional focal erosion of the mucosa. The epithelium in the affected region was focally raised with accumulation of inflammatory cellular infiltrates in the subjacent lamina propria and submucosa.

The hyperplasia was considered to be an adaptive response to the local irritation by the test article as indicated by the inflammatory response. The papilloma, considered to have arisen from the hyperplasia, presented as solitary exophytic benign growths with a narrow stalk and complex fronds of proliferating epithelium supported by branching fibrovascular connective tissue core, projecting into the lumen of the stomach. The epithelium was often hyperkeratotic but maintained normal organization of the squamous epithelial layers. Mitotic figures were rare, and no cellular atypia or local invasion was observed. Oesophagus, the other region of the upper gastrointestinal tract lined by a similar epithelium as the forestomach, was unremarkable.

In the NMU positive control group, compared to vehicle control groups, there were statistically significant ($p \leq 0.002$) increased incidences of the following tumours: papilloma in the skin ($p<0.001$), papilloma in the stomach ($p<0.001$), lymphoma ($p<0.001$), adenoma in the lung ($p=0.002$), and polyp in uterus/cervix ($p<0.001$) in the females; and papilloma in skin ($p<0.001$), papilloma in the stomach ($p<0.001$), and lymphoma ($p<0.001$) in the males. The high incidence of these tumours was an expected outcome of NMU treatment used as positive control and it demonstrated the response of the transgenic rasH2 mice to this carcinogen.

A summary of the postmortem non-neoplastic and hyperplasia/neoplastic histopathological changes is included below.

Table 5: Test-article-related post-mortem findings

	Females				Males			
Dose (mg/kg/day):	0	10	100	300	0	5	25	150
Number of Animals:	75	25	25	25	75	25	25	25
Histomorphology (Incidence)								
Stomach								
Non-glandular mucosa, hyperplasia, reactive, focal	0	0	0	6	0	0	0	0
Non-glandular mucosa, benign papilloma	1	0	0	2	1	0	1	0
Liver								
Hypertrophy	0	0	0	24	0	0	0	25

Statistical analysis

In males, there were no statistically significant increasing trends in tumour incidence through the 150 mg/kg/day dose group.

In females, an increasing trend for papilloma in stomach was not statistically significant through the top dose of 300 mg/kg/day after the multiplicity adjustment. A statistically significant increasing trend in tumour incidence through the 300 mg/kg/day dose was found for papilloma in stomach in female mice prior to multiplicity adjustment (p = 0.035). After multiplicity adjustment, the increasing trend was not statistically significant (adjustment p = 0.097).

Letermovir plasma concentration

Three satellite animals per group were sampled at 1 hour post dose on Day 182.

Letermovir concentrations in plasma from all control group animals at 1 hours post dose were below the lower limit of quantitation of the bioanalytical method. At 1 hour post-dose, mean letermovir concentrations increased in a dose-related manner in males (5 to 150 mg/kg/day) and females (10 to 300 mg/kg/day).

Table 6: Mean plasma letermovir concentrations in mice following oral gavage dosing of letermovir, Study Day 182

		Dose (mg/kg/day)											
		5		10		25		100		150		300	
		Group											
		4		4		5		5		6		6	
Time (hr)	Sex	Mean (ng/mL)	SE (ng/mL)	Mean (ng/mL)	SE (ng/mL)	Mean (ng/mL)	SE (ng/mL)	Mean (ng/mL)	SE (ng/mL)	Mean (ng/mL)	SE (ng/mL)	Mean (ng/mL)	SE (ng/mL)
1	Female			2,440	53.6			17,200	3,190			28,400	4,250
	Male	841	130			8,940	859			21,100	7,550		

WoE-based carcinogenicity risk assessment

In lieu of conducting a 2-year rat carcinogenicity study post-marketing as previously agreed with US FDA and Japan PMDA, a WoE-based carcinogenicity risk assessment has been developed in accordance with the recently (04-AUG-2022) adopted ICH S1B(R1) Addendum to Testing for Carcinogenicity for Pharmaceuticals.

The WoE carcinogenic human risk assessment based on a comprehensive review of all available

pharmacological, biological, and toxicological data (see below) demonstrates that the carcinogenic risk of letermovir to humans is negligible. As such, according to the MAH, the conduct of a 2-year rat carcinogenicity study would not add value to human carcinogenicity risk assessment and is not warranted to support the continuous use of letermovir for up to 200 days post-transplant in kidney transplant recipients, as per ICH S1B(R1) Addendum to Testing for Carcinogenicity for Pharmaceuticals. Of note, scientific advice from EMA CHMP was previously obtained (MAY-2018), and the Agency concluded that "the omission of a carcinogenicity study to support administration for up to 200 days could be agreed, provided that there are no signals for development of neoplasms detected during review of the final application dossier". US FDA and Japan PMDA concurrence on the WoE carcinogenicity risk assessment is being sought.

• Letermovir pharmacological target is an exogeneous target which has no mammalian counterpart

Letermovir is a non-nucleoside small molecule inhibitor of the CMV terminase complex, which plays a key role in cleavage and packaging of genomic CMV DNA. The mechanism of action of letermovir is distinct from other currently licensed CMV agents, which inhibit the viral DNA polymerase. Letermovir does not inhibit DNA replication. There is no human counterpart of the viral terminase complex, and pharmacologically mediated target related toxicities are not expected.

• Secondary pharmacology screens did not identify any off-target effects of concern Letermovir is not expected to pose a carcinogenic risk due to off-target effects

Letermovir did not show significant off-target binding activity in a panel (63 assays) of radioligand binding assays (interaction with mammalian receptors and enzymes) at the concentration tested (10 µM) [data submitted in the original marketing application].

• Non-clinical repeat-dose toxicity studies did not reveal signals that suggest potential for carcinogenicity

There were no histologic findings indicative of a potential risk for carcinogenicity (e.g., proliferative changes) in mouse, rat, and monkey repeat-dose toxicity studies [data submitted in the original marketing application].

In rats, target organs of toxicity were limited to the male reproductive organs at ≥180 mg/kg/day (≥3-fold the clinical exposure at the recommended dose of 480 mg, $AUC_{0\text{-}24hr}$ of ~100,000 ng*hr/mL). Findings consisted of bilateral seminiferous tubular degeneration, decreased testis weight resulting in decreased sperm count and motility, and decreased male fertility. In addition, slight non-adverse hepatocellular hypertrophy and increase in liver weight were observed in repeat dose toxicity studies at doses ≥60 mg/kg/day and did not progress to liver hyperplasia in studies of up to 6 months in duration (approximately 1/4 to 1/5 rat life expectancy). This non-adverse liver change is related to induction of metabolizing enzymes. In vitro studies in human hepatocytes demonstrate that letermovir induced the expression of CYP3A4 mRNA and to a minor extent, CYP2B6 mRNA [data submitted in the original marketing application]. These results support the assertion that letermovir-induced hepatocellular hypertrophy in rats is through CAR/PXR activation which is deemed not to be a relevant mechanism for hepatocarcinogenesis in humans (Elcombe et al 2014). Importantly, the liver findings were shown to be reversible (or showed a trend towards recovery) after a 4-week treatment-free period. Overall, in the repeat dose study in rats, there was no evidence of diffuse and/or focal cellular hyperplasia, persistent tissue injury and/or chronic inflammation, pre-neoplastic changes, or tumours, which may be indicative of a carcinogenicity risk.

In mouse repeat-dose toxicity studies, there were no target organs of toxicity. Histological changes

were limited to non-adverse hepatocellular hypertrophy (associated with increased liver weight). The liver hypertrophy did not progress to hyperplasia in the 6-month rasH2-Tg mouse carcinogenicity study. As in rats, this non-adverse liver change is related to induction of metabolizing enzymes.

In monkeys, no target organ of toxicity was identified by histomorphological examination in studies up to 9 months in duration.

• There was no evidence of carcinogenic risk associated with endocrine or hormonal perturbations

There were no test article-related organ weight or histomorphological changes in any endocrine organs in the repeat-dose toxicity study in mice and monkeys. In rats, male reproductive organ findings, including decreased testis weight, bilateral seminiferous tubular degeneration, decreased sperm count and motility, and resultant decreased male fertility were observed. There were no organ weight or histomorphological changes in any other endocrine organs, indicating that the male reproductive organ findings were related to a direct effect of letermovir on these organs. The associated decreased serum inhibin B was considered secondary to the observed effect of letermovir on Sertoli cells. These findings are consistent with those observed with boceprevir (a hepatitis C virus (HCV) NS3/4A protease inhibitor) where testicular degeneration (including Sertoli cell toxicity) was only seen in rats (no testicular toxicity in mice and monkeys), monitoring of inhibin B and semen in Phase 1 and 2 clinical trials showed no evidence of testicular toxicity in humans, and no drug-related neoplasms were observed in a 2-year carcinogenicity study in rats. In Phase 3 trials with letermovir, there was no evidence of letermovir-related testicular toxicity in male participants based on analysis of biomarkers used to monitor gonadotoxicity (serum inhibin B, LH, FSH, and testosterone). The lack of findings in the male reproductive system following letermovir dosing in monkeys and mice, and the lack of changes in biomarkers of testicular toxicity in the Phase 3 clinical trials suggests that testicular findings in rats are specific to this species.

There were no changes in the rat female fertility study, no findings related to hormonal perturbation in the embryo-foetal development and pre- and postnatal studies, and no changes of concern in any other endocrine organs were observed.

There were no hormonal changes (testosterone, inhibin B and FSH levels) in a 3-month fertility study in monkeys and no test article-related organ weight or histomorphological endocrine changes in the repeat-dose toxicity studies in monkeys.

There were no changes in endocrine organ weight or histomorphological changes in the 6-month rasH2-Tg mouse study.

In summary, according to the MAH, there is no evidence of a carcinogenic risk associated with endocrine or hormonal perturbations in any of the toxicity studies or in any of the reproductive toxicity studies.

• Letermovir was non-genotoxic *in vitro* and *in vivo*

Letermovir was nongenotoxic in a battery of *in vitro* or *in vivo* studies carried out according to ICH guidance that included a microbial mutagenesis assay, a chromosomal aberrations assay, and in vivo assays for micronucleus induction in bone marrow in mice. In the *in vitro* genotoxicity studies, letermovir was tested for clastogenicity and mutagenicity up to concentrations that caused cytotoxicity. Similarly in the micronucleus study in male mice, doses up to the limit of toxicity were used.

• There was no evidence that letermovir is immunosuppressive

There was no evidence of immune suppression in the repeat dose non-clinical toxicity studies. There were no haematological changes such as leukopenia/leucocytosis, granulocytopenia/granulocytosis, or lymphopenia/lymphocytosis in any species up to the highest doses tested. No alterations in organ weights and/or histology were identified in immune tissues (lymphoid tissue, bone marrow, thymus). There were no significant changes on relevant clinical chemistry parameters such as serum globulins. Specific immunotoxicity endpoints were evaluated in the repeat-dose toxicity studies in rats including determination of spleen cell counts, immunophenotyping of splenocytes, serum antibody titers and/or the Plaque Forming Cell Assay. Of these endpoints, the changes noted in the study report were limited to slight increased CD4 T cells, B cells, antigen presenting cells, and CD45total and CD45low cells and decreased CD45high cells [data submitted in the original marketing application]. Upon consideration of the totality of the non-clinical data, according to the MAH, these findings are not considered adverse and are not indicative of immunosuppression.

• The 6-month rasH2-Tg mouse carcinogenicity study did not reveal signals of concern

In the 6-month oral rasH2-Tg mouse carcinogenicity study, letermovir-related proliferative changes were limited to benign papilloma and focal reactive hyperplasia in the non-glandular stomach (forestomach) observed at the high dose (300 mg/kg/day) in female mice only. The benign papilloma did not progress to carcinoma, indicating the relatively slow rate of growth of the papillomatous tissue. These findings were considered, by the MAH, a nongenotoxic, adaptive response to the prolonged presence of high concentration of a poorly soluble and irritant test article in the rodent forestomach and were not relevant to humans because humans do not have a forestomach.

• Metabolism and distribution of letermovir is similar across humans and animal toxicology species

Qualitatively, the *in vitro* metabolism of letermovir across humans and toxicology species is similar and predictive of the *in vivo* biotransformation route. In ADME studies, letermovir and an oxidative metabolite (M5) are the major radioactive components circulating in rat plasma with M5 being the main drug related material after 24 hours. In humans, letermovir is the major (~97%) radioactive component circulating in plasma, indicative of no major circulating metabolites.

• No safety signals related to cancer have been identified post-marketing

No safety signals related to cancer have been identified in the post-marketing cumulative data from 01-NOV-2017 (IBD) through 01-May-2022 including approximately 111,957 patients exposed to letermovir.

• Letermovir is not intended to be administered over a substantial part of a patient's lifetime

The continuous use of letermovir is expected to be for up to 200 days, i.e., 6 months and approximately 2 weeks. This duration is not a substantial part of a patient's lifetime and negligibly exceeds the duration of continuous clinical use (at least 6 months) specified in ICH S1A guideline as one of the considerations in assessing the need for carcinogenicity studies. The duration of 200 days (6.5 months) vs. 6 months is not considered a toxicologically meaningful difference in duration in a patient’s lifetime. In addition, letermovir is not intended to be used repeatedly or in the treatment of chronic or recurrent conditions.

Overall, according to the MAH, the human carcinogenic risk of letermovir has been assessed adequately and is negligible, based on the WoE-based risk assessment provided above. A 2-year rat carcinogenicity study would not add value to a human carcinogenicity risk assessment and is not warranted, as per the ICH S1B(R1) Addendum to Testing for Carcinogenicity for Pharmaceuticals.

2.2.5. Ecotoxicity/environmental risk assessment

The MAH did not provide an updated ERA for the active ingredient letermovir. Instead, a justification for not submitting an updated environmental risk assessment has been proved as outlined below.

In the current variation application for PREVYMIS™ (letermovir), an Environmental Risk Assessment has not been included.

The approved indication for PREVYMIS is:
"PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT)."

The environmental risk assessment for letermovir was approved on 8 Jan 2018 as part of the initial MAA for PREVYMIS (EMEA/H/C/004536/0000).

With this variation application, the proposed indication is:
"For prophylaxis of cytomegalovirus (CMV) infection and disease in adult D+/R- (CMV seropositive organ donor/CMV seronegative organ recipient) kidney transplant recipients."

In the Notice to MAHs for the CTD format (Vol. 2B, May 2008), it is stated for Module 1.6 that:
"Applications for marketing authorizations should include in Annex to Module 1 an indication of any potential risks presented by the medicinal product for the environment" and "in case of a new indication with significant increase of the extent of use."

The MAH does not consider these requirements to be applicable since the assumptions in the approved ERA regarding patient population, dose, and market penetration are relevant today. Therefore, the approved ERA included in the initial MAA is also applicable for the current variation application. No significant increase in use of PREVYMIS compared to the estimates in the approved environmental risk assessment is expected to occur as a result of this variation application.

The results of the cited assessment showed letermovir is unlikely to pose a risk to the environment. The estimated predicted environmental concentration/predicted no-effect concentration ratios were all well below levels of concern. Based on the measured octanol- water partition coefficient, letermovir is not expected to bioaccumulate and is not considered to be a persistent, bio accumulative and toxic compound. Therefore, no further action is necessary and no special precautionary or safety measures need to be taken for the storage, labelling, administration, and disposal of letermovir.

2.2.6. Discussion on non-clinical aspects

In support of the initial MAA (EMEA/H/C/004536/0000), a comprehensive non-clinical program was completed. This program included *in vitro* and *in vivo* genetic toxicity studies, oral and IV acute toxicity studies in rats and mice, repeat-dose oral toxicity studies (up to 3, 6, and 9 months in duration in mice, rats, and monkeys, respectively), 4-week IV toxicity studies in rats and monkeys, local IV tolerability studies in rats and rabbits, a series of reproductive and developmental studies in rats and rabbits, and a toxicity study in juvenile male rats.

In this variation, a 26-week carcinogenicity study in CByB6F1-Tg(HRAS)2Jic hemizygous mice has been completed to support the application for indications where the duration of continuous treatment is longer than 6 months (e.g. 200 days). In addition, a WoE-based carcinogenicity risk assessment has been provided in accordance with the recently adopted ICH S1B(R1) Addendum to Testing for Carcinogenicity for Pharmaceuticals.

The maximum dose (480 mg/day) is the same in both indications, and the clinical exposures are

comparable. The highest projected median letermovir systemic exposure in kidney transplant recipients, based on oral exposure and bioavailability ($AUC_{0\text{-}24hr}$ = 104,000 ng.hr/mL at 480 mg IV) is comparable to the highest clinical median exposure ($AUC_{0\text{-}24hr}$ = 99, 960 ng.hr/mL achieved at 480 mg IV) in HSCT recipients.

In the 6-month oral carcinogenicity study in CByB6F1 Tg(HRAS)2Jic hemizygous mice, treatment-related neoplastic changes were observed in female mice at 300 mg/kg/day. These findings included an increased incidence of focal reactive hyperplasia in 6/25 mice and benign papilloma in the squamous mucosa of the non-glandular stomach (forestomach) in 2/25 mice. No proliferative, or neoplastic changes were present in females or males at lower doses. The letermovir-related focal reactive hyperplasia and benign squamous papilloma in the forestomach observed in female mice at 300 mg/kg/day are likely a consequence of persistent local irritation and not considered translatable to humans. The proposed update of SmPC section 5.3 is acceptable.
A 6-month oral carcinogenicity study in RasH2 transgenic (Tg.RasH2) mice showed no evidence of human-relevant tumorigenesis up to the highest doses tested, 150 mg/kg/day and 300 mg/kg/day in males and females, respectively.

In addition, the WoE-based carcinogenicity risk assessment supports the conclusion that the carcinogenic risk of letermovir to humans is negligible. As such, the conduct of a 2-year rat carcinogenicity study would not add value to human carcinogenicity risk assessment and is not warranted to support the continuous use of letermovir for up to 200 days. Of note, scientific advice from EMA CHMP was previously obtained and the Agency concluded that "the omission of a carcinogenicity study to support administration for up to 200 days could be agreed, provided that there are no signals for development of neoplasms detected during review of the final application dossier".

In conclusion, results from the previously conducted comprehensive non-clinical program along with the additional assessment of potential carcinogenicity support the extended treatment duration of letermovir, and the proposed indication in adult kidney transplant recipients. Based on the weight of evidence assessment performed in accordance with the principles laid out in the ICH S1B(R1) addendum, and in light of the 3R principles, a 2-year carcinogenicity study in rats is not considered warranted.

In clinical trials, there is a concern that letermovir may have a more immunologically depressive effect in kidney transplant patient compared to HSCT-patients. This is heavily confounded by kidney transplanted patients being immunosuppressed due to other medication, however, there is a clinical concern that letermovir may contribute to a carcinogenic risk through impaired immune-surveillance in the kidney transplanted patient population. No immunotoxicity was observed in rats for up to 13-weeks for letermovir, though it has not been investigated if there could be a more significant potential for an immunotoxic response and a related carcinogenic mechanism due to co-mediation. However, overall, based on the complete weight of evidence assessment, the carcinogenic potential appears low, and further carcinogenic studies are not considered warranted in order to support the extension of indication of Prevymis, either prior to or following marketing authorization, i.e. as a post-authorisation measure.

Regarding the ERA, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of letermovir. Letermovir is not classified as a PBT or vPvB candidate and is not expected to pose a risk to the environment.

2.2.7. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental

exposure further to the use of letermovir.

- Considering the above data, letermovir is not expected to pose a risk to the environment.

In conclusion, the comprehensive non-clinical program previously conducted in support of the original marketing authorization of letermovir along with the additional assessment of carcinogenicity support the extended use of letermovir by PO or IV administration.

2.3. Clinical aspects

2.3.1. Introduction

Letermovir is a viral DNA terminase complex inhibitor, currently approved in the EU for the prophylaxis of CMV reactivation and disease in adult CMV R+ of an allogeneic HSCT. The first Phase 3 pivotal study of LET, Protocol 001 (P001), supported the approval for CMV prophylaxis in adult CMV R+ of an allogeneic HSCT.

The current application includes an extension of indication for use of letermovir for CMV prophylaxis in kidney transplant recipients and a modification of the current indication to extend the prophylaxis from 100 to 200 days post HSCT transplant. In support of this application, the MAH presented data from the following clinical studies:

- Protocol 002 was a Phase 3 clinical study that evaluated the efficacy and safety of LET through Week 28 post-transplant (approximately 200 days) for the prevention of CMV disease in adult kidney transplant recipients with a negative CMV serostatus who received a kidney transplant from a donor with a positive CMV serostatus (D+/R−).

- Protocol 040 was a Phase 3 clinical study that evaluated the efficacy and safety of LET to support extending the dosing regimen from 100 days to 200 days post-transplant for the prophylaxis of CMV infection and/or disease in adult R+ recipients of an allogeneic HSCT.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

2.3.2. Pharmacokinetics

The clinical pharmacology profile of LET is well characterized by the data submitted to support the initial marketing application. The DDI potential of LET was previously characterized in the initial marketing application. No new DDI studies were conducted and no new DDIs were identified on review of the concomitant medications used in P002.

The characterization of LET PK in kidney transplant recipients (P002) is based on a PopPK modelling approach. New PK data from study P002 as well as P042 were included in the provided popPK analysis in this application. An overview of study P002 and P042 are shown below:

Overview of LET Phase 3 Studies in Kidney Transplant Recipients

Study Number	Design/Primary Endpoint	Number of Participants by Intervention Group	Study Population	PK sampling
MK-8228-002 (completed) [Ref. 5.3.5.1: P002MK8228]	Design: Randomized, double-blind, multi-site, active comparator-controlled study to evaluate the efficacy and safety of LET versus VGCV for the prevention of CMV disease in adult kidney transplant recipients. Eligible participants were randomized within 7 days post-transplant in a 1:1 ratio to receive LET or VGCV through Week 28. All participants randomized to the LET group also received ACV for HSV and VZV prophylaxis. Each participant was followed until Week 52. Primary Endpoint: The proportion of participants with adjudicated CMV disease through Week 52 post-transplant.	**LET Group:** LET 480 mg QD (oral or IV) (without CsA) ACV 400 mg BID (oral) or ACV 250 mg/m^2 BSA BID (IV) OR LET 240 mg QD (oral or IV) (with CsA) ACV 400 mg BID (oral) or ACV 250 mg/m^2 BSA BID (IV) Randomized: 301 Treated: 292 Completed study intervention: 246 **VGCV Group:** VGCV 900 mg QD (oral) or GCV 5 mg/kg QD (IV) Randomized: 300 Treated: 297 Completed study intervention: 224	D+/R- kidney transplant recipients ≥18 years of age. Gender: 422M/167F Median (range) age: 51 (18 to 82) years	Intensive PK sample (Week 1 for oral and IV administration: pre-dose, 1, 2.5, 8, and 24 hr postdose Sparse PK sample: predose on week 2, 4, 6, 8, 10, 12, 16, 20, 24 and 28
MK-8228-042 (ongoing) [Ref. 5.3.5.2: P042V01MK8228]	Design: Nonrandomized, single-arm, multi-site, open-label study to evaluate the safety, efficacy, and pharmacokinetics of LET for the prevention of CMV infection and disease in adult Japanese kidney transplant recipients.Eligible participants were enrolled within 7 days post-transplant to receive LET through Week 28. Each participant is followed until Week 52. Primary Endpoint: Adverse events and study drug discontinuations due to adverse events.	**LET Group (oral or IV):** 480 mg QD (without CsA) OR 240 mg QD (with CsA) Enrolled: 22 Treated: 22 Completed study intervention: 17	Japanese D+ and/or R+ kidney transplant recipients ≥18 years of age. Gender: 16M/6F Median (range) age: 47 (25 to 70) years	Intensive PK sample (Week1 for oral and IV administration : pre-dose, 1, 2.5, 5, 8, and 24 hr postdose Sparse PK sample: predose on week 2, 4 ,6 , 8, 10, 12, 16, 20, 24 and 28

ACV=acyclovir; CMV=cytomegalovirus; CsA=cyclosporin A; D+=CMV seropositive donor; F=female; HSCT=hematopoietic stem cell transplantation; HSV=herpes simplex virus; IV=intravenous; LET=letermovir; M=male; PK=pharmacokinetics; PopPK=population pharmacokinetic; QD=once daily; R-=CMV seronegative recipient; R+=CMV seropositive recipient; VGCV=valganciclovir; VZV=varicella zoster virus.

popPK analysis

In order to build a robust popPK model for Phase 3 in KT recipients (Study P002), where PK sampling was conducted using both sparse and rich sampling schedules, additional Phase 1 PK data from Phase 1 studies and the Phase 3 Japanese KT recipients (Study P042) were included. These additional data on (near) steady-state PK data in subjects receiving either 240 mg (with CsA) or 480 mg PO and IV helped to strengthen the popPK description of the Phase 3 Study P002.

The software package nonlinear mixed-effects modelling (NONMEM) (Version 7.4.3; ICON Development Solutions, Ellicott City, MD, USA) was used in the popPK analysis.

The PK analysis dataset included 7540 measurable PK observations from 455 subjects. Intensively sampled concentration-time profiles were available in 108 subjects from Phase 1 and 53 subjects from Phase 3 studies. Sparse data were available in 304 subjects. The LET dose range was 480 mg and 240 mg (plus CsA coadministration) QD.

Two continuous covariates (CRCL and WT) and 3 categorical covariates (Asian versus non-Asian, healthy subjects versus KT subjects, and CsA coadministration) were tested in the popPK analysis.

The final popPK model parameter estimates were contained within the 95% CI determined by a robust bootstrap analysis based on 903 replicates (out of a 1000 runs, 97 runs failed to minimize). The bootstrap 95% CIs are shown in the parameter table for the final model (Table 7).

Table 7: LET popPK Final Model Parameter Estimate

Parameter	Estimate	Bootstrap Estimate	%RSE	95% CI	Shrinkage
Typical values					
CL: Clearance (L/h)	4.11	3.96	5.31	3.56 – 4.43	
Vc: Central Volume (L)	31.8	31.0	9.68	25.6 – 37.5	
Vp: Peripheral Volume (L)	20.6	20.2	11.0	16.5 – 25.1	
Q: Inter-compartmental Clearance (L/h)	1.47	1.45	11.1	1.12 – 1.91	
Ka: Absorption rate constant (/h)	0.513	0.653	10.0	0.463 – 1.03	
Tlag: Absorption lag (h)	0.414	0.599	4.05	0.386 – 0.715	
F1: Bioavailability in HV	0.852	0.817	7.19	0.716 – 0.950	
Relative change in bioavailability KT subject versus HV[a]	-0.297	-0.291	21.0	-0.405 – -0.161	
D1: Duration of infusion (h)	0.864	0.834	4.90	0.742 – 1.01	
Covariate effect CRCL-CL[b]	0.128	0.130	36.8	0.0415 – 0.224	
Covariate effect Asian-Vp[c]	-0.375	-0.391	20.9	-0.534 – -0.209	
Relative increase in bioavailability with CsA coadministration[d]	0.856	0.861	20.5	0.564 – 1.27	
Covariate effect HV-Vc[e]	-0.537	-0.506	9.83	-0.627 – -0.369	
Between-subject variability					
On CL	0.0719	0.0694	13.6	0.0517 – 0.0897	31.0%
On F1	0.267	0.259	13.4	0.193 – 0.325	29.4%
Residual error					
Exponential error	0.586	0.588	3.36	0.551 – 0.623	8.80%

Source: prm-table-Letermovir-v3.Rmd

[a] Covariate effect HV-F1 implementation: IF(RICH.EQ.1) F1RICH=(1+THETA(x)) ELSE F1RICH=1(RICH=1 refers to HV subjects only)

[b] Covariate effect CRCL-CL implementation: CLCRCL = ((CRCL/73.15)**THETA(y))

[c] Covariate effect Asian-Vp implementation: IF(RACE.EQ.3) VPASIAN=(1+THETA(z)) ELSE VPASIAN=1

[d] Covariate effect CsA-F1 implementation: IF(CSA.EQ.1) F1CSA=(1+THETA(i)) ELSE F1CSA=1

[e] Covariate effect HV-Vc implementation: IF(RICH.EQ.1) VPRICH=(1+THETA(j)) ELSE VPRICH=1(RICH=1 refers to HV subjects only)

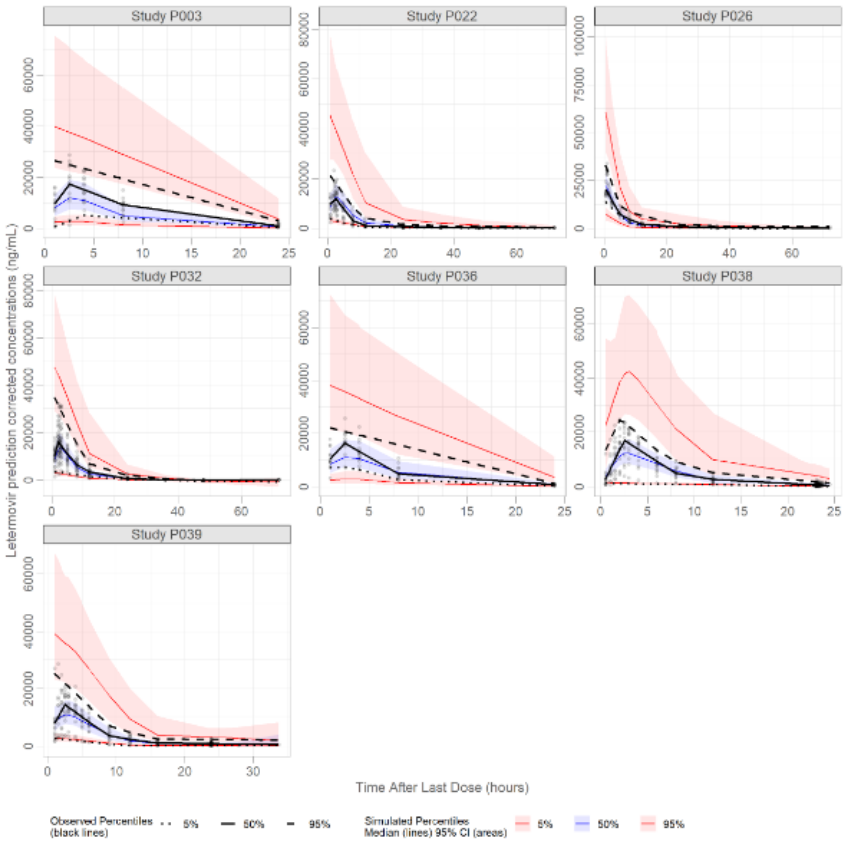
Notes: The covariate effect implementation as described was multiplied with the typical value of the relevant parameter. The CsA coadministration covariate effect on bioavailability captures both the drug-drug-interaction of CsA on clearance and bioavailability and the dose nonlinearity between 240 and 480 mg LET (Section 6). Standard allometric scaling was applied for CL, Q, Vc, and Vp with scalars of 0.75, 0.75, 1, and 1, respectively.

Abbreviations: %RSE=percentage of the relative standard error; F1=Bioavailability; CI=confidence interval; CL=clearance; CRCL=creatinine clearance; D1=duration of infusion; HV=healthy volunteer; Ka=absorption rate constant; KT=kidney transplant; LET=letermovir; popPK=population pharmacokinetic; Q=intercompartmental clearance; Tlag=absorption lag; Vc=central volume of distribution; Vp=peripheral volume of distribution

The pcVPCs for Phase 1 are displayed and stratified by study in Figure 1. The final popPK model was able to predict the observed median and p5 and p95 of observed LET concentrations with good accuracy in the Phase 1 studies. The pcVPCs for the Phase 3 studies are shown in Figure 2. The final popPK model was able to predict the observed median and p5 and p95 of observed LET concentrations with reasonable accuracy in Study P002. For Study P002, the median concentration was mostly captured throughout the profiles except for the absorption phase where it went outside the predicted band. Observed p5 and p95 were slightly outside the predicted bands for short segments of the time

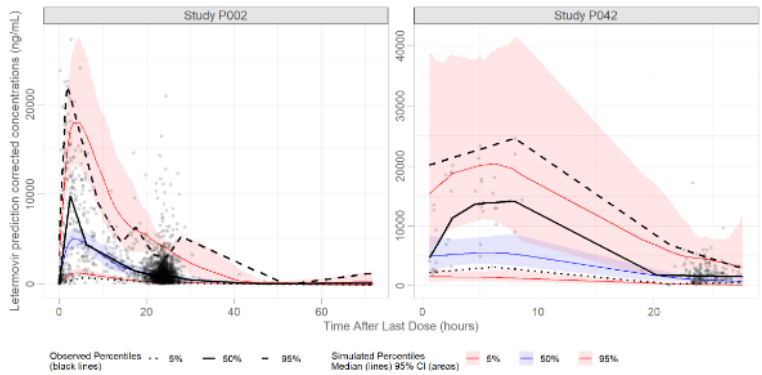
course but generally predicted well. For Study P042, the median profile was not well captured except for the $C_{trough,ss}$ concentrations at 24 hours. In contrast, the observed p5 and p95 were generally predicted well.

Figure 1: pcVPC for Phase 1 Studies



Source: vpc-poppk-letermovir-v4.Rmd
Notes: Gray dots are the observed data points; the black solid line is the observed median; red lines are the observed p5 and p95. The blue area is the 95% PI of the simulated median, and pink areas are the 95% PI of the simulated p5 and p95.
Abbreviations: CI=confidence interval; p5=5th percentile; p95=95th percentile; pcVPC=prediction-corrected visual predictive check; PI=prediction interval

Figure 2: pcVPC Phase 3 Studies P002 and P042



Source: vpc-poppk-letermovir-v4.Rmd
Notes: Gray dots are the observed data points; the black solid line is the observed median; dotted and slashed lines are the observed p5 and p95. The blue area is the 95% PI of the simulated median, and pink areas are the 95% PI of the simulated p5 and p95.
Abbreviations: CI=confidence interval; p5=5th percentile; p95=95th percentile; pcVPC=prediction-corrected visual predictive check; PI=prediction interval

Model predicted exposure

In the kidney transplant population, the predicted overall median AUC0-24 at steady-state following 480 mg oral LET was estimated to be 62,200 ng·hr/mL, with a 90% prediction interval of 28,900 to 145,000 ng·hr/mL [Table 2.7.2-ktpro: 1]. This oral exposure in the kidney transplant population is approximately ~1.8 times higher when compared to the HSCT (Hematopoietic stem cell transplant) population, which had a predicted steady-state AUC0-24 of approximately 34,400 ng·hr/mL (90% prediction interval of 16,900 to 73,700 ng·hr/mL). In the kidney transplant population, bioavailability of LET was estimated to be approximately 60%, based on the PopPK analysis, which is higher than the bioavailability observed in the HSCT recipients (35%). The LET exposure following oral coadministration of 240 mg LET with CsA in kidney transplant recipients was comparable to the exposure following oral 480 mg LET alone. The bioavailability of LET 240 mg when given with CsA could not be estimated accurately independent of clearance. LET PK in kidney transplant recipients after 480 mg IV administration are not available as only a small number of participants (n=3) in P002 received IV LET for a short duration. The projected IV exposure of LET (AUC 104,000 ng·hr/mL) in the kidney transplant population is comparable to the IV exposure in HSCT recipients.

Table 8: Predicted LET AUC (ng hr/mL) in the Phase 3 Kidney Transplant Population (P002)

Treatment	AUC0-24† (ng·hr/mL)	90% Prediction interval
480 mg Oral, no CsA	62,200	(28,900-145,000)
240 mg Oral, with CsA	57,700	(26,900-135,000)
† PopPK AUC estimates are steady-state median values and (90% prediction interval). Values are rounded to 3 significant digits AUC= area under the curve; CsA= Cyclosporin A		

Source: [Ref. 5.3.5.3: 084SQW]

CRCL and WT were identified as significant intrinsic factors for exposure. Based on multivariate simulations, the GM exposure ratios (AUCss,0-24h) for CRCL categories (relative to normal renal function, CRCL ≥90 mL/min) were 1.35 (90% CI: 1.17 - 1.55), 1.27 (90% CI: 1.17 - 1.38), and 1.12 (90% CI: 1.02 - 1.21), respectively, for ≥15 to <30 mL/min, ≥30 to <60 mL/min, and ≥60 to <90

mL/min. For WT (>80 kg relative to ≤80 kg), the GM exposure ratio (AUC ss,0-24h) was 0.741 (90% CI: 0.703 - 0.782). For both covariates, this was not considered clinically meaningful.

Target exposure

Clinical comparability bounds (0.5, 3.0) for LET have been established as reflecting the range of relative change in AUC that would be expected to be clinically comparable to 480 mg QD LET adjusted to 240 mg QD LET when co-administered with CsA in kidney transplant recipients with respect to safety and efficacy. In establishing the lower clinical bound, the E-R efficacy analysis of Phase 3 (P002) data in kidney transplant recipients was examined and showed that there was no exposure. There were no PK data available following 480 mg IV LET in kidney transplant recipients. Therefore, the steady state LET AUC following 480 mg IV was projected based oral exposure and estimated bioavailability. This projected IV AUC of 104,000 ng·hr/mL in the kidney transplant population is comparable to the IV exposure in HSCT recipients that was generally well-tolerated, as described in the initial marketing application. As such, the upper bound was constructed using the overall clinical experience to date dependence on the occurrence of adjudicated CMV disease in this patient population

Effects of intrinsic and extrinsic factors within this range and are not considered clinically relevant. No dose adjustments are recommended for LET based on the intrinsic factors assessed in kidney transplant recipients, including the impact of renal impairment post-transplantation, weight, age, and gender. As such, the highest IV and oral exposures achieved in the Phase 1 studies are around 3-fold higher than the projected IV exposure for the kidney transplant recipient following 480 mg LET (Table 9).

Table 9: Summary of LET Exposure Informing the Clinical Bounds in Kidney Transplant Recipients

LET Dose/Population	AUC (ng·hr/mL)[a]	AUC Fold Change
Phase 3 Participants		
480 mg oral – Kidney Transplant Recipients PopPK (P002)	62,200 [28,900-145,000]	--
480 mg IV[b] – Projected in Kidney Transplant Recipients	104,000	--
Phase 1 – Healthy Participants		
720 mg oral BID LET following 14 days (P026)	328,000[c] (44.8%)	3.2-fold[d]
960 mg IV single dose LET (P004)	282,000[c] (23.3%)	2.7-fold[d]

[a]PopPK AUC estimates are steady-state median values and (90% prediction interval). Values are rounded to 3 significant digits.
[b]No IV data are available in kidney transplant recipients. The projected IV exposure was calculated by using steady state AUC following 480 mg oral administration (62,200 ng·hr/mL), the bioavailability of 60% and assuming clearance is similar between kidney transplant recipients and the healthy participants.
[c]P026 AUC estimate is a geometric mean (2 x 164,000 ng·hr/mL AUC0-12) and (GCV%)
[d]reference is the 480 mg IV projected AUC
[c]P004 AUC estimate is a geometric mean and (GCV%)
AUC=area under curve; BID=twice daily; GCV=geometric coefficient of variation; HSCT=hematopoietic stem cell transplantation; IV=intravenous; LET=letermovir; PopPK=population pharmacokinetics
Data from P001, P004 and P026 can be found in the original marketing application.

2.3.3. PK/PD modelling

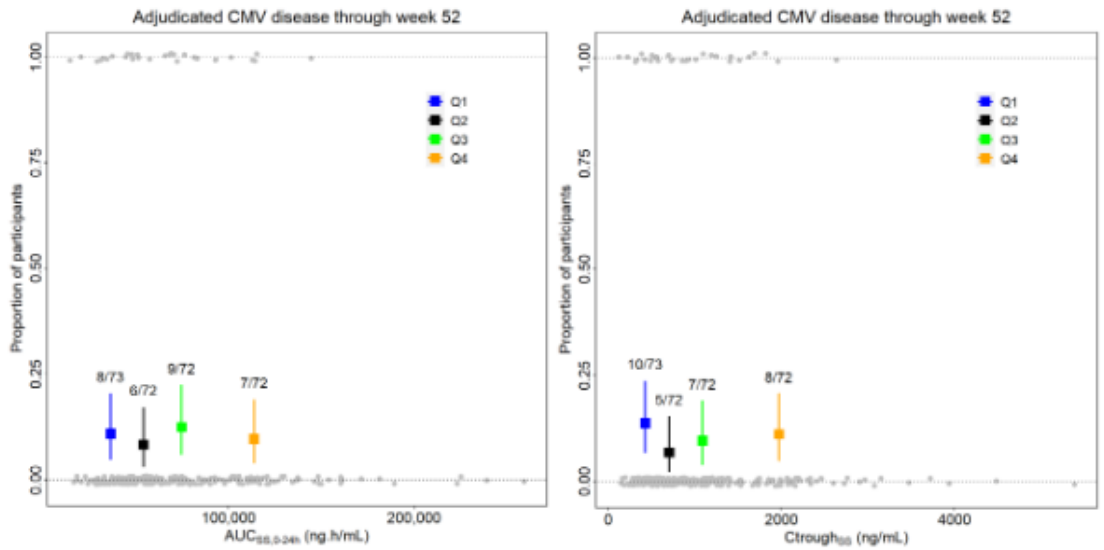
The E-R analysis was based on the FAS of the Phase 3 Study P002. In total, 289 subjects in the FAS had popPK model-predicted steady-state AUC and C trough measures, albeit that for 15 subjects, no

evaluable PK observations were available. Their exposure measures were imputed based on typical population values adjusted for their covariates.

After approximately 28 weeks of LET treatment post-transplant, subjects were followed through Week 52 to assess for late-onset CMV disease and DNAemia in Study P002.

Figure 3 shows the observed LET E-R relationships for adjudicated CMV disease and through Week 52 post-transplant.

Figure 3: LET E-R Relationship for Adjudicated CMV Disease Through Week 52 Post-Transplant Using Steady-State AUC (Left Panel) and C_{trough} (Right Panel) as Exposure Metrics in Study P002



Source: ER-analysis.R

Notes: Gray circles indicate data from individual subjects. Closed squares (error bars) show the observed proportion of subjects (95% CI) with adjudicated CMV disease through 52 weeks post-transplant by exposure quartile and are plotted at the median exposure of each quartile. The numbers above the error bars (x/y) represent the number of subjects who achieved the response (x) and the total number of subjects (y) in each of the quartiles.

Abbreviations: AUC=area under the concentration-time curve; $AUC_{ss,0\text{-}24h}$=area under the concentration-time curve over 24 hours at steady state; CI=confidence interval; CMV=cytomegalovirus; C_{trough}=minimum concentration; $Ctrough_{ss}$=minimum concentration at steady state; E-R=exposure-response; LET=letermovir; Q1=first exposure quartile; Q2=second exposure quartile; Q3=third exposure quartile; Q4=fourth exposure quartile

Table 10: Number (%) of Participants with Efficacy Events by Steady-state AUC Exposure Quartile in Study P002

Endpoint	Q1 (N=73)	Q2 (N=72)	Q3 (N=72)	Q4 (N=72)	Total (N=289)
CMV disease through week 28 post-transplant[a]	0	0	0	0	0
CMV disease through week 52 post-transplant[a]	8 (11%)	6 (8.3%)	9 (12.5%)	7 (9.7%)	30 (10.4%)
Documented CMV DNAemia through week 28 post-transplant	3 (4.1%)	1 (1.4%)	0 (0%)	2 (2.8%)	6 (2.1%)
[a] CMV disease was adjudicated. CMV=cytomegalovirus; N=number of participants, Q1-Q4=first to fourth exposure quartile AUC (ng·hr/mL) quartile: Q1=45,380.74, Median = 61,628.53, Q3= 87,378.90 AUC (ng·hr/mL) range (Min-Max): 14,337.67- 259,334.48					

Source: [Ref. 5.3.5.3: 084SQW]

No LET E-R relationship was observed for adjudicated CMV disease through 52 weeks post-transplant or its time to onset. In summary, E-R analysis demonstrated no dependence of efficacy endpoints on LET exposures over the range of exposures assessed using exposure quartile.

2.3.4. Pharmacodynamics

Introduction

Phenotypic Analysis of Letermovir Against CMV UL56 AND UL89 Genotypic Variants (Post-marketing Requirement 3295-1)

Letermovir (LET) is a potent inhibitor of cytomegalovirus (CMV) that targets the CMV DNA terminase required for viral DNA processing and packaging. Two CMV genes (UL56 and UL89) encode subunits of the CMV DNA terminase complex. In the MK-8228 P001 clinical trial, DNA was isolated from plasma obtained from recipients of a hematopoietic stem cell transplant who met the primary endpoint of clinically significant CMV infection (CS-CMVi) through Week 24 post-transplant, and the UL56 and UL89 protein coding regions were amplified by PCR and were sequenced using next-generation DNA sequencing (NGS). Deduced amino acid changes (relative to a LET-susceptible CMV reference strain) in pUL56 and pUL89 were identified, but it is not known whether these are natural polymorphisms or resistance-associated variants that emerge during exposure to LET prophylaxis.

The MAH has submitted a report of the results of P001 phenotypic analysis to determine if any of these substitutions had an impact on susceptibility to LET.

Methods

Selecting CMV UL56 and UL89 Genotypic Variants (GVs) for Phenotyping

GVs from the Phase 3 trial were selected for phenotyping based on the following criteria:

- The GV was detected in ≥ 5% of the next-generation sequencing (NGS) reads at that codon
- The GV is at a conserved amino acid in pUL56 or pUL89
- The GV has not been previously characterized for susceptibility to letermovir

- The GV was detected in ≤ 2 LET subjects

EC50 values were calculated for newly phenotyped recombinants and matching control strains (baseline susceptible strain and LET resistant strains with lower and higher levels of resistance). The fold-shift in mean LET EC50 value conferred by each substitution, relative to the UL56/UL89 wild-type CMV reference strain, was also determined. CMV strains with substitutions that conferred reduced susceptibility to LET were also tested for susceptibility to the CMV DNA polymerase inhibitors ganciclovir (GCV), foscarnet (FOS), and cidofovir (CDV).

Results

The MAH and the FDA conducted independent analyses to select genotypic variants in the CMV UL56 and UL89 genes for recombinant phenotyping. The FDA analysis identified 8 substitutions in pUL56 and 1 in pUL89 for phenotyping; six additional pUL56 substitutions were identified in the MAH's analysis.

Drug susceptibility of recombinant CMV strains with substitutions identified in the FDA analysis

Eight pUL56 substitutions (M3V, E237G, S255L, C325W, E485G, E485G + SNS445- 447deletion, Y575C, and R816W) and one pUL89 substitution (I531T) were identified in the FDA analysis. The LET EC50 values for the reference strains in these experiments were comparable to previously reported values. Seven of the nine novel substitutions had no significant impact on susceptibility to LET (EC50 ratios ranged from 0.9 to 1.1), but CMV strains with the pUL56 C325W or pUL56 E237G substitutions were less susceptible to LET (EC50 shifts of 8262- and 13-fold, respectively). When the susceptibility of these two recombinant strains to the CMV DNA polymerase inhibitors GCV, FOS, and CDV was measured, there was a small shift (2.1-fold) in the GCV EC50 for the mutant CMV strain with the pUL56 E237G substitution. This strain was similar to wild-type in susceptibility to FOS (1.3-fold) and CDV (1.4-fold). There were no significant changes in susceptibility to GCV / FOS / CDV for the mutant CMV strain with the pUL56 C325W substitution.

Growth phenotype of recombinant CMV strains with substitutions identified in the FDA analysis

The recombinant CMV strain with the pUL89 I531T substitution had a growth defect. In contrast, all eight CMV strains in this analysis with substitutions in pUL56 grew as well as the UL56 wild-type reference strain.

Drug susceptibility of recombinant CMV strains with additional substitutions identified in the MAH's analysis

Six additional substitutions in pUL56 (R369T, F626S, L726V, T775I, AVS789-791deletion, and V814A) identified in the MAH's analysis were evaluated using recombinant phenotyping. Five of these substitutions met criteria outlined above (see Methods), another (pUL56 R369T) was detected as part of longitudinal genotyping of the subject with the pUL56 C325W substitution (testing plasma samples collected before and after detection of this mutation). Susceptibility to LET was equivalent to the UL56 wild-type CMV reference strain for four of these recombinant viruses - EC50 ratios were 1.0 for strains with L726V, T775I, AVS789- 791deletion, or V814A substitutions in pUL56. The CMV strain with a F626S substitution in pUL56 had an EC50 that was one-half the wildtype value. In contrast, the pUL56 R369T substitution conferred a 52-fold increase in the EC50 for LET. For the CMV strain with the pUL56 R369T substitution, slight differences compared to the UL56 wild-type strain in susceptibility to GCV was observed (1.5-fold), FOS (1.1-fold), and CDV (1.2-fold).

Growth phenotype of recombinant CMV strains with additional substitutions identified in the MAH's analysis
The CMV strain with a F626S substitution in pUL56 had a growth defect (requiring 8 days to reach the same SEAP activity that the UL56 wild-type CMV reference strain achieved in 6 days).

Participants with E237G, C325W, and R369T substitutions

The GV encoding the pUL56 E237G substitution was identified in a participant's plasma sample collected 32 days after discontinuation of LET prophylaxis on Study Week 6 (post-transplant Day 47). There were < 151 copies/mL of CMV DNA in the sample and E237G was detected in 4% of the CMV UL56 NGS reads. A recombinant CMV strain with the pUL56 E237G substitution had a 13-fold shift in the LET EC50 and a 2.1-fold shift in the EC50 for GCV. This substitution had no apparent impact on the replicative fitness of CMV. This participant received approximately 3 weeks of valganciclovir therapy after discontinuation of LET prophylaxis, and plasma CMV DNA levels were either <151 copies/mL or undetectable during this period (through Study Week 48).

The pUL56 C325W substitution confers a significant (8262-fold) decrease in susceptibility to LET in a cell-culture model of infection. The mutation encoding this substitution and 3 other pUL56 C325 variants (C325F/R/Y) have been described in recent publications (Chou et al 2018; Chou et al 2015). In the MK-8228 P001 trial, the genetic variation encoding the pUL56 C325W substitution was detected in a participant with clinically significant CMV infection at the time LET prophylaxis was discontinued and anti-CMV therapy was initiated, (99% of the NGS reads in a plasma sample with 28096 copies/mL of CMV DNA). The participant had detectable CMV DNA (<151 copies/mL) in a plasma sample collected when LET prophylaxis was initiated. The pUL56 C325W substitution does not impair the growth of CMV in cell culture and does not impact susceptibility to the CMV DNA polymerase inhibitors GCV, FOS, or CDV.

The genetic variant encoding pUL56 R369T was identified in plasma samples as part of a longitudinal analysis of the pUL56 C325W substitution. The pUL56 R369T variant was first detected on Day 25 following discontinuation of LET prophylaxis (12% NGS reads, 7003 CMV DNA copies/mL); however, this GV was not detected in plasma containing high concentrations of CMV DNA collected previously.

Because this GV was not detected at the time the participant met the primary endpoint, the association between the pUL56 R369T substitution and virologic breakthrough is unclear. Other substitutions at pUL56 R369 (R369G/M/S) that confer a modest decrease in susceptibility to LET in cell culture have been described previously (Goldner et al 2014). There was no impact of the pUL56 R369T substitution on CMV replicative fitness in the cell-culture model of infection and no significant impact on susceptibility to GCV/FOS/CDV.

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology of LET, including DDIs, have been previously assessed during the initial marketing authorisation application. No new DDI or phase 1 studies have been submitted. PK from study P002 (completed) and P042 (ongoing) were included in the popPK dataset together with phase 1 data. This approach is generally considered sufficient for this type II extension of indication for the use of Prevymis for CMV prophylaxis in kidney transplant recipient.

The provided pcVPCs indicate some model misspecification, especially for study P002 where Cmax does not appear to be well captured. The MAH has described the model misspecification and discussed that the model is adequate for AUC but not Cmax.
The modelling is not considered to be of high regulatory impact. AUC may also be affected by the

model misspecification, but it is agreed that this is to a lesser extent than Cmax.

The systemic exposure of letermovir is higher in kidney transplant recipients compared to HSCT patients due to higher bioavailability according to the MAH. Kidney transplantation may also affect clearance to some degree.

With regards to safety, the exposure is around 3-fold lower than phase I trials P026 and P004. Also, the safety data from study P002 does not indicate any new safety concerns which supports the proposed dosing.

The PK-profile in the Japanese study has a different shape and the exposure is higher compared to study P002. The model does not have a good prediction of the data from the Japanese study. The SmPC Section 5.2 includes the effect of Asian race on LET PK based on Phase 1 population PK analysis, having increased exposure.

CRCL and body weight were predicted to be influential on exposure of LET. Body weight in the KT population ranged from 40.4 kg to 147 kg. In univariate assessment, the impact of WT was evaluated by keeping all other covariates at their reference level. For KT recipients weighing 114 kg (95th percentile of WT), LET AUC is 24% lower, and for KT recipients weighing approximately 48 kg (5th percentile of WT), LET AUC is 44% higher, compared to KT recipients weighing approximately 79 kg (50th percentile of WT). The overall change in LET exposures due to WT across the body weight extremes evaluated was within the clinical comparability bounds (0.5 to 3) for the program. Thus, the effect of body weight on LET exposure is not considered clinically significant.

Pharmacodynamics

In the pivotal trial MK-8228 P001, DNA was isolated from plasma obtained from recipients of a hematopoietic stem cell transplant who met the primary endpoint of clinically significant CMV infection through Week 24 post-transplant. The MAH has submitted a report of the results of P001 phenotypic analysis to determine if any of the identified substitutions had an impact on susceptibility to LET.

Of the 14 pUL56 and 1 pUL89 substitutions tested, 12 had no significant impact on susceptibility to LET (pUL56 substitutions M3V, S255L, E485G, E485G + SNS445- 447deletion, Y575C, F626S, L726V, T775I, AVS789-791deletion, V814A, and R816W; pUL89 substitution I531T). The other 3 substitutions in pUL56 (E237G, C325W, and R369T) conferred a reduction in susceptibility to LET in a cell-culture model of CMV infection, with shifts in the LET EC50 relative to a UL56 wild-type CMV reference strain of 13-, 8262-, and 52-fold, respectively.

The replicative fitness of CMV virus with either of these three substitutions were not impaired. Susceptibility to GCV/FOS/CDV was overall maintained, only a slight shift (2.1-fold) in the GCV EC50 for the mutant CMV strain with the pUL56 E237G substitution.

The C325W was detected in a participant with clinically significant CMV infection at the time LET prophylaxis was discontinued (99% of the NGS reads). E237G was found in a plasma sample 32 days after discontinuation of LET and only in 4% of NGS reads. The pUL56 R369T substitution was not detected at the time the participant met the primary endpoint, but at Day 25 following discontinuation of LET in 12% NGS reads. The clinical significance of E237G and R369T substitutions is still unclear.

2.3.6. Conclusions on clinical pharmacology

The E-R was used for dose selection, however the adequacy of the proposed posology used in the pivotal study will be based on the assessment of the clinical efficacy and safety data.

The exposure in kidney transplant recipients is higher than in the previously approved indication (HSCT) based on the popPK analysis.

The PK-profile in the Japanese study has a different shape and the exposure is higher compared to study P002, the current text in the SmPC regarding the Asian population is deemed adequate.

CRCL and body weight were predicted to be influential on exposure of LET. Body weight in the KT population ranged from 40.4 kg to 147 kg.

The clinical pharmacology of LET, including DDIs, have previously been assessed during the initial marketing authorisation application. This data, together with the popPK analysis provided are considered sufficient regarding clinical pharmacology.

Pharmacodynamics

The three substitutions identified from participant's plasma samples with reduced susceptibility to LET (E237G, C325W, and R369T) are known resistance associate variants previously identified in vitro and already mentioned in the SmPC Section 5.1.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Rationale for Dose Selection for P002 and P040

The currently approved dose of LET is 480 mg once daily, administered orally or IV. The dose of LET should be reduced to 240 mg once daily when co-administered with cyclosporine. This dose of LET was selected for both P002 and P040 clinical studies. For P002, the LET dosage regimen was further supported by the E-R analysis for efficacy that indicated the range of exposures (LET AUC by quartiles) achieved in the kidney transplant recipients was efficacious (see also Clinical Pharmacology Section 2.3.3 and 2.3.4).

2.4.2. Main studies

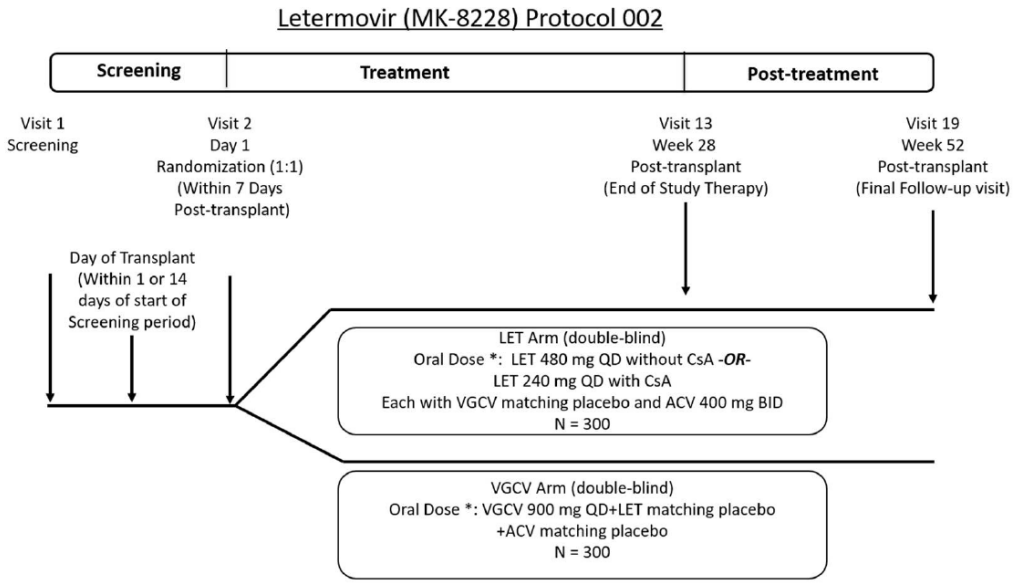
2.4.2.1. Study P002MK8228

Title: A Phase III, Randomized, Double-Blind, Active Comparator- Controlled Study to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) Versus Valganciclovir for the Prevention of Human Cytomegalovirus (CMV) Disease in Adult Kidney Transplant Recipients

Methods

P002 was a phase III, randomized, active-controlled, multi-site, double-blind study to evaluate the efficacy and safety of letermovir (LET) compared with valganciclovir (VGCV) administered for 200 days post-transplant for the prevention of cytomegalovirus (CMV) disease in adult seropositive donor/seronegative recipient (D+/R) kidney transplant recipients.

Figure 4: Study design



Screening of potentially eligible participants may begin on the day of transplantation (ie, prior to transplantation) or as early as one day before transplantation for participants receiving a kidney from a deceased donor and up to 14 days prior to (including the day of transplantation [ie, prior to transplantation]) transplantation for participants receiving a kidney from a living donor.

Dose of ACV, VGCV, and GCV will be modified based on creatinine clearance, see Section 7.2.

* If participants are unable to tolerate swallowing of tablets after randomization, then (in a blinded manner) IV formulations may be administered as follows: LET arm: IV LET 480 mg QD without CsA or 240 mg QD without CsA or 240 mg QD with CsA and IV ACV 250 mg/m^2 BID; VGCV arm: IV GCV 5 mg/kg QD and IV ACV matching placebo BID

ACV = acyclovir; BID = twice daily; CsA = cyclosporine A; GCV = ganciclovir; IV = intravenous; LET = letermovir; QD = once daily; VGCV = valganciclovir

After completion of study intervention at Week 28 post-transplant, participants were followed for efficacy, safety, and diagnosis of CMV disease through Week 52 post-transplant. Participants who discontinued study intervention early (i.e., before Week 28 post-transplant) were to complete all remaining treatment period visits through Week 28 post-transplant, as well as all remaining visits through Week 52 post-transplant. All scheduled study visits were to be completed regardless of when cessation of study intervention occurred.

The primary endpoint was the proportion of patients with CMV disease up to week 52 – that is 24 weeks post planned discontinuation of study therapy.

Study participants

Key inclusion criteria include:

1. Had a documented negative serostatus for CMV (i.e., recipient CMV immunoglobulin G (IgG) seronegative [R-]) within 180 days prior to randomization.
2. Anticipate receiving a primary or secondary allograft kidney from a CMV IgG D+ at the time of screening AND have received a primary or secondary allograft kidney from a documented D+ donor at the time of randomization.

Note: A donor who is seropositive solely based on having received a CMV seropositive transfusion immediately prior to organ donation is not considered to be a D+ in this study.

3. Be within 0 (i.e., day of transplantation) to 7 days (inclusive) post-kidney transplant at the time of randomization.

Key exclusion criteria include:

1. Received a previous solid organ transplant or HSCT.

Note: Participants who had received a prior primary allograft kidney were enrolled, provided that all other inclusion/exclusion criteria were met.

2. Was a multi-organ transplant recipient (e.g., kidney-pancreas).

Note: Double kidney transplant recipients (i.e., transplant of 2 kidneys from the same donor to the same recipient simultaneously) were excluded.

3. Had a history of CMV disease or suspected CMV disease within 6 months prior to randomization.
4. Had suspected or known hypersensitivity to active or inactive ingredients of LET formulations, VGCV, GCV, and/or ACV formulations.
5. Was on dialysis or plasmapheresis at the time of randomization.
6. Had post-transplant renal function of CrCl ≤10 mL/min at randomization (measured locally).
7. Had Child Pugh Class C severe hepatic insufficiency at screening.
8. Had both moderate hepatic insufficiency AND moderate-to-severe renal insufficiency at screening.
9. Had received within 30 days prior to randomization or planned to receive during the study any of the following anti-CMV IgG antibody treatment or anti-CMV drug therapy including: Cidofovir, CMV hyper-immune globulin, Any investigational CMV antiviral agent/biologic therapy
10. Had received within 7 days prior to randomization or planned to receive during the study any of the following anti-CMV drug therapy including: LET, GCV, VGCV, Foscarnet, ACV (at doses >3200 mg PO per day or >25 mg/kg IV per day), Valaciclovir (at doses >3 g PO per day), Famciclovir (at doses >1500 mg PO per day)

Note: The exclusion of LET, GCV, and VGCV applied to prior use and no additional unblinded use of LET, GCV, or VGCV outside of the context of the study.

Treatments

LET Arm:

- LET 480 mg once daily given orally (as one 480 mg tablet or two 240 mg tablets). If LET was co-administered with cyclosporine A (CsA), the dosage of LET was decreased to 240 mg once daily
- Two VGCV-matching placebo tablets
- Two aciclovir (ACV) 400 mg capsules or tablets (each capsule or tablet given every 12 hours) for prophylaxis of herpes simplex virus (HSV) and varicella zoster virus (VZV)

VGCV Arm:

- One 480 mg LET-matching placebo tablet or two 240 mg LET-matching placebo tablets
- Two VGCV 450 mg tablets
- Two ACV-matching placebo capsules or tablets (each capsule or tablet given every 12 hours)

An IV formulation was available for participants unable to tolerate swallowing and/or who had a condition interfering with the absorption of the oral formulation. The IV formulation of VGCV was GCV

5 mg/kg. Aciclovir was given for prophylaxis against HSV and VZV in participants in the LET group in order to mirror the anti-HSV and anti-VZV activities of VGCV.

Objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of LET versus VGCV, as measured by the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant. **Hypothesis (H1):** LET is noninferior to VGCV in the prevention of CMV disease through 52 weeks post-transplant. **Hypothesis (H2):** LET is superior to VGCV in the prevention of CMV disease through 52 weeks post-transplant. Hypothesis testing will be performed only if noninferiority is demonstrated.	CMV disease
Secondary	
To evaluate the efficacy of LET versus VGCV, as measured by the proportion of participants with adjudicated CMV disease through 28 weeks post-transplant.	CMV disease
To evaluate the efficacy of LET versus VGCV, as measured by the time to onset of adjudicated CMV disease through 52 weeks post-transplant.	Time to onset of adjudicated CMV disease through 52 weeks post-transplant
To evaluate the safety and tolerability of LET versus VGCV.	Accumulated safety data (adverse events (AE), laboratory, vital signs, etc.)
Tertiary/Exploratory	
To evaluate the proportion of participants with quantifiable CMV DNAemia in LET versus VGCV as measured by the central laboratory through 28 weeks post-transplant and 52 weeks post-transplant.	Quantifiable CMV DNAemia
To evaluate the proportion of participants who develop leukopenia and neutropenia in LET versus VGCV during the treatment phase.	Laboratory and AEs of leukopenia and neutropenia

Objectives	Endpoints
To evaluate the proportion of participants experiencing allograft dysfunction and/or rejection in LET versus VGCV through 28 weeks post-transplant and 52 weeks post-transplant.	Allograft dysfunction and/or rejection
To evaluate the incidence of NODAT in LET versus VGCV through 28 weeks post-transplant and 52 weeks post-transplant.	NODAT
To evaluate health outcomes in LET versus VGCV through 28 weeks post-transplant and 52 weeks post-transplant.	Health outcomes
To evaluate the antiviral resistance to LET in prophylaxis failures through 52 weeks post-transplant.	Antiviral resistance to LET
To explore the relationship between CMV glycoprotein B (gB) genotype and response to the treatments administered	CMV glycoprotein B (gB) genotype determined by DNA sequencing of the CMV UL55 gene in plasma samples collected from participants who meet the criteria for confirmed CMV disease or in whom study therapy was stopped and CMV treatment was started
To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. • Variation across the human genome will be analyzed for association with clinical data collected in this study. • Variation in the SLCO1B1 (OATP1B1) and UGT1A1 genes will also specifically be evaluated.	Genetic analyses
To evaluate patient-reported outcomes in LET versus VGCV through 52 weeks post-transplant.	EuroQol (EQ)-5D and 36-Item Short Form Health Survey Version 2.0 (SF 36v2®) scores
To evaluate the pharmacokinetics of LET.	Pharmacokinetic endpoints

Appropriateness of Measurements

To standardize the clinical diagnosis of investigator-reported cases of CMV disease, an independent blinded Clinical Adjudication Committee was established for this study. All cases of investigator reported CMV disease were reviewed by the Clinical Adjudication Committee and required confirmation that each case of CMV disease met the criteria for CMV disease provided in the study protocol.

Definitions:

CMV infection is defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen.

CMV disease consists of the two following clinical definitions:

1) CMV end-organ disease; alternatively

2) "probable CMV syndrome" (which will be termed "CMV syndrome").

- CMV end-organ disease may be further described by:
    - The specific type of end-organ disease (e.g., pneumonia, gastrointestinal disease, or hepatitis); and
    - By appropriate clinical signs/symptoms with documentation of CMV by:
        - Histopathology, virus isolation, rapid culture, immunohistochemistry, or DNA hybridization in tissue (proven CMV end-organ disease); or
        - High viral DNA levels detected in tissue from the relevant organ (possible CMV end-organ disease).
- CMV syndrome requires detection of CMV in blood by virus isolation, rapid culture, antigenemia, or nucleic acid testing with at least two of the following criteria:
    1. Fever ≥38°C for at least 2 days
    2. New or increased malaise or new or increased fatigue
    3. Leukopenia or neutropenia on two separate measurements at least 24 hours apart
    4. ≥5% atypical lymphocytes
    5. Thrombocytopenia
    6. Elevation of ALT or AST to 2 × ULN

Sample size

Three hundred (300) participants were to be randomized into each treatment arm for a total of 600 participants. Assuming the true proportion of participants with adjudicated CMV disease is 0.17 for both treatment arms, this study has 90% power to demonstrate that LET is non-inferior to VGCV at an overall two-sided 5% alpha-level, using a non-inferiority margin of 0.10.

The minimum criterion for success is that the upper bound of 95% CI of difference (LET minus VGCV) <0.10. The observed proportion of participants in the LET arm needs to be less than 4% higher than that in the VGCV arm in order to declare non-inferiority. If the observed proportion of participants in the LET arm is approximately 9% lower than in the VGCV arm, this is expected to demonstrate superiority with 90% power.

The adjudicated CMV disease incidence of 17% is supported by the results of the IMPACT study. In this study, the primary efficacy endpoint was the proportion of D+/R – participants who developed CMV disease adjudicated by the CAC.

Rationale for Non-Inferiority Margin

The 10% non-inferiority margin used in this study is based on the preservation of the majority of efficacy (>50%) of VGCV compared to placebo in preventing CMV disease after renal transplantation under a number of scenarios.

From the VGCV label for 200-day treatment, the CMV disease rate at 12 months post-transplant in the VGCV group was 16.8% (26 out of 155), which corresponds to a disease-free rate of 83.2% with a 95% confidence interval (CI) of (76.4%, 88.7%). The proportion of participants with CMV disease in a placebo group at 52 weeks post-transplant was extrapolated from Lowance, et al. [Lowance, D. et al 1999], which showed that the CMV disease rate was 45% at 90 days after renal transplantation (corresponding to a disease-free rate of 55%). Since it is expected that more cases of CMV disease would occur between 90 days and 12 months post-transplant, it is reasonable to assume the disease-free rate in a placebo group at 12 months post-transplant is 50% or less.

The table below shows the percent of efficacy retained in this study using a 10 percent point margin

for a range of disease-free rates consistent with the above assumptions for the VGCV and placebo groups. The percent retained was based on the lower bound of the 95% CI of difference in the disease-free rate (VGCV - Placebo), assuming 300 participants per group.

For example, in the scenario where the VGCV disease-free rate = 90% and the placebo disease-free rate = 50%, the 95% two-sided CI for the VGCV rate (270/300) minus the placebo rate (150/300) is (33%, 46%) using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. A 10 percentage point non-inferiority margin would indicate that the lower bound for this difference in the study could be as low as 23% (33% minus 10%); thus, the percent retained would be 23/33 = 69.7%.

According to the MAH this is a conservative approach since the lower bound of the 95% CI was used as the historical effect and a range of possible placebo rates were used in the calculations. In the majority of scenarios in Table 1, more than 50% of the efficacy is retained using the 10 percentage point margin. Thus, a 10 percentage point margin is proposed in this study.

Table 11: Percentage of Efficacy Retained with 10 percentage point Margin (n = 300/arm)

	Placebo Disease-free Rate			
VGCV Disease-free Rate	**0.50**	**0.45**	**0.40**	**0.35**
0.9	69.7%	73.7%	76.7%	79.2%
0.85	64.3%	69.7%	73.7%	76.7%
0.8	56.5%	64.3%	69.7%	73.7%
0.75	41.2%	54.5%	63.0%	68.8%
VGCV = valganciclovir				

Randomisation

All eligible participants will be randomly allocated and will receive a treatment/randomization number. A single participant cannot be assigned more than 1 treatment/randomization number. A total of 601 D+/R- kidney transplant recipients were randomized within 7 days post-transplant in a 1:1 ratio to receive LET or VGCV from Day 1 (day of randomization) through Week 28 post-transplant. Randomized participants were stratified by the use or non-use of highly cytolytic antilymphocyte immunotherapy during induction, which is associated with risk for CMV infection.

Blinding (masking)

A double-blinding technique with in-house blinding was used. IV LET, IV GCV, IV ACV (for participants in the LET arm), and IV ACV matching placebo (for participants in the VGCV arm) will be prepared in a blinded fashion by an unblinded pharmacist (or qualified study site personnel designated to prepare blinded IV study therapy). If a participant's dose of VGCV or VGCV matching placebo is modified due to renal insufficiency, the blinding to VGCV or VGCV matching placebo will be maintained. Similarly, if a participant's dose of ACV or ACV matching placebo is modified due to renal insufficiency, the blinding to ACV or ACV matching placebo will be maintained.

A total of 5 incidents of participant unblinding occurred during the study through Week 52 post-transplant:

- Two participants were inadvertently unblinded to a blinded non-site staff clinical research associate during the study. Although the blinded clinical research associate was inadvertently

unblinded, it was confirmed that the blinded site personnel did not see the unblinded documentation and unblinding did not occur. The clinical research associate was subsequently removed from the study. These events were reported as important protocol deviations and were not considered clinically important.

- Three participants were unblinded per protocol in order to receive the most appropriate treatment for CMV disease. Two of the participants were unblinded after completion of the study, and the third participant was unblinded due to lack of efficacy after completion of treatment. These events were not considered to be protocol deviations.

Statistical methods

The primary efficacy endpoint was the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant. If the primary objective of non-inferiority was achieved, superiority of LET versus VGCV were to be evaluated by comparing the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant.

Analysis Populations

Full Analysis Set (FAS): The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who received at least one dose of study treatment, are D+/R-, and had no detectable CMV viral DNA (measured by central laboratory) on Day 1.

Per Protocol (PP): The PP population will serve as a supportive analysis population. The PP population excludes participants due to important deviations from the protocol that may substantially affect the results of the primary and secondary efficacy endpoints.

All Subjects as Treated (ASaT): The *ASaT* population will be used for the analysis of safety data in this study.

Efficacy Analysis

To test the primary hypothesis that LET is non-inferior to VGCV in the prevention of CMV disease, the difference between the two treatment arms in the proportions of participants with adjudicated CMV disease through 52 weeks post-transplant and the associated two-sided 95% CI will be calculated using the stratum-adjusted Mantel-Haenszel method with stratification by highly cytolytic anti-lymphocyte therapies. LET will be concluded to be non-inferior to VGCV if the upper bound of the two-sided 95% CI for the difference in proportion of participants with adjudicated CMV disease (LET - VGCV) is no higher than 0.10.

The primary efficacy analysis will be performed on the FAS population, with the PP population considered a supportive approach. A sensitivity analysis including those participants who were assessed by the investigator to have CMV disease regardless of the CAC determination will be performed. An additional sensitivity analysis will be performed where any participant who discontinues study treatment but thereafter is started on CMV prophylaxis at the discretion of the investigator is considered a failure. Provided non-inferiority is established, a hypothesis that LET is superior to VGCV in the prevention of CMV disease will be tested. The stratum-adjusted Mantel-Haenszel method (with continuity correction) will be used to compare the two treatment arms with respect to the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant using the stratification factor of highly cytolytic anti-lymphocyte therapies.

LET will be concluded to be superior to VGCV if the upper bound of the two-sided 95% CI for the difference in proportion of participants with adjudicated CMV disease (LET - VGCV) is less than 0.

To assess the difference in the proportion of participants with adjudicated CMV disease through 28 weeks post-transplant, the same method as for primary endpoint will be used. Formal hypothesis testing will be done on this endpoint in the event that the second primary hypothesis of superiority is met.

Time to onset of adjudicated CMV disease through 52 weeks post-transplant will be estimated using the nonparametric Kaplan-Meier method. The Kaplan-Meier curve will be plotted by treatment arm and a p-value for the between arm difference in time to onset of adjudicated CMV disease will be provided using the stratified log-rank test with stratification by highly cytolytic anti-lymphocyte therapies. Observations will be censored at the time of discontinuation from the study, or at completion of the study.

Missing Data Handling

The primary missing data approach will be the Observed Failure (OF) approach. Using this approach, participants who discontinue prematurely from the study for any reason are not considered failures. The Non-Completer = Failure (NC = F) approach will be used as a supportive analysis. Non-completers refers to participants who prematurely discontinue from the study for any reason without having developed CMV disease. Using the NC = F approach, these participants will also be considered failures. Additional analysis to evaluate the potential effect of violations in assumptions about the missing data may be performed.

Interim Analyses

No interim analyses for efficacy were planned or performed.

Multiplicity

The primary efficacy hypothesis for non-inferiority will be tested at a two-sided alpha level of 5% because no interim efficacy analyses will be performed. If the primary efficacy hypothesis testing for non-inferiority of LET is met, the second primary hypothesis of superiority will be tested at the two-sided Type I error rate of 5%. If the second primary hypothesis of superiority is met, similar step-down hypothesis testing will be performed for the secondary endpoint of adjudicated CMV disease through 28 weeks post-transplant. Other efficacy analyses will be considered secondary or explanatory.

Results

Participant flow

A total of 693 participants were screened, 601 were randomized and 589 received at least 1 dose of study intervention. All nonrandomized participants were screen failures.

Table 12: Participant disposition

	LET Arm		VGCV Arm		Total	
	n	(%)	n	(%)	n	(%)
Participants In Population	301		300		601	
Treated	292	(97.0)	297	(99.0)	589	(98.0)
Not Treated	9	(3.0)	3	(1.0)	12	(2.0)
Completed Study Medication	246	(81.7)	224	(74.7)	470	(78.2)
Discontinued Study Medication	46	(15.3)	73	(24.3)	119	(19.8)
Adverse Event	13	(4.3)	40	(13.3)	53	(8.8)
Death	2	(0.7)	0	(0.0)	2	(0.3)
Lack Of Efficacy	0	(0.0)	11	(3.7)	11	(1.8)
Noncompliance With Study Drug	3	(1.0)	0	(0.0)	3	(0.5)
Physician Decision	6	(2.0)	7	(2.3)	13	(2.2)
Protocol Deviation	4	(1.3)	1	(0.3)	5	(0.8)
Withdrawal By Subject	18	(6.0)	14	(4.7)	32	(5.3)
Completed Study	256	(85.0)	266	(88.7)	522	(86.9)
Discontinued Study	36	(12.0)	31	(10.3)	67	(11.1)
Death	3	(1.0)	3	(1.0)	6	(1.0)
Lost To Follow-Up	1	(0.3)	2	(0.7)	3	(0.5)
Other	1	(0.3)	2	(0.7)	3	(0.5)
Physician Decision	3	(1.0)	3	(1.0)	6	(1.0)
Withdrawal By Subject	28	(9.3)	21	(7.0)	49	(8.2)

Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

Recruitment

Study centres: This study was conducted at 94 centres in 16 countries: New Zealand, Australia, Austria, Belgium, France, Germany, Italy, Spain, United Kingdom, Poland, Argentina, Colombia, Mexico, Canada, USA and Hungary.

Study status: This study is complete; this report is based on the final analysis.

First Patient, First Visit	Last Patient, Last Visit	Database Lock Date
03-MAY-2018	05-APR-2022	27-JUL-2022

Conduct of the study

Changes to the planned analyses

Changes to the planned analysis not previously described in a protocol amendment or in the supplemental SAP are described below.

The protocol specified that the time to onset of adjudicated CMV disease through Week 52 post-transplant (secondary endpoint) would be calculated in days from the day of randomization to the day of onset. However, the time to onset was instead calculated in days from the day of transplant to the day of onset.

The study protocol definition for leukopenia or neutropenia described a WBC count of ≤3500 cells/µL and ≤1000 cells/µL, respectively. The actual analyses defined leukopenia and neutropenia as <3500 cells/µL and <1000 cells/µL, respectively. There were no changes in the planned analyses following study unblinding and no post-hoc analyses were performed due to the COVID-19 pandemic or any

other reason.

Protocol amendments

P002-05, 27-Aug-2019: To add the requirement that the intravenous (IV) formulation of letermovir (LET) supplied by the Sponsor to sites as study medication must be administered through a sterile 0.2-micron or 0.22-micron polyethersulfone (PES) in-line filter and using diethylhexyl phthalate (DEHP)-free IV bags and infusion set materials (the same applies for placebo and aciclovir to maintain blinding). This requirement is being added to prevent the possible administration of product-related particulate matter. The presence of visible product-related particulate matter is an expected characteristic of new clinical supplies of the IV formulation of LET.

P002-04, 11-Feb-2019 : To add strong and moderate inducers of transporters (e.g., Pglycoprotein [P-gp]) and/or enzymes (e.g., uridine diphosphate glucuronosyltransferase [UGT]) to the list of prohibited medications due to the potential for co-administration to result in a decrease in letermovir plasma concentrations.

P002-03, 29-May-2018: To permit potential participants to be consented and screened up to 5 days (inclusive) after transplant surgery instead of requiring the completion of all screening procedures prior to transplant.

P002-02, 21-Feb-2018: To add two laboratory exclusion criteria for consistency with the valganciclovir (VGCV) product circular information.

P002-01, 07-Dec-2017: To add a letermovir (LET) 240 mg dose group when administered intravenously (IV) without cyclosporine (CsA). LET has previously been evaluated in a Phase 3 trial in hematopoietic stem cell transplant (HSCT) recipients at doses of 240 mg PO or IV when administered with CsA, and 480 mg PO or IV when administered without CsA. All doses were generally well-tolerated and efficacious; however, LET exposures (steady state median AUC) in HSCT recipients with the 480 mg IV dose (without CsA) were higher than in the other three dose groups. Population pharmacokinetic (PK) simulations using data from the Phase 3 trial in HSCT recipients suggest that a 240 mg IV dose (without CsA) will provide exposures comparable to exposures obtained following administration of a 480 mg PO dose (without CsA). Therefore, an additional dose group of 240 mg IV (without CsA) is being added to the current protocol to evaluate the PK, efficacy, and safety of this dose in transplant recipients. Participants who receive IV LET (without CsA) will be randomized 1:1 to receive either a 480 mg or 240 mg dose.

P002-00, 21-Sep-2017: Original protocol

Protocol Deviations

Important protocol deviations were reported for 100 (33.2%) participants in the LET group and 105 (35.0%) participants in the VGCV group. Of these, 63 (20.9%) participants in the LET group and 61 (20.3%) participants in the VGCV group had important protocol deviations that were considered clinically important.

The most frequently reported clinically important protocol deviations in both intervention groups were:

- Related to study procedures (LET: 39 [13.0%]; VGCV: 34 [11.3%]): CMV disease visit procedures, including collection of blood samples for safety monitoring, were not performed prior to starting anti-CMV therapy.
- Administration of improperly stored study intervention (LET: 16 [5.3%]; VGCV: 14 [4.7%]).

The protocol deviations were comparably distributed between intervention groups. Participants data were excluded from the efficacy analyses due to important protocol deviations (i.e., PP population). A sensitivity analysis of the PP population showed no impact on the primary endpoint (performed on FAS).

No important protocol deviations were classified as a serious GCP noncompliance issue. Part of this study was conducted during the COVID-19 pandemic. Important and not important protocol deviations associated with the pandemic were reported for 98 (32.6%) participants in the LET group and 107 (35.7%) participants in the VGCV group. All clinically important protocol deviations associated with the pandemic were related to study procedures and the administration of improperly stored study intervention.

Baseline data

Table 13: Participant Characteristics (All Participants as Treated)

	LET Arm		VGCV Arm		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	292		297		589	
Sex						
Male	213	(72.9)	209	(70.4)	422	(71.6)
Female	79	(27.1)	88	(29.6)	167	(28.4)
Age (Years)						
18 - 35	62	(21.2)	62	(20.9)	124	(21.1)
36 - 50	78	(26.7)	84	(28.3)	162	(27.5)
51 - 64	104	(35.6)	96	(32.3)	200	(34.0)
65 - 74	42	(14.4)	47	(15.8)	89	(15.1)
≥ 75	6	(2.1)	8	(2.7)	14	(2.4)
Participants with data	292		297		589	
Mean (SD)	49.5 (14.7)		49.6 (15.1)		49.6 (14.9)	
Median (Range)	52.0 (18 to 82)		51.0 (18 to 78)		51.0 (18 to 82)	
Race						
American Indian Or Alaska Native	3	(1.0)	4	(1.3)	7	(1.2)
Asian	4	(1.4)	10	(3.4)	14	(2.4)
Black Or African American	21	(7.2)	33	(11.1)	54	(9.2)
Multiple	9	(3.1)	6	(2.0)	15	(2.5)
American Indian Or Alaska Native, White	8	(2.7)	5	(1.7)	13	(2.2)
Native Hawaiian Or Other Pacific Islander, White	1	(0.3)	0	(0.0)	1	(0.2)
White, Asian	0	(0.0)	1	(0.3)	1	(0.2)
White	253	(86.6)	243	(81.8)	496	(84.2)
Missing	2	(0.7)	1	(0.3)	3	(0.5)
Ethnicity						
Hispanic Or Latino	54	(18.5)	44	(14.8)	98	(16.6)
Not Hispanic Or Latino	223	(76.4)	238	(80.1)	461	(78.3)
Not Reported	6	(2.1)	9	(3.0)	15	(2.5)
Unknown	5	(1.7)	4	(1.3)	9	(1.5)
Missing	4	(1.4)	2	(0.7)	6	(1.0)

	LET Arm		VGCV Arm		Total	
	n	(%)	n	(%)	n	(%)
Stratum: Highly Cytolytic Anti-lymphocyte Immunotherapya						
Use	134	(45.9)	138	(46.5)	272	(46.2)
Non-use	158	(54.1)	159	(53.5)	317	(53.8)
Primary Reason for Transplant						
Alport's syndrome	4	(1.4)	6	(2.0)	10	(1.7)
Chronic kidney disease / End stage renal disease	19	(6.5)	20	(6.7)	39	(6.6)
Congenital cystic kidney disease	52	(17.8)	50	(16.8)	102	(17.3)
Diabetes / Diabetic nephropathy	39	(13.4)	46	(15.5)	85	(14.4)
Glomerulonephritis	37	(12.7)	30	(10.1)	67	(11.4)
Hypertension	42	(14.4)	53	(17.8)	95	(16.1)
IgA nephropathy	36	(12.3)	26	(8.8)	62	(10.5)
Lupus	2	(0.7)	5	(1.7)	7	(1.2)
Mesangioproliferative glomerulonephritis	2	(0.7)	1	(0.3)	3	(0.5)
Renal atrophy	5	(1.7)	3	(1.0)	8	(1.4)
Tubulointerstitial nephritis	3	(1.0)	7	(2.4)	10	(1.7)
Urinary obstruction	8	(2.7)	4	(1.3)	12	(2.0)
Otherb	43	(14.7)	46	(15.5)	89	(15.1)
Donor Type						
Living Related	56	(19.2)	64	(21.5)	120	(20.4)
Living not Related	65	(22.3)	51	(17.2)	116	(19.7)
Deceased	171	(58.6)	182	(61.3)	353	(59.9)
Transplantation Duration (hours)						
Living Donor						
Participants with data	121		115		236	
Mean (SD)	3.3 (1.4)		3.2 (1.4)		3.2 (1.4)	
Median (Range)	3.1 (0.3 to 9.5)		2.9 (0.3 to 6.7)		3.0 (0.3 to 9.5)	
Deceased Donor						
Participants with data	170		178		348	
Mean (SD)	3.0 (1.7)		2.9 (1.8)		2.9 (1.8)	
Median (Range)	2.7 (0.4 to 14.7)		2.7 (0.4 to 22.0)		2.7 (0.4 to 22.0)	

	LET Arm		VGCV Arm		Total	
	n	(%)	n	(%)	n	(%)
Ex Vivo Time (hours)						
Living Donor						
Participants with data	116		103		219	
Mean (SD)	2.2 (2.1)		2.3 (2.7)		2.3 (2.4)	
Median (Range)	1.3 (0.0 to 15.4)		1.6 (0.1 to 24.5)		1.4 (0.0 to 24.5)	
Deceased Donor						
Participants with data	169		175		344	
Mean (SD)	15.4 (9.5)		14.6 (7.8)		15.0 (8.7)	
Median (Range)	14.0 (0.3 to 86.0)		14.0 (1.6 to 60.2)		14.0 (0.3 to 86.0)	
Post-Transplant Dialysis (Including Hemofiltration) Prior to Randomization						
Yes	9	(3.1)	10	(3.4)	19	(3.2)
No	283	(96.9)	287	(96.6)	570	(96.8)
Days From Transplantation to Randomization						
Participants with data	292		297		589	
Mean (SD)	4.3 (1.9)		4.4 (1.9)		4.3 (1.9)	
Median (Range)	5.0 (1.0 to 7.0)		5.0 (1.0 to 7.0)		5.0 (1.0 to 7.0)	
Days From Transplantation to Start of Study Therapy						
Participants with data	292		297		589	
Mean (SD)	4.4 (1.8)		4.5 (1.9)		4.4 (1.9)	
Median (Range)	5.0 (1.0 to 8.0)		5.0 (1.0 to 8.0)		5.0 (1.0 to 8.0)	
Recipient CMV Serostatus						
Positive	1	(0.3)	0	(0.0)	1	(0.2)
Negative	291	(99.7)	297	(100.0)	588	(99.8)
Donor CMV Serostatus						
Positive	292	(100.0)	297	(100.0)	589	(100.0)

[a] Use of highly cytolytic anti-lymphocyte immunotherapy is use of one or more of the following: horse-derived or rabbit-derived anti-thymocyte globulin, alemtuzumab (CAMPATHTM), or muromonab CD3 (OKT3). Stratum based on confirmation of highly cytolytic anti-lymphocyte immunotherapy received at time of transplant.

[b] Other reasons for transplant are provided in section 14.

Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

Medical History

Reported medical history conditions were as expected for the adult kidney transplant population and were generally comparable between intervention groups. Overall, the 3 most frequently reported medical history conditions were hypertension, end-stage renal disease, and anaemia.

Prior and Concomitant Medications/Treatments

Reported prior and concomitant medications were generally comparable between intervention groups. The 3 most frequently reported prior therapies were tacrolimus, paracetamol, and furosemide. The 3 most frequently reported concomitant therapies during both the Treatment Phase (through Week 28 post-transplant) and the Treatment and Follow-up Phase (through Week 52 post-transplant) were tacrolimus, prednisone, and mycophenolate mofetil.

Numbers analysed

Table 14: Data sets analysed

Population	Definition	Use	Number of Participants
FAS	Includes all randomized participants who received at least one dose of study intervention, were D+/R-, and had no detectable CMV viral DNA (measured by central laboratory) on Day 1.	Primary Analysis Population Exploratory Analysis	N=586
PP	Excludes participants due to important deviations from the protocol that may substantially affect the results of the primary and secondary efficacy endpoints.	Supportive Analysis Population	N=532
APaT	Excludes participants who were randomized and did not receive study intervention.	Safety Population	N=589

APaT=All Participants as Treated; CMV=cytomegalovirus; D+=seropositive donor; DNA=deoxyribonucleic acid; FAS=Full Analysis Set; PP=Per Protocol; R-=seronegative recipient

Participants Included in the Efficacy Analyses

The primary efficacy analyses were conducted using the FAS population. Of the 601 randomized participants, 15 participants were excluded from the FAS population (12 participants did not receive study intervention [5 of whom also had incorrect serostatus], 2 participants had detectable CMV DNA on Day 1, and 1 participant entered the study with incorrect serostatus. The remaining 586 randomized participants received at least 1 dose of study intervention and were included in the FAS population. Supportive efficacy analyses were conducted using the PP population.

Safety Analysis Population

Safety analyses were based on the APaT population, which included all 589 randomized participants who received at least 1 dose of study intervention according to the study intervention they received.

Outcomes and estimation

Primary efficacy endpoint

CMV Disease Through Week 52 Post-transplant

Table 15: Analysis of Proportion of Participants With CMV Disease Through Week 52 Post-Transplant (OF Approach, Full Analysis Set Population)

Parameter	LET Arm (N=289) n (%)	VGCV Arm (N=297) n (%)
Failures	**30 (10.4)**	**35 (11.8)**
CMV Disease[a] Through Week 52	30 (10.4)	35 (11.8)
CMV Syndrome	24 (8.3)	34 (11.4)
CMV End-organ Disease	6 (2.1)	1 (0.3)
Stratum-adjusted Treatment Difference (LET Arm-VGCV Arm)[b]		
Difference (95% CI)	-1.4 (-6.5, 3.8)	
Conclusion[c]	Non-inferior	

Approach to handling missing values: Observed failure (OF) approach. With OF approach, participants who discontinue prematurely from the study for any reason are not considered failures.

[a] CMV disease cases confirmed by an independent adjudication committee.

[b] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction).

[c] LET is concluded non-inferior to VGCV if the upper bound of the two-sided 95% CI for difference in proportion of participants with adjudicated CMV disease (LET – VGCV) is no higher than 10%. LET is concluded superior to VGCV if the upper bound of the two-sided 95% CI for difference in proportion of participants with adjudicated CMV disease (LET – VGCV) is less than 0.

Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

Table 16: Summary of CMV Disease Cases Through Week 52 Post-Transplant (Full Analysis Set Population)

	LET Arm		VGCV Arm		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	**289**		**297**		**586**	
With CMV Disease[a] Cases	30	(10.4)	35	(11.8)	65	(11.1)
With no CMV Disease Cases	259	(89.6)	262	(88.2)	521	(88.9)
CMV End-Organ Disease	**6**	**(2.1)**	**1**	**(0.3)**	**7**	**(1.2)**
GI Disease	5	(1.7)	0	(0.0)	5	(0.9)
Pneumonia	1	(0.3)	1	(0.3)	2	(0.3)
CMV Syndrome	**24**	**(8.3)**	**34**	**(11.4)**	**58**	**(9.9)**
CMV Syndrome Findings[b]						
Elevation of ALT or AST Greater than or Equal to 2 X ULN	12	(4.2)	11	(3.7)	23	(3.9)
Fever	6	(2.1)	8	(2.7)	14	(2.4)
Greater than or Equal to 5% Atypical Lymphocytes	1	(0.3)	3	(1.0)	4	(0.7)
Leukopenia or Neutropenia	14	(4.8)	25	(8.4)	39	(6.7)
Malaise or Fatigue New or Increased	19	(6.6)	27	(9.1)	46	(7.8)
Thrombocytopenia	6	(2.1)	11	(3.7)	17	(2.9)
CMV DNAemia	24	(8.3)	34	(11.4)	58	(9.9)

[a] CMV disease cases confirmed by an independent adjudication committee.

[b] Participants will have at least 2 CMV syndrome findings in addition to CMV DNAemia.

Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

Concordance between the adjudication committee and the investigator assessment of CMV disease was comparable for the LET and VGCV groups. Of the 105 investigator-reported cases, 65 were adjudicated "yes" and 40 were adjudicated "no". Most of the CMV disease events adjudicated "no" were end-organ disease events that lacked sufficient documentation of tissue invasive disease (i.e., biopsy or bronchial lavage were not performed) as specified in the adjudication charter.

Sensitivity analyses

Results of a sensitivity analysis using the NC=F approach in the FAS population and the OF approach in the PP population were consistent with the primary analysis (see tables below).

Table 17: Analysis of Proportion of Participants With CMV Disease Through Week 52 Post-Transplant (NC=F Approach, Full Analysis Set Population)

Parameter	LET Arm (N=289) n (%)	VGCV Arm (N=297) n (%)
Failures	**86 (29.8)**	**88 (29.6)**
CMV Disease[a] Through Week 52	30 (10.4)	35 (11.8)
CMV Syndrome	24 (8.3)	34 (11.4)
CMV End-organ Disease	6 (2.1)	1 (0.3)
Discontinued From Study Before Week 52	32 (11.1)	28 (9.4)
Missing Outcome in Week 52 Visit Window	24 (8.3)	25 (8.4)
Stratum-adjusted Treatment Difference (LET Arm-VGCV Arm)[b]		
Difference (95% CI)	0.3 (-7.1, 7.6)	

Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all participants who were adjudicated as having CMV disease or prematurely discontinued from the study.

[a] CMV disease cases confirmed by an independent adjudication committee.

[b] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction).

Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

Table 18: Analysis of Proportion of Participants With CMV Disease Through Week 52 Post-Transplant (OF Approach, Per Protocol Population)

Parameter	LET Arm (N=266) n (%)	VGCV Arm (N=266) n (%)
Failures	**29 (10.9)**	**33 (12.4)**
CMV Disease[a] Through Week 52	29 (10.9)	33 (12.4)
CMV Syndrome	24 (9.0)	32 (12.0)
CMV End-organ Disease	5 (1.9)	1 (0.4)
Stratum-adjusted Treatment Difference (LET Arm-VGCV Arm)[b]		
Difference (95% CI)	-1.4 (-6.9, 4.1)	

Approach to handling missing values: Observed failure (OF) approach. With OF approach, participants who discontinue prematurely from the study for any reason are not considered failures.

[a] CMV disease cases confirmed by an independent adjudication committee.

[b] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction).

Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

Secondary efficacy endpoints

Adjudicated CMV Disease Through 28 Weeks Post-transplant

Table 19: Analysis of Proportion of Participants With CMV Disease Through Week 28 Post-Transplant (OF Approach, Full Analysis Set Population)

Parameter	LET Arm (N=289) n (%)	VGCV Arm (N=297) n (%)
Failures	**0 (0.0)**	**5 (1.7)**
CMV Disease[a] Through Week 28	0 (0.0)	5 (1.7)
CMV Syndrome	0 (0.0)	5 (1.7)
CMV End-organ Disease	0 (0.0)	0 (0.0)
Stratum-adjusted Treatment Difference (LET Arm-VGCV Arm)[b]		
Difference (95% CI)	-1.7 (-3.4, 0.1)	

Approach to handling missing values: Observed failure (OF) approach. With OF approach, participants who discontinue prematurely from the study for any reason are not considered failures.

[a] CMV disease cases confirmed by an independent adjudication committee.

[b] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction).

Note: LET is given concomitantly with aciclovir. VGCV is given concomitantly with a placebo to aciclovir.

The results of a supportive analysis using the NC=F approach in the FAS population were consistent with the OF approach.

Table 20: Analysis of Proportion of Participants With CMV Disease Through Week 28 Post-Transplant (NC=F Approach, Full Analysis Set Population)

Parameter	LET Arm (N=289) n (%)	VGCV Arm (N=297) n (%)
Failures	**49 (17.0)**	**48 (16.2)**
CMV Disease[a] Through Week 28	0 (0.0)	5 (1.7)
CMV Syndrome	0 (0.0)	5 (1.7)
CMV End-organ Disease	0 (0.0)	0 (0.0)
Discontinued From Study Before Week 28	28 (9.7)	19 (6.4)
Missing Outcome in Week 28 Visit Window	21 (7.3)	24 (8.1)
Stratum-adjusted Treatment Difference (LET Arm-VGCV Arm)[b]		
Difference (95% CI)	0.9 (-5.1, 6.9)	

Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all participants who were adjudicated as having CMV disease or prematurely discontinued from the study.

[a] CMV disease cases confirmed by an independent adjudication committee.

[b] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction).

Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

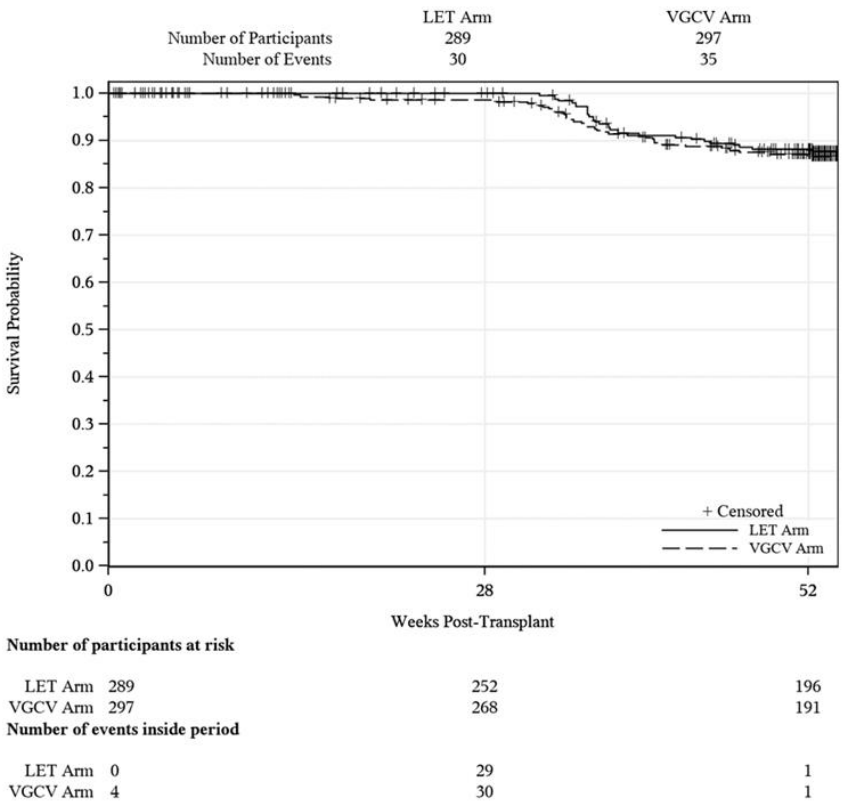
Time to Onset of Adjudicated CMV Disease Through 52 Weeks Post-transplant

Table 21: Analysis of Time to Onset of CMV Disease Through Week 52 Post-transplant (Full Analysis Set Population)

Treatment	N	Number of Events (%)	Person-day	Event Rate/ 100 Person-days	Median Time (days) to CMV Disease[a] (95% CI)[b]	CMV Disease[a]-Free Rate at Week 52 Post-Transplant % (95% CI)[b]	
LET Arm	289	30 (10.4)	91532.0	0.0	NR (NR, NR)	88.2 (83.4, 91.6)	
VGCV Arm	297	35 (11.8)	96402.0	0.0	NR (NR, NR)	87.1 (82.4, 90.6)	
Comparisons						Hazard Ratio (95% CI)[c]	p-Value[d]
LET Arm vs. VGCV Arm						0.90 (0.56, 1.47)	0.6802

[a] CMV disease cases confirmed by an independent adjudication committee.
[b] From product-limit (Kaplan-Meier) method for censored data.
[c] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by stratum (use / nonuse of highly cytolytic anti-lymphocyte immunotherapy). Hazard ratio < 1 favors the LET (200 days LET) group.
[d] Two-sided p-value based on log-rank test stratified by stratum (use / nonuse of highly cytolytic anti-lymphocyte immunotherapy).
NR = Not reached.
Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

Figure 5: Kaplan-Meier Plot of Time to Onset of CMV Disease Through Week 52 Post-Treatment (Full Analysis Set Population)



Ancillary analyses

Quantifiable CMV DNAemia

Table 22: Proportion of Participants With Quantifiable CMV DNAemia Through Week 28 and 52 Post-Transplant (Full Analysis Set Population)

	LET Arm (N=289)		VGCV Arm (N=297)	
Response Variable	n	% (95% CI)	n	% (95% CI)
Quantifiable CMV DNAemia Through Week 28	6	2.1 (0.8, 4.5)	26	8.8 (5.8, 12.6)
Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir. Quantifiable CMV DNAemia is defined as any detected CMV with a numeric value (≥ 137 IU/mL).				

	LET Arm (N=289)		VGCV Arm (N=297)	
Response Variable	n	% (95% CI)	n	% (95% CI)
Quantifiable CMV DNAemia Through Week 52	92	31.8 (26.5, 37.5)	112	37.7 (32.2, 43.5)
Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir. Quantifiable CMV DNAemia is defined as any detected CMV with a numeric value (≥ 137 IU/mL).				

Subgroup analyses

Table 23: Participants with CMV Disease Through Week 52 Post-transplant by Baseline Characteristics (OF Approach, Full Analysis Set Population)

	LET Arm		VGCV Arm		LET Arm vs. VGCV Arm Difference in % (95% CI)[a]
	n/N	% (95% CI)	n/N	% (95% CI)	
Total					
Gender					
Male	25/210	11.9 (7.9, 17.1)	24/209	11.5 (7.5, 16.6)	0.5 (-5.8, 6.8)
Female	5/79	6.3 (2.1, 14.2)	11/88	12.5 (6.4, 21.3)	-6.3 (-15.5, 2.9)
Age (Years)					
< 65	26/242	10.7 (7.1, 15.3)	23/242	9.5 (6.1, 13.9)	1.2 (-4.2, 6.7)
>= 65	4/47	8.5 (2.4, 20.4)	12/55	21.8 (11.8, 35.0)	-12.5 (-27.0, 2.1)
Race Subgroup					
White	28/250	11.2 (7.6, 15.8)	29/243	11.9 (8.1, 16.7)	-0.7 (-6.4, 5.0)
non-White	2/37	5.4 (0.7, 18.2)	6/53	11.3 (4.3, 23.0)	-5.7 (-18.1, 6.7)
Missing	0/2	0.0 (0.0, 84.2)	0/1	0.0 (0.0, 97.5)	NA
Region					
US	15/118	12.7 (7.3, 20.1)	16/116	13.8 (8.1, 21.4)	-1.3 (-10.0, 7.5)
Ex-US	15/171	8.8 (5.0, 14.1)	19/181	10.5 (6.4, 15.9)	-1.7 (-8.0, 4.6)
Induction Therapy (use, non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction)					
Use	18/131	13.7 (8.4, 20.8)	17/138	12.3 (7.3, 19.0)	1.4 (-6.7, 9.6)
Non-use	12/158	7.6 (4.0, 12.9)	18/159	11.3 (6.8, 17.3)	-3.7 (-10.3, 2.8)

[a] 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction).

Treatment difference and 95% CI were not calculated for subgroups with small sample size (<15 participants in either treatment group) per protocol.

Note: Approach to handling missing values: Observed Failure (OF) approach.

Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

NA = Not Applicable.

Patient-reported Outcomes

EQ-5D

The EQ-5D VAS score was comparable at baseline for the LET and VGCV groups. The mean scores from baseline improved, and mean changes in scores were comparable at Week 52 post-transplant and at the CMV disease/Early Discontinuation Visit in both groups.

SF-36v2

For the SF-36v2, baseline mean scores were comparable in the LET and the VGCV groups. For both groups there were improvements in mean scores on the 8 domains and 2 components from baseline to Week 52 post-transplant. Mean change in scores from baseline to Week 52 post-transplant trended higher in the LET group compared with the VGCV group for the vitality, bodily pain, and role emotional domains. For all remaining domains and the 2 component scores, mean changes from baseline to Week 52 post-transplant were comparable between the LET and VGCV groups.

Viral Resistance Through Week 52 Post-transplant

Resistance testing was performed on samples obtained from participants prior to initiation of CMV treatment or who had suspected or confirmed CMV disease. The proportion of participants with resistance-associated substitutions was 0% in the LET group (LET resistance-associated substitution: pUL51, pUL56, pUL89) and 12.1% in the VGCV group (VGCV resistance-associated substitution: pUL54, pUL97). An additional 4 participants in the VGCV group had VGCV resistance-associated substitutions identified at a visit after a CMV disease visit (6 days after the CMV disease visit [n=1], 1 month after a CMV disease visit [n=2], and 4 months after the CMV disease visit [n=1]).

Table 24: Resistance Data for Participants With CMV Disease or Early Discontinuation Visit Variants Detected at a Frequency of ≥ 5% (All Participants as Treated)

	LET Arm		VGCV Arm		Total	
	n	(%)	n	(%)	n	(%)
Participants with CMV Disease or early discontinuation visit	52		66		118	
With resistance data available	52		66		118	
With any known LET resistance mutation	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
pUL51	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
pUL56	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
pUL89	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
With any known VGCV resistance mutation	**2**	**(3.8)**	**8**	**(12.1)**	**10**	**(8.5)**
pUL54	**0**	**(0.0)**	**2**	**(3.0)**	**2**	**(1.7)**
F412S	0	(0.0)	1	(1.5)	1	(0.8)
Q783R	0	(0.0)	1	(1.5)	1	(0.8)
pUL97	**2**	**(3.8)**	**7**	**(10.6)**	**9**	**(7.6)**
A594V	0	(0.0)	2	(3.0)	2	(1.7)
C592G	0	(0.0)	1	(1.5)	1	(0.8)
C603W	0	(0.0)	1	(1.5)	1	(0.8)
L405P	1	(1.9)	0	(0.0)	1	(0.8)
L595S	0	(0.0)	1	(1.5)	1	(0.8)
M460I	1	(1.9)	4	(6.1)	5	(4.2)

n (%) = Number (percent) in each sub-category among participants with resistance data available.
Amino acid variants detected at a frequency of 5% or greater of total sequence reads are reported.
Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

CMV gB genotypes

CMV is divided into four genotypes according to the polymorphisms in UL55 gene that encodes for envelope glycoprotein B. It has previously been shown that the activity of letermovir is not significantly affected by the gB genotype of CMV.

Genetic variation of the CMV gB genotype was evaluated by DNA sequencing from samples obtained from participants prior to initiation of CMV treatment or who had suspected or confirmed CMV disease. The distribution among the 5 gB genotypes was comparable for the LET and VGCV groups. The most common (42.8% overall) genotype observed in both intervention groups was gB1.

Table 25: Prevalence of gB Genotypes Observed (All Participants as Treated)

	LET Arm		VGCV Arm		Total	
	n	(%)	n	(%)	n	(%)
Participants with gB(UL55) testing	84		93		177	
Participants with gB(UL55) results	65		80		145	
gB1	33	(50.8)	29	(36.3)	62	(42.8)
gB2	8	(12.3)	15	(18.8)	23	(15.9)
gB3	14	(21.5)	25	(31.3)	39	(26.9)
gB4	8	(12.3)	10	(12.5)	18	(12.4)
gB5	2	(3.1)	1	(1.3)	3	(2.1)

n (%) = Number (percent) in each sub-category among participants with gB Genotype result available.
gB Genotype is assessed at first timepoint with evaluable UL55 sequence data; gB genotype detected (≥ 90% of mapped reads).
gB = glycoprotein B; UL = unique long.
Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

Summary of main study

Title: A Phase III, Randomized, Double-Blind, Active Comparator- Controlled Study to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) Versus Valganciclovir for the Prevention of Human Cytomegalovirus (CMV) Disease in Adult Kidney Transplant Recipients		
Study identifier	P002MK8228	
Design	Duration of main phase:	Participants were treated for 28 weeks post-transplant and followed until week 52 post-transplant
Hypothesis	Non-inferiority	

Treatments groups	Letermovir	n=301 randomized n=292 treated • LET 480 mg once daily given orally (as one 480 mg tablet or two 240 mg tablets). If LET was co-administered with cyclosporine A (CsA), the dosage of LET was decreased to 240 mg once daily • Two VGCV-matching placebo tablets • Two aciclovir (ACV) 400 mg capsules or tablets (each capsule or tablet given every 12 hours) for prophylaxis of herpes simplex virus (HSV) and varicella zoster virus (VZV)	
	Valganciclovir	n= 300 randomized n=297 treated • One 480 mg LET-matching placebo tablet or two 240 mg LET-matching placebo tablets • Two VGCV 450 mg tablets • Two ACV-matching placebo capsules or tablets (each capsule or tablet given every 12 hours)	
Endpoints and definitions	Primary endpoint	Proportion of Participants With CMV Disease Through Week 52 Post-Transplant (OF Approach, Full Analysis Set Population) CMV disease was defined as CMV syndrome or CMV end-organ disease	
	Secondary endpoint	Proportion of Participants With CMV Disease Through Week 28 Post-Transplant (OF Approach, Full Analysis Set Population)	
Database lock	27-JUL-2022		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Full analysis Set (FAS) Week 52 post-transplant		
Descriptive statistics and estimate variability	Treatment group	Letermovir	Valganciclovir
	Number of subject	289	297
	CMV Disease CMV syndrome CMV end-organ disease	30 (10.4%) 24 (8.3%) 6 (2.1%)	35 (11.8%) 34 (11.4%) 1 (0.3%)
	Difference in CMV disease (95% CI)	Letermovir vs. valganciclovir	-1.4 (-6.5, 3.8)
Analysis description	Secondary analysis		

Analysis population and time point description	FAS Week 28 post-transplant		
Descriptive statistics and estimate variability	Treatment group	Letermovir	Valganciclovir
	Number of subjects	289	297
	CMV Disease CMV syndrome CMV end-organ disease	0 (0%) 0 (0%) 0 (0%)	5 (1.7%) 5 (1.7%) 0 (0%)
	Difference in CMV disease (95% CI)	Letermovir vs. valganciclovir	-1.7 (-3.4, 0.1)

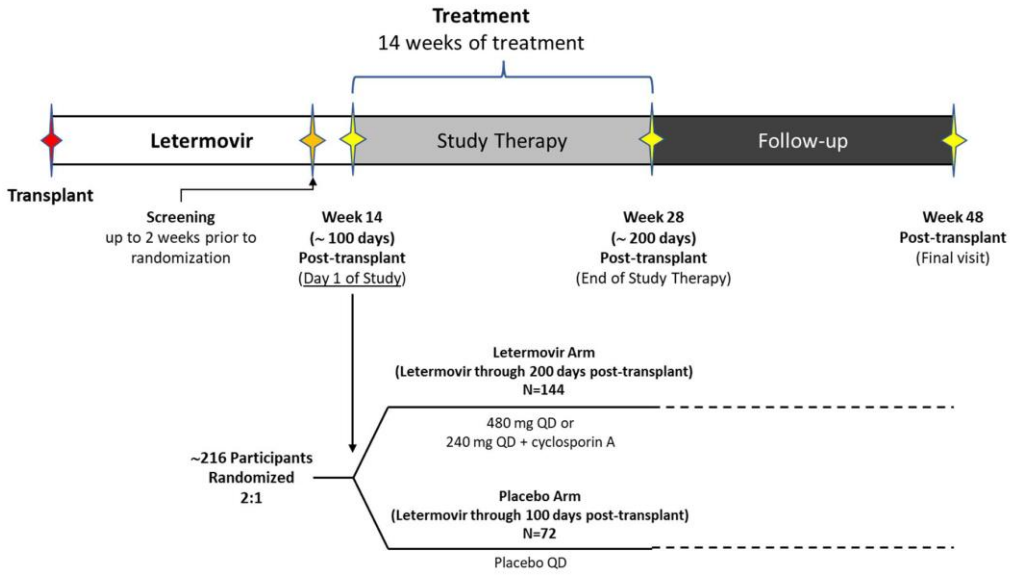
2.4.2.2. Study P040MK8228

Title: A Phase 3 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of letermovir (LET) prophylaxis when extended from 100 days to 200 days post-transplant in cytomegalovirus (CMV) seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT)

Methods

This was a randomized, placebo-controlled, parallel assignment, multicentre, double-blind, efficacy and safety study evaluating extending LET prophylaxis to 200 days post-transplant in CMV-seropositive recipients (R+) of an allogeneic HSCT who had received LET prophylaxis through Week 14 (~100 days) post-transplant and who were at high risk for CMV infection and/or disease after completion of LET prophylaxis through 100 days post-transplant.

Figure 6: P040 Study design



Part of this study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its Standard Operating Procedures for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate impact on study conduct.

The primary efficacy endpoint will be the proportion of participants with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant.

Study participants

Participants were eligible to be included in the study only if all of the following criteria applied:

1. had documented positive CMV serostatus (CMV IgG seropositive) for recipient (R+) at the time of transplant.
2. history of allogeneic HSCT within ~100 days prior to randomization.
3. had undetectable CMV DNA or detectable/not quantifiable CMV DNA (central laboratory) from a plasma sample collected within 14 days prior to randomization.
4. had received LET as primary prophylaxis that started within 28 days of HSCT and continued through Week 14 post-transplant (100 days) ±1 week prior to randomization.
5. at high risk of CMV infection and/or disease, defined as meeting 1 or more of the following criteria:
    - had a related donor with at least 1 mismatch at 1 of the specified 3 HLA gene loci (HLA-A, B, or DR);
    - had an unrelated donor with at least 1 mismatch at 1 of the specified 4 HLA gene loci (HLA-A, B, C, and DRB1);
    - had a haploidentical donor;
    - had umbilical cord blood as the stem-cell source;
    - had ex-vivo T-cell–depleted grafts;
    - receipt of anti-thymocyte globulin (Note: enrolment of participants whose ONLY high-risk factor was the use of anti-thymocyte globulin was restricted to ≤20% of all enrolled participants);
    - receipt of alemtuzumab;
    - had GVHD or other conditions, requiring the use of systemic prednisone (or equivalent) at a dose of ≥1 mg/kg of body weight per day within 6 weeks of randomization.
6. Participant was ≥18 years of age at the time of signing the informed consent.

Key Exclusion criteria

Participants were excluded from the study if any of the following criteria apply:

1. had a history of CMV end-organ disease or PET for CMV after HSCT prior to randomization.
2. had a history of >14 days total of LET interruption during the first 100 days post-transplant prior to randomization.

3. had severe hepatic insufficiency defined as Child-Pugh Class C within 14 days prior to randomization.
4. had serum AST or ALT >5× the ULN within 14 days prior to randomization.
5. had end-stage renal impairment with a creatinine clearance less than 10 mL/min, as calculated by the Cockcroft-Gault equation within 14 days prior to randomization.
6. had both moderate hepatic insufficiency AND moderate-to-severe renal insufficiency.
7. had an uncontrolled infection on the day of enrolment.
8. required mechanical ventilation or was hemodynamically unstable at the time of enrolment.
9. had a documented positive result for a HIV Ab test at any time prior to screening, or for HCV Ab with detectable HCV RNA, or HBsAg within the 6 months prior to screening.
10. had active solid tumour malignancies (with the exception of localized basal cell or squamous cell skin cancer).
11. received ganciclovir or valganciclovir, foscarnet, aciclovir, valaciclovir, famciclovir within 7 days prior to screening.
12. received cidofovir and CMV immunoglobulin within 30 days prior to screening.

Treatments

Eligible participants were randomized in a 2:1 ratio to receive LET (a dose of 480 mg once daily and adjusted to 240 mg once daily for participants on cyclosporin A, administered orally or intravenously) through Week 28 (LET through 200 days) post-transplant or to receive oral or intravenous placebo once daily through Week 28 (LET through 100 days) post-transplant.

Objectives and endpoints

Objectives	Endpoints
Primary	
• Objective: To evaluate the efficacy of letermovir (LET) versus placebo when LET prophylaxis is extended from 100 to 200 days post-transplant, as measured by the proportion of participants with clinically significant cytomegalovirus (CMV) infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant • Hypothesis (H1): LET is superior to placebo in the prevention of clinically significant CMV infection when LET prophylaxis is extended from 100 to 200 days post-transplant	• Clinically significant CMV infection (defined as initiation of pre-emptive therapy [PET] for documented CMV viremia and/or CMV end-organ disease)
Secondary	
• To evaluate the safety and tolerability of LET versus placebo when LET prophylaxis is extended from 100 to 200 days post-transplant based on the proportion of participants with adverse events (AEs) from Week 14 post-transplant through Week 28 post-transplant.	• AEs • Study drug discontinuations due to AEs

• To evaluate the efficacy of LET versus placebo when LET prophylaxis is extended from 100 to 200 days post-transplant, as measured by the following:
  • Proportion of participants with clinically significant CMV infection from Week 14 post-transplant through Week 38 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant
  • Time to onset of clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant
	• Clinically significant CMV infection
	• Initiation of anti-CMV PET for documented CMV viremia
	• All-cause mortality

Objectives	Endpoints
• Proportion of participants with PET for CMV viremia from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant • Proportion of participants with all-cause mortality from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant • Time to all-cause mortality from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant	
Tertiary/Exploratory	

• To evaluate the efficacy of LET versus placebo when LET prophylaxis is extended from 100 to 200 days post-transplant, as measured by the following:
  • Proportion of participants with CMV end-organ disease from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant
  • Proportion of participants with documented CMV viremia from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant
	• CMV end-organ disease
	• Documented CMV viremia ≥300 copies/mL

Sample size

Data from P001 in participants who were in the high-risk stratum as defined in P001 were used to estimate the clinically significant CMV infection rates for this study, since these populations are similar between the two studies. The 100-day arm in this study is similar to those in the high-risk stratum on LET who completed treatment without any clinically significant CMV infection in P001, in which 20.5% had clinically significant CMV infection after completing treatment and through Week 24 post-transplant. This would be expected to be slightly higher through Week 28 post-transplant leading to an estimate of 22% for through Week 28 post-transplant in this study. The event rate for the 200-day arm is expected to be similar to the event rate at the end of LET treatment at Week 14 post-transplant for participants in the P001-defined high-risk stratum, which was 10.8% (11/102, including 4 participants who had discontinued LET due to AEs and then developed CS-CMVi). Since this study will enrol participants who will have already tolerated LET for 100 days, it is expected that a lower percentage of patients will discontinue treatment due to AEs, thus lowering the overall failure rate in the 200-day arm to ~8%.

This study will randomize a total of 216 participants (in a 2:1 ratio) with 144 in the LET (200-day) arm and 72 in the placebo (100-day) arm which will have 80% power at an overall one-sided, 2.5% alpha-level, to demonstrate the primary hypothesis that extending LET prophylaxis to 200 days post-

transplant is superior to 100 days of LET prophylaxis post-transplant in the prevention of clinically significant CMV infection. This assumes incidence rates of CS-CMVi of 8% for LET (200-day arm) and 22% for placebo (100-day arm). The minimum criterion for success is that the upper bound of 95% CI of difference < 0. Given the assumed response rate in 200-day arm, this may occur when the observed difference between treatment groups is approximately -10% or smaller.

Randomisation

Eligible participants were randomized in a 2:1 ratio to receive LET (a dose of 480 mg once daily and adjusted to 240 mg once daily for participants on cyclosporin A, administered orally or intravenously) through Week 28 (LET through 200 days) post-transplant or to receive oral or intravenous placebo once daily through Week 28 (LET through 100 days) post-transplant.

Treatment allocation/randomization will be stratified by:

1) study centre and

2) haploidentical donor (yes/no).

Blinding (masking)

In this study a double-blinding technique with in-house blinding was used. In order to maintain the blinding to the IV study therapy, the unblinded pharmacist (or qualified study site personnel designated to prepare blinded IV study therapy) was responsible solely for the preparation of the IV study therapy. No confirmed events of premature unblinding were reported for this study.

Statistical methods

The primary efficacy endpoint will be the proportion of participants with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant.

Analysis Populations

Full Analysis Set (FAS): The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who received at least one dose of study treatment.

All Participants as Treated (APaT): Safety Analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study treatment.

Efficacy Analysis

To test the primary hypothesis that LET is superior to placebo in the prevention of clinically significant CMV infection when LET prophylaxis is extended from 100 to 200 days post-transplant, the stratum-adjusted Mantel-Haenszel method (with continuity correction) will be used to compare the proportion of subjects with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant between the two treatment groups [Koch, G. G., et al 1990]. The stratification factor of haploidentical donor (yes/no) will be included in the primary efficacy analysis. Cochran Mantel-Haenszel weights will be used to calculate the overall between-group differences across strata. LET is concluded superior to placebo if 1-sided p-value is less than or equal to 0.0249. Due to the anticipated large number of study centres, study centre will not be included as a

stratification factor in the primary efficacy analysis but may be explored as a sensitivity analysis. The primary efficacy analysis will be performed on the FAS population. A sensitivity analysis excluding those subjects who had quantifiable CMV viral DNA on Day 1 will be provided. The primary missing data approach will be the OF approach; supportive analyses using different missing data approaches will also be conducted.

Two additional sensitivity analyses for the primary endpoint will be performed to assess 1) the proportion of participants with either CMV disease or PET initiation based on CMV viremia ≥300 copies/mL (i.e., participants who initiated PET without meeting the threshold will not be considered a case of CS-CMVi), and 2) the proportion of participants with either CMV disease or CMV viremia of ≥300 copies/mL regardless of whether PET was initiated.

Since the use of a therapy with anti-CMV activity may confound the results of this study, an additional sensitivity analysis will be conducted in which participants who start a therapy with anti-CMV activity will be censored at the time they begin such therapy. Subjects with CS-CMVi prior to taking a therapy with anti-CMV activity will be classified as having CS-CMVi. Those who did not have CS-CMVi prior to taking a therapy with anti-CMV activity (including subjects who subsequently develop CS-CMVi) will be classified as not having CS-CMVi and censored at the time they started taking the anti-CMV therapy.

For binary secondary endpoints similar methods was used as for the primary endpoint.

Time to onset of clinically significant CMV infection from Week 14 post-transplant through 28 weeks post-transplant and from Week 14 post-transplant through Week 48 post-transplant will be estimated using the nonparametric Kaplan-Meier method. The Kaplan-Meier curve will be plotted by treatment arm and a nominal p-value for the between-arm difference in time to onset of clinically significant CMV infection will be provided using the stratified log-rank test stratified by haploidentical donor (yes/no). Observations will be censored at last assessment. Time to all-cause mortality from Week 14 post-transplant through 28 weeks post-transplant and from Week 14 post-transplant through Week 48 post-transplant will be estimated similarly.

Missing Data Handling

There are three types of missing values:

- Intermittent missing values due to a missed or skipped visit.
- Monotone (non-intermittent) missing due to premature discontinuation from the study: viremia at study discontinuation.
- Monotone missing due to premature discontinuation from the study: no viremia at study discontinuation.

Summary of Approaches to Handle Missing Values

Approach	Intermittent Missing	Monotone Missing	
		No Viremia at Study Discontinuation	Viremia at Study Discontinuation
OF	No failure	No failure	Failure
NC=F	Failure	Failure	Failure
DAO	Excluded	Excluded	Excluded
F = failure; NC = Non-Completer; OF = Observed Failure; DAO = Data-As-Observed			

The primary missing data approach will be the Observed Failure (OF) approach in order to obtain an estimate of the proportion of clinically significant CMV infection in participants who receive prophylaxis study treatment. Using this approach, participants who develop clinically significant CMV infection or participants who discontinue prematurely from the study with viremia will be counted as failures, and participants who discontinue prematurely from the study for any reason without viremia or those who are missing data at the time points of interest are not considered failures. Imputing all participants who discontinue from the study prematurely without viremia as failures is likely to substantially overestimate the proportion of participants with clinically significant CMV infection.

Two secondary missing data approaches will be used for supportive analyses. The first is the Data-As-Observed (DAO) approach. In the DAO approach, any participant with missing value for a particular endpoint, either because they discontinued from the study without the endpoint or are missing data at the key time point (e.g., missed visit, missing lab value), will be excluded from the analysis. The second approach is the Non-Completer = Failure (NC=F) approach, which provides the worse-case scenario estimate of the proportion of clinically significant CMV infection. Non-completers refer to participants who prematurely discontinue from the study for any reason without having developed CMV infection or participants who are missing data at the time points of interest. These participants will be considered failures using the NC=F approach.

Interim Analyses

No formal interim analyses for efficacy are planned for this study. However, to allow for an assessment of benefit-risk, efficacy data will be included as part of the periodic safety reviews when at least 40% of the participants have completed treatment or discontinued prior to completing treatment. The DMC will monitor the trial with suggested periodic reviews occurring approximately every 6 months. Treatment-level results from the interim analysis will be provided to the DMC by the unblinded statistician. Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

Multiplicity

The DMC will be provided with unblinded descriptive summaries of the efficacy data at their periodic safety reviews when at least 40% of the participants have completed treatment or discontinued prior to completing treatment for an assessment of benefit-risk. No formal efficacy analyses will be provided and there is no intention of stopping the trial due to overwhelming efficacy at any of these safety reviews. Nevertheless, since unblinded efficacy data are being periodically reviewed, using a Haybittle-

Peto α-spending approach, a small amount of alpha (α = 0.0001) will be allocated for each of these looks before testing the primary efficacy hypothesis at Week 28 post-transplant. An allowance will be made such that a total of up to three of these unblinded efficacy reports may be presented at these periodic safety reviews.

Results

Participant flow

A total of 220 participants were randomized. The rate of discontinuation of study intervention was higher in the placebo (100 days LET) group (24.0%) than in the LET (200 days LET) group (17.2%). One participant discontinued study intervention due to an AE associated with the COVID-19 pandemic.

Among the treated participants, 16.8% participants discontinued the study before Week 48 post-transplant. The most common reasons for discontinuation were withdrawal by participant and death.

Three participants discontinued the study due to COVID-19 pandemic.

Of the 35 nonrandomized participants, 34 were screen failures due to not meeting inclusion criteria or meeting exclusion criteria, and 1 was due to physician decision.

Table 26: Disposition of participants

	LET (200 days LET)		PBO (100 days LET)		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	145		75		220	
Treated	144	(99.3)	74	(98.7)	218	(99.1)
Not Treated	1	(0.7)	1	(1.3)	2	(0.9)
Completed Study Medication	119	(82.1)	56	(74.7)	175	(79.5)
Discontinued Study Medication	25	(17.2)	18	(24.0)	43	(19.5)
Adverse Event	7	(4.8)	1	(1.3)	8	(3.6)
Death	1	(0.7)	0	(0.0)	1	(0.5)
Lack Of Efficacy	1	(0.7)	16	(21.3)	17	(7.7)
Lost To Follow-Up	1	(0.7)	0	(0.0)	1	(0.5)
Non-Compliance With Study Drug	0	(0.0)	1	(1.3)	1	(0.5)
Physician Decision	3	(2.1)	0	(0.0)	3	(1.4)
Withdrawal By Subject	12	(8.3)	0	(0.0)	12	(5.5)
Completed Study	118	(81.4)	63	(84.0)	181	(82.3)
Discontinued Study	26	(17.9)	11	(14.7)	37	(16.8)
Death	9	(6.2)	3	(4.0)	12	(5.5)
Lost To Follow-Up	1	(0.7)	2	(2.7)	3	(1.4)
Other	2	(1.4)	0	(0.0)	2	(0.9)
Physician Decision	2	(1.4)	4	(5.3)	6	(2.7)
Withdrawal By Subject	12	(8.3)	2	(2.7)	14	(6.4)

n (%) = Number (percent) of participants in each sub-category.
LET = Letermovir; PBO = Placebo
Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).

Recruitment

Study centres: This study was conducted at 32 centres in 6 countries: France, Germany, Italy, Japan, the United Kingdom, and the US.

This study is ongoing at this current interim analysis (the final analysis)

First Patient, First Visit	Last Patient, Last Visit	Database Lock Date
21-JUN-2019	16-MAR-2022	24-MAY-2022

Conduct of the study

Protocol Amendments

Changes in the conduct of the study implemented by protocol amendment are summarized in below. There were no changes in the planned conduct of the study implemented by protocol amendment due to the COVID-19 pandemic.

Amendment 02, 10-JAN-2020: The primary purpose of this protocol amendment is to limit enrolment of participants who have anti-thymocyte globulin as the only high-risk category for CMV reactivation to ≤20% of the total trial population. This is to ensure that the preponderance of evidence does not come from participants with anti-thymocyte globulin as the only high-risk category for late CMV reactivation.

Amendment, 01 23-AUG-2019: The primary purpose of this protocol amendment is to add the requirement that the intravenous (IV) formulation of letermovir (and placebo) supplied by the Sponsor to sites as study medication must be administered through a sterile 0.2- micron or 0.22-micron polyethersulfone (PES) in-line filter and using diethylhexyl phthalate (DEHP)-free IV bags and infusion set materials. This requirement is being added to prevent the possible administration of product-related particulate matter. The presence of visible product-related particulate matter is an expected characteristic of new clinical supplies of IV formulation of LET.

Original Protocol (Version 00) 03-DEC-2018

Protocol Deviations

Important protocol deviations were reported for 39 participants in the LET group and 14 participants in the placebo group. Of these, 20 participants in the LET group and 5 in the placebo group had at least 1 clinically important protocol deviation.

Part of this study was conducted during the COVID-19 pandemic. Important and non-important protocol deviations associated with the pandemic were reported for 33 participants in the LET group and 22 participants in the placebo group. There was only 1 important protocol deviation associated with the pandemic and it was in the LET group. None of the protocol deviations associated with the pandemic were clinically important. No participants were excluded from any analyses due to protocol deviations associated with the pandemic.

No participants were excluded from any analyses due to an important protocol deviation.

No protocol deviations were classified as a serious GCP compliance issue.

Baseline data P040

Table 27: Participant Characteristics at Study Entry (All Participants as Treated)

	LET (200 days LET)		PBO (100 days LET)		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	144		74		218	
Sex						
Male	92	(63.9)	43	(58.1)	135	(61.9)
Female	52	(36.1)	31	(41.9)	83	(38.1)
Age (Years)						
18 - 35	26	(18.1)	10	(13.5)	36	(16.5)
36 - 50	31	(21.5)	19	(25.7)	50	(22.9)
51 - 64	55	(38.2)	34	(45.9)	89	(40.8)
65 - 74	32	(22.2)	11	(14.9)	43	(19.7)
>= 75	0	(0.0)	0	(0.0)	0	(0.0)
Mean	51.9		52.7		52.2	
SD	14.3		12.9		13.8	
Median	55.0		55.0		55.0	
Range	22 to 74		20 to 74		20 to 74	
Race						
Asian	16	(11.1)	8	(10.8)	24	(11.0)
Black Or African American	3	(2.1)	1	(1.4)	4	(1.8)
Multiple	2	(1.4)	1	(1.4)	3	(1.4)
American Indian Or Alaska Native, White	0	(0.0)	1	(1.4)	1	(0.5)
Black Or African American, Asian	1	(0.7)	0	(0.0)	1	(0.5)
Black Or African American, White	1	(0.7)	0	(0.0)	1	(0.5)
Native Hawaiian Or Other Pacific Islander	2	(1.4)	0	(0.0)	2	(0.9)
White	113	(78.5)	60	(81.1)	173	(79.4)
Missing[a]	8	(5.6)	4	(5.4)	12	(5.5)
Ethnicity						
Hispanic Or Latino	13	(9.0)	8	(10.8)	21	(9.6)
Not Hispanic Or Latino	106	(73.6)	53	(71.6)	159	(72.9)
Not Reported	23	(16.0)	11	(14.9)	34	(15.6)
Unknown	2	(1.4)	2	(2.7)	4	(1.8)
Region						
Asia-Pacific	13	(9.0)	4	(5.4)	17	(7.8)

	LET (200 days LET)		PBO (100 days LET)		Total	
	n	(%)	n	(%)	n	(%)
Europe	98	(68.1)	52	(70.3)	150	(68.8)
North America	33	(22.9)	18	(24.3)	51	(23.4)
Region Subgroup						
US	33	(22.9)	18	(24.3)	51	(23.4)
Ex-US	111	(77.1)	56	(75.7)	167	(76.6)
Stratum						
Haploidentical donor	45	(31.3)	22	(29.7)	67	(30.7)
Non-haploidentical donor	99	(68.8)	52	(70.3)	151	(69.3)
CMV DNA on Day of Randomization						
Undetectable	139	(96.5)	71	(95.9)	210	(96.3)
Detectable, not quantifiable	4	(2.8)	2	(2.7)	6	(2.8)
Quantifiable	1	(0.7)	0	(0.0)	1	(0.5)
Missing	0	(0.0)	1	(1.4)	1	(0.5)
Primary Reason for Transplant						
Acute lymphocytic leukaemia	23	(16.0)	9	(12.2)	32	(14.7)
Acute myeloid leukaemia	61	(42.4)	30	(40.5)	91	(41.7)
Aplastic anaemia	3	(2.1)	0	(0.0)	3	(1.4)
Chronic lymphocytic leukaemia	4	(2.8)	0	(0.0)	4	(1.8)
Chronic myeloid leukemia	0	(0.0)	1	(1.4)	1	(0.5)
Lymphoma	8	(5.6)	9	(12.2)	17	(7.8)
Myelodysplastic syndrome	17	(11.8)	6	(8.1)	23	(10.6)
Myelofibrosis	8	(5.6)	5	(6.8)	13	(6.0)
Plasma cell myeloma	4	(2.8)	3	(4.1)	7	(3.2)
Other[b]	16	(11.1)	11	(14.9)	27	(12.4)
Donor CMV Serostatus						
Positive	86	(59.7)	56	(75.7)	142	(65.1)
Negative	58	(40.3)	16	(21.6)	74	(33.9)
Unknown	0	(0.0)	2	(2.7)	2	(0.9)
Recipient CMV Serostatus						
Positive	143	(99.3)	74	(100.0)	217	(99.5)
Negative	1	(0.7)	0	(0.0)	1	(0.5)

	LET (200 days LET)		PBO (100 days LET)		Total	
	n	(%)	n	(%)	n	(%)
Donor Type						
Matched related	17	(11.8)	11	(14.9)	28	(12.8)
Mismatched related	48	(33.3)	23	(31.1)	71	(32.6)
Matched unrelated	37	(25.7)	23	(31.1)	60	(27.5)
Mismatched unrelated	42	(29.2)	17	(23.0)	59	(27.1)
Stem Cell Source						
Peripheral blood	117	(81.3)	62	(83.8)	179	(82.1)
Bone marrow	19	(13.2)	7	(9.5)	26	(11.9)
Cord blood	8	(5.6)	5	(6.8)	13	(6.0)
Conditioning Regimen Use						
Myeloablative	73	(50.7)	33	(44.6)	106	(48.6)
Reduced intensity conditioning	46	(31.9)	27	(36.5)	73	(33.5)
Non-myeloablative	25	(17.4)	14	(18.9)	39	(17.9)
GVHD at Study Entry						
Acute	25	(17.4)	9	(12.2)	34	(15.6)
Chronic	3	(2.1)	1	(1.4)	4	(1.8)
Acute and Chronic	2	(1.4)	0	(0.0)	2	(0.9)
None	114	(79.2)	64	(86.5)	178	(81.7)

[a] Missing race where participant did not know race or chose not to report due to local regulations.
[b] Other reasons for transplant are provided in section 14.
n (%) = Number (percent) of participants in each sub-category.
LET = Letermovir; PBO = Placebo
Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).

Table 28: Participant Risk Factors for CMV Infection and/or Disease at Study Entry (All Participants as Treated)

	LET (200 days LET)		PBO (100 days LET)		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	144		74		218	
Number of CMV Risk Factors						
One factor	52	(36.1)	26	(35.1)	78	(35.8)
Two factors	72	(50.0)	41	(55.4)	113	(51.8)
Three or more factors	20	(13.9)	7	(9.5)	27	(12.4)
CMV Risk Factors						
Human Leukocyte Antigen (HLA)-Related (Sibling) Donor With at Least One Mismatch at One of the Following Three HLA-Gene loci: HLA-A, -B or -DR	48	(33.3)	23	(31.1)	71	(32.6)
Unrelated Donor with at Least One Mismatch at One of the Following Four HLA-Gene loci: HLA-A, -B, -C and -DRB1	42	(29.2)	17	(23.0)	59	(27.1)
Haploidentical Donor	45	(31.3)	22	(29.7)	67	(30.7)
Use of Umbilical Cord Blood as Stem Cell Source	8	(5.6)	5	(6.8)	13	(6.0)
Use of Ex Vivo T-Cell-Depleted Grafts	15	(10.4)	7	(9.5)	22	(10.1)
Receipt of Anti-Thymocyte Globulin	67	(46.5)	35	(47.3)	102	(46.8)
Receipt of Alemtuzumab	13	(9.0)	9	(12.2)	22	(10.1)
Use of Systemic Prednisone (or Equivalent) as Defined in the Protocol[a]	19	(13.2)	11	(14.9)	30	(13.8)

[a] Having GVHD or other conditions requiring the use of systemic prednisone (or equivalent) at a dose of ≥ 1 mg/kg of body weight per day within 6 weeks of randomization.
n (%) = Number (percent) of participants in each sub-category.
LET = Letermovir; PBO = Placebo
Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).

Medical History

Medical history conditions were generally comparable between the LET (200 days LET) and placebo (100 days LET) groups. The most frequently reported medical conditions were acute myeloid leukaemia (41.3%), hypertension (39.4%), and anaemia (27.1%).

Prior and Concomitant Medications

Overall, the distribution of prior and concomitant medications was generally comparable between the LET and placebo groups.

The most frequently reported classes of prior medications included antivirals for systemic use (100%), ophthalmologicals (99.1%), and immunosuppressants (97.7%). The majority of participants (87.6%) had received calcineurin inhibitors and approximately half of all participants (48.6%) had received systemic corticosteroid before study entry. The most frequently reported classes of concomitant medications during the treatment phase were ophthalmologicals (97.7%), antivirals for systemic use (95.0%), and immunosuppressants (92.2%). The majority of participants (83.5%) received calcineurin inhibitors and approximately half of all participants (54.1%) received systemic corticosteroids during the treatment phase.

Numbers analysed

Efficacy analysis population

Of the 220 randomized participants, 2 participants did not receive study intervention and were excluded from any further analyses. The primary efficacy population was the FAS, defined as all randomized participants who received at least 1 dose of study intervention. The FAS population included all 218 treated participants with no participant excluded from efficacy analyses.

Safety Analysis Population

Safety analyses were conducted on the "all participants as treated" (APaT) population, which included all randomized participants who received at least 1 dose of study intervention according to the study intervention they received. The APaT population included 218 participants.

Outcomes and estimation

Primary endpoint

Clinically Significant CMV Infection

Table 29: Proportion of Participants with Clinically Significant CMV Infection From Week 14 (~100 days) Through Week 28 (~200 days) Post-transplant (OF Approach, Full Analysis Set Population)

Parameter	LET (200 days LET) (N=144) n (%)	PBO (100 days LET) (N=74) n (%)
Failures[a]	**4 (2.8)**	**14 (18.9)**
Clinically significant CMV infection through Week 28[b]	2 (1.4)	13 (17.6)
Initiation of PET based on documented CMV viremia	1 (0.7)	11 (14.9)
CMV end-organ disease	1 (0.7)	2 (2.7)
Discontinued from study with CMV viremia before Week 28	2 (1.4)	1 (1.4)
Stratum-adjusted treatment difference (LET (200 days LET)-PBO (100 days LET))[c]		
Difference (95% CI)	-16.1 (-25.8, -6.5)	
p-value	0.0005	

[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

[b] Clinically significant CMV infection was defined as CMV end organ disease (proven or probable) or initiation of PET based on documented CMV viremia and the clinical condition of the participant.

[c] 95% CIs and one-sided p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no). A one-sided p-value ≤0.0249 was used for declaring statistical significance.

Note: Approach to handling missing values: Observed Failure (OF) approach. With the OF approach, failure was defined as all participants who develop clinically significant CMV infection or discontinue prematurely from the study with CMV viremia from week 14 (~100 days) through week 28 (~200 days) post-transplant.

N = Number of participants in each treatment group.

n (%) = Number (percent) of participants in each sub-category.

LET = Letermovir; PBO = Placebo

Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).

Table 30: Proportion of Participants with Clinically Significant CMV Infection From Week 14 (~100 days) Through Week 28 (~200 days) Post-transplant (NC=F Approach, Full Analysis Set Population)

Parameter	LET (200 days LET) (N=144) n (%)	PBO (100 days LET) (N=74) n (%)
Failures[a]	**21 (14.6)**	**18 (24.3)**
Clinically significant CMV infection through Week 28[b]	2 (1.4)	13 (17.6)
Initiation of PET based on documented CMV viremia	1 (0.7)	11 (14.9)
CMV end-organ disease	1 (0.7)	2 (2.7)
Discontinued from study before Week 28	16 (11.1)	1 (1.4)
Missing outcome in Week 28 visit window	3 (2.1)	4 (5.4)
Stratum-adjusted treatment difference (LET (200 days LET)-PBO (100 days LET))[c]		
Difference (95% CI)	-9.7 (-21.3, 1.9)	
p-value	0.0505	

[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

[b] Clinically significant CMV infection was defined as CMV end organ disease (proven or probable) or initiation of PET based on documented CMV viremia and the clinical condition of the participant.

[c] 95% CIs and one-sided p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no). A nominal one-sided p-value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all participants who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome from week 14 (~100 days) through week 28 (~200 days) post-transplant visit window.

N = Number of participants in each treatment group.

n (%) = Number (percent) of participants in each sub-category.

LET = Letermovir; PBO = Placebo

Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).

Sensitivity analyses

Several sensitivity analyses established consistency with the primary endpoint when accounting for various potentially confounding factors (table below).

Table 31: Summary of Sensitivity Analyses for Primary Endpoint (Full Analysis Set Population)

	LET (200 days LET) (N=144)	PBO (100 days LET) (N=74)	Difference[a]	
	n (%)	n (%)	Difference(95% CI)	p-value
Primary Endpoint				
Clinically significant CMV infection through Week 28 post-transplant	4 (2.8)	14 (18.9)	-16.1 (-25.8, -6.5)	0.0005
Sensitivity Analyses of Primary Endpoint				
Including CMV DNA results from the local laboratory	5 (3.5)	16 (21.6)	-18.1 (-28.3, -8.0)	0.0002
PET initiation based on CMV viremia ≥ 300 copies/mL	3 (2.1)	13 (17.6)	-15.5 (-24.8, -6.1)	0.0006
Viral load threshold of ≥ 300 copies/mL with or without PET initiation	7 (4.9)	17 (23.0)	-18.1 (-28.6, -7.6)	0.0004
Excluding CMV quantifiable at study entry[b]	4 (2.8)	14 (18.9)	-16.1 (-25.8, -6.4)	0.0006
Excluding participants starting therapy with anti-CMV activity[b]	4 (2.8)	14 (19.7)	-16.9 (-26.9, -6.9)	0.0005
Including participants starting therapy with anti-CMV activity as failures	6 (4.2)	17 (23.0)	-18.8 (-29.2, -8.3)	0.0002

[a] 95% CIs and one-sided p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A one-sided p-value ≤ 0.0249 was used for declaring statistical significance for primary analysis of the primary endpoint. Nominal one-sided p-values (not adjusted for multiplicity) are provided for other analyses as a measure of the strength of the relationship between treatment and response.

[b] Excluded participants excluded from denominator.

Approach to handling missing values: Observed Failure (OF) approach. With OF approach, failure was defined as all participants who develop clinically significant CMV infection or discontinue prematurely from the study with viremia.

N = Number of participants in analysis population.

n = Number of participants with outcome.

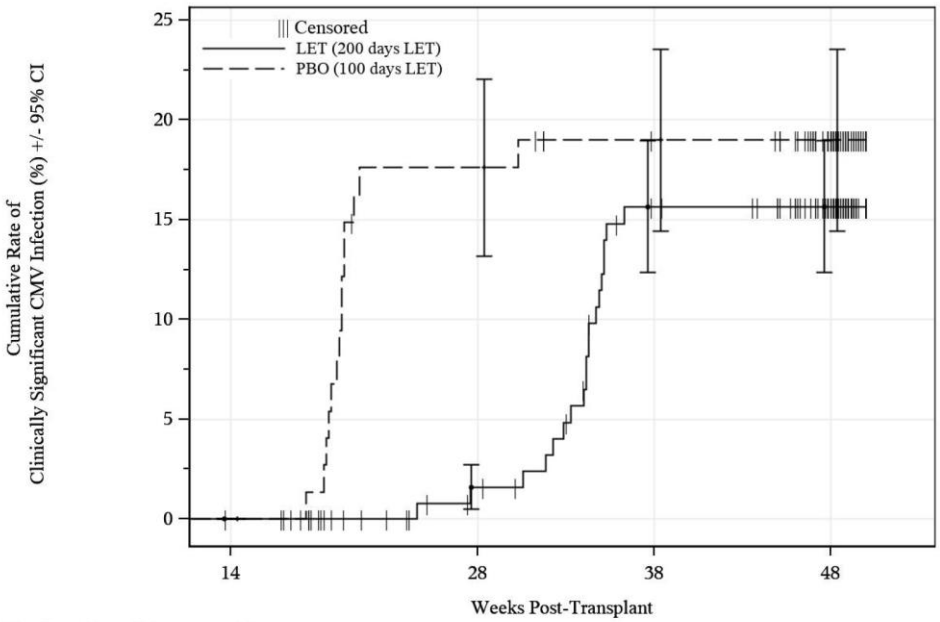
LET = Letermovir; PBO = Placebo

Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).

Secondary Efficacy Endpoints

Time to Onset of Clinically Significant CMV Infection

Figure 7: Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection From Week 14 (~100 days) Through Week 48 Post-transplant (Full Analysis Set Population)



Number of participants at risk

LET (200 days LET)	143	123	99	74
PBO (100 days LET)	74	60	55	38

Number of events inside period

LET (200 days LET)	2	17	0	0
PBO (100 days LET)	13	1	0	0

Proportion of participants with PET for CMV viremia

Table 32: Proportion of Participants with Initiation of PET for CMV Viremia From Week 14 (~100 days) Through Week 28 (~200 days) Post-transplant (OF Approach, Full Analysis Set Population)

Parameter	LET (200 days LET) (N=144) n (%)	PBO (100 days LET) (N=74) n (%)
Failures[a]	**3 (2.1)**	**12 (16.2)**
Initiation of PET based on documented CMV viremia	1 (0.7)	11 (14.9)
Discontinued from study with CMV viremia	2 (1.4)	1 (1.4)
Stratum-adjusted treatment difference (LET (200 days LET)-PBO (100 days LET))[b]		
Difference (95% CI)	-14.1 (-23.3, -5.0)	
p-value	0.0012	

[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

[b] 95% CIs and one-sided p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no). A nominal one-sided p-value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.

Note: Approach to handling missing values: Observed Failure (OF) approach. With the OF approach, failure was defined as all participants who develop clinically significant CMV infection or discontinue prematurely from the study with CMV viremia from week 14 (~100 days) through week 28 (~200 days) post-transplant.

N = Number of participants in each treatment group.

n (%) = Number (percent) of participants in each sub-category.

LET = Letermovir; PBO = Placebo

Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).

The proportion of participants with initiation of PET for CMV viremia through Week 48 post-transplant was comparable between treatment groups.

Proportion of participants with all-cause mortality

Proportions of participants with all-cause mortality from week 14 (~100 days) through week 28 post-transplant were 3/144 (2.1%) vs. 1/74 (1.4%) in the LET and placebo groups respectively. From week 14 through week 48 post-transplant proportions of participants with all-cause mortality were 12/144 (8.3%) vs. 6/74 (8.1%) in the LET and placebo groups respectively.

Time to all-cause mortality

Table 33: Analysis of Time to All-Cause Mortality From Week 14 Post-Transplant Through Week 28 and 48 Post-Transplant (Full Analysis Set Population)

Treatment	N	Number of Events (%)	Person-day	Event Rate/ 100 Person-days	Median Time (days) to Survival (95% CI) [a]	Survival Rate at Week 28 Post-Transplant % (95% CI) [a]
LET (200 days LET)	144	3 (2.1)	29615.0	0.0	NR (NR, NR)	98.6 (94.4, 99.6)
PBO (100 days LET)	74	1 (1.4)	15420.0	0.0	NR (NR, NR)	98.6 (90.7, 99.8)

Comparisons	Hazard Ratio (95% CI) [b]	p-Value [c]
LET (200 days LET) vs. PBO (100 days LET)	1.61 (0.17, 15.46)	0.6611

Treatment	N	Number of Events (%)	Person-day	Event Rate/ 100 Person-days	Median Time (days) to Survival (95% CI) [a]	Survival Rate at Week 48 Post-Transplant % (95% CI) [a]
LET (200 days LET)	144	12 (8.3)	46768.0	0.0	NR (NR, NR)	91.9 (85.8, 95.4)
PBO (100 days LET)	74	6 (8.1)	24444.0	0.0	NR (NR, NR)	91.8 (82.6, 96.2)

Comparisons	Hazard Ratio (95% CI) [b]	p-Value [c]
LET (200 days LET) vs. PBO (100 days LET)	1.07 (0.40, 2.85)	0.5526

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by stratum (haploidentical donor yes or no). Hazard ratio < 1 favors the LET (200 days LET) group.

[c] One-sided nominal p-value based on log-rank test stratified by stratum (haploidentical donor yes or no).

NR = Not reached.

LET = Letermovir; PBO = Placebo

Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).

Ancillary analyses

Subgroups analyses

Table 34: Summary of the Proportion of Participants with Clinically Significant CMV Infection From Week 14 (~100 days) Through Week 28 (~200 days) Post-transplant (OF Approach, Full Analysis Set Population)

Participant Characteristic Subgroup	LET (200 days LET) n/N	LET (200 days LET) % (95% CI)	PBO (100 days LET) n/N	PBO (100 days LET) % (95% CI)	LET (200 days LET) vs. PBO (100 days LET) Difference in % (95% CI)[a]
Total					
Age (Years)					
< 65	3/112	2.7 (0.6, 7.6)	12/63	19.0 (10.2, 30.9)	-16.3 (-26.9, -5.6)
>= 65	1/32	3.1 (0.1, 16.2)	2/11	18.2 (2.3, 51.8)	-14.5 (-43.3, 14.4)
Gender					
Male	2/92	2.2 (0.3, 7.6)	6/43	14.0 (5.3, 27.9)	-11.8 (-23.4, -0.1)
Female	2/52	3.8 (0.5, 13.2)	8/31	25.8 (11.9, 44.6)	-22.0 (-39.3, -4.6)
Race					
White	3/113	2.7 (0.6, 7.6)	10/60	16.7 (8.3, 28.5)	-14.0 (-24.4, -3.6)
Black	0/3	0.0 (0.0, 70.8)	0/1	0.0 (0.0, 97.5)	NA
Asian	0/16	0.0 (0.0, 20.6)	3/8	37.5 (8.5, 75.5)	-40.2 (-72.9, -7.5)
Other	0/4	0.0 (0.0, 60.2)	0/1	0.0 (0.0, 97.5)	NA
Systemic steroid exposure within 6 weeks prior to randomization					
Yes	0/19	0.0 (0.0, 17.6)	3/11	27.3 (6.0, 61.0)	-28.7 (-62.5, 5.2)
No	4/125	3.2 (0.9, 8.0)	11/63	17.5 (9.1, 29.1)	-14.3 (-24.6, -4.0)
Donor type					
Matched related	1/17	5.9 (0.1, 28.7)	1/11	9.1 (0.2, 41.3)	-3.2 (-27.8, 21.4)
Mismatched related	1/48	2.1 (0.1, 11.1)	4/23	17.4 (5.0, 38.8)	-15.2 (-32.1, 1.7)
Matched unrelated	2/37	5.4 (0.7, 18.2)	5/23	21.7 (7.5, 43.7)	-16.3 (-35.7, 3.0)
Mismatched unrelated	0/42	0.0 (0.0, 8.4)	4/17	23.5 (6.8, 49.9)	-23.5 (-45.0, -2.1)

[a] 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no).

Treatment difference and 95% CI were not calculated for subgroups with small sample size (<10% per treatment group) per protocol.

Note: Approach to handling missing values: Observed Failure (OF) approach. With OF approach, failure was defined as all participants who develop clinically significant CMV infection or discontinue prematurely from the study with viremia.

N = Number of participants in each treatment group.

n (%) = Number (percent) of participants in each sub-category.

NA = Not Applicable; LET = Letermovir; PBO = Placebo

Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).

Participant Characteristic Subgroup	LET (200 days LET) n/N	LET (200 days LET) % (95% CI)	PBO (100 days LET) n/N	PBO (100 days LET) % (95% CI)	LET (200 days LET) vs. PBO (100 days LET) Difference in % (95% CI)[a]
Haploidentical donor					
Yes	1/45	2.2 (0.1, 11.8)	4/22	18.2 (5.2, 40.3)	-16.0 (-33.7, 1.8)
No	3/99	3.0 (0.6, 8.6)	10/52	19.2 (9.6, 32.5)	-16.2 (-27.7, -4.7)
Cord blood					
Yes	0/8	0.0 (0.0, 36.9)	2/5	40.0 (5.3, 85.3)	NA
No	4/136	2.9 (0.8, 7.4)	12/69	17.4 (9.3, 28.4)	-14.4 (-24.2, -4.7)
T-cell depleted grafts					
Yes	1/15	6.7 (0.2, 31.9)	0/7	0.0 (0.0, 41.0)	NA
No	3/129	2.3 (0.5, 6.6)	14/67	20.9 (11.9, 32.6)	-18.5 (-29.0, -8.1)
Receipt of anti-thymocyte globulin					
Yes	1/67	1.5 (0.0, 8.0)	5/35	14.3 (4.8, 30.3)	-12.7 (-25.9, 0.6)
No	3/77	3.9 (0.8, 11.0)	9/39	23.1 (11.1, 39.3)	-19.2 (-33.8, -4.5)
Receipt of anti-thymocyte globulin alone					
Yes	0/24	0.0 (0.0, 14.2)	2/11	18.2 (2.3, 51.8)	-18.2 (-44.0, 7.6)
No	4/120	3.3 (0.9, 8.3)	12/63	19.0 (10.2, 30.9)	-15.7 (-26.3, -5.0)

[a] 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no).

Treatment difference and 95% CI were not calculated for subgroups with small sample size (<10% per treatment group) per protocol.

Note: Approach to handling missing values: Observed Failure (OF) approach. With OF approach, failure was defined as all participants who develop clinically significant CMV infection or discontinue prematurely from the study with viremia.

N = Number of participants in each treatment group.

n (%) = Number (percent) of participants in each sub-category.

NA = Not Applicable; LET = Letermovir; PBO = Placebo

Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).

Viral resistance

Next generation sequencing of the CMV terminase complex genes, UL51, UL56, and UL89 was performed on plasma samples collected at the CMV infection visit, next scheduled visit, or early discontinuation visit, to identify the presence of known LET resistance-associated amino acid variants. Among participants with resistance samples collected at a CMV infection visit or an early discontinuation visit, 32 (19 in the LET group and 13 in the placebo group) had evaluable LET resistance data available. In the LET group 2 (10.5%) participants had previously characterized resistance-associated amino acid variants detected in the pUL56 gene: one had a single R369S variant detected and another had both F261L and R369S variants detected. No LET resistance-associated mutations were observed in the placebo group.

CMV sequence data was also available from an additional 3 participants (2 in the LET group and 1 in the placebo group) who had resistance samples collected at a visit other than a CMV infection visit or an early discontinuation visit. Among these 3 participants, 1 in the LET group had a pUL56 E237G variant and 1 in the placebo group had 2 variants, pUL56 F261L and R369S, detected.

In all cases, the LET resistance-associated variants were present at low allele frequencies (≤3%), below the validated assay limit of 5%. Therefore, the clinical significance of these findings is unknown. No known LET resistance-associated variants were detected in the UL51 or UL89 genes in any participant with evaluable sequence data.

Summary of main study

Title: A Phase 3 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of letermovir (LET) prophylaxis when extended from 100 days to 200 days post-transplant in cytomegalovirus (CMV) seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT)			
Study identifier	P040MK8228		
Design	Duration of main phase:		From Week 14 (~100 days) post-transplant through Week 28 (~200 days)
Hypothesis	Superiority		
Treatments groups	Letermovir		n=145 randomized n=144 treated LET 480 mg once daily. If LET was co-administered with cyclosporine A (CsA), the dosage of LET was decreased to 240 mg once daily.
	Placebo		n= 75 randomized n=74 treated matching placebo
Endpoints and definitions	Primary endpoint	Clinically significant CMV infection (defined as initiation of pre-emptive therapy [PET] for documented CMV viremia and/or CMV end-organ disease)	
Database lock	24-MAY-2022		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Full analysis Set (FAS) From Week 14 (~100 days) Through Week 28 (~200 days)		
Descriptive statistics and estimate variability	Treatment group	Letermovir	Placebo
	Number of subjects	144	74
	Failures	4 (2.8%)	14 (18.9%)
	Clinically significant CMV infection	2 (1.4%)	13 (17.6%)
	Initiation of PET based on documented CMV viremia	1 (0.7%)	11 (14.9%)
	CMV end-organ disease	1 (0.7%)	2 (2.7%)
	Difference (95% CI) p-value	-16.1 (-25.8, -6.5) 0.0005	

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study P002

This was a phase III, randomized, active-controlled, multi-site, double-blind study to evaluate the efficacy and safety of letermovir (LET) compared with valganciclovir (VGCV) administered for 28 weeks post-transplant for the prevention of cytomegalovirus (CMV) disease in adult seropositive donor/seronegative recipient (D+/R) kidney transplant recipients. Participants were followed through 52 weeks post-transplant and 292 participants were treated with LET and 297 participants were treated with VGCV.

To test the primary hypothesis that LET is noninferior to VGCV in the prevention of CMV disease, the difference between the two treatment arms in the proportions of participants with adjudicated CMV disease through Week 52 post-transplant and the associated two-sided 95% confidence interval (CI) were calculated using the stratum-adjusted Mantel-Haenszel method with stratification by receipt or no receipt of highly cytolytic anti-lymphocyte therapies. LET was concluded to be noninferior to VGCV if the upper bound of the two-sided 95% CI for the difference in proportion of participants with adjudicated CMV disease (LET - VGCV) was no higher than 0.10. The primary analysis was stratified using the same stratification as the randomisation. This is in accordance with guidelines and is endorsed.

The FAS population were the primary population for efficacy analysis. The FAS population included all randomized participants who received at least one dose of study treatment, were D+/R-, and had no detectable CMV viral DNA on Day 1. This deviation from the ITT principle is acceptable in this setting. A per protocol-based analysis was used as supportive analysis.

The prespecified analysis used for the primary endpoint was observed failure (OF) approach where participants who discontinued prematurely from the study are not counted as failures. A sensitivity analysis was performed where participants who discontinued prematurely or had missing outcome Week 52 were counted as failures (Non-Completer=Failure). With a relatively low frequency of actual failures in both treatment arms and a rather high frequency of missing data, both these methods are highly impacted by the amount of missing data. A tipping point analysis exploring the deviation from MAR assumption that would be needed for the conclusion to shift and a discussion of the plausibility of this deviation would be useful in the interpretation of the results and was therefore requested. Furthermore, the MAH was asked to provide baseline characteristics for key prognostic factors for subjects with missing and non-missing data respectively for each treatment group. In the answers to request for supplementary information the requested analysis and discussion were provided. The tipping point analysis and baseline disease and demographic characteristics provided confirms robustness of the primary non-inferiority analysis.

The type I error was controlled with a closed testing procedure which is accepted.

The primary endpoint CMV disease included CMV end-organ disease and "probable CMV syndrome" defined by CMV viremia together with two or more criteria including laboratory measures or clinical symptoms to be fulfilled. It is important to note that overall, the definition of CMV syndrome was comparable to the definitions used in the valganciclovir and placebo studies from which the non-inferiority margin was calculated.

The study was double-blinded, however, given the difference in effect of letermovir and valganciclovir on blood cells counts, cytopenia being a common to very common adverse drug reaction of VGCV, it is

likely that the investigators could have become aware of the allocated treatment for some participants.

Patients in the LET arm in study P002 were treated concomitantly with aciclovir for HSV and VZV prophylaxis. While valaciclovir at the dose of 2g X 4 has shown clinically significant anti-CMV effects, this is not anticipated from the dose of aciclovir which was selected (400 mg x 2).

The original protocol (dated 21-Sep-2017) was amended five times. Changes included adding a 240 mg I.V dose (without CsA), laboratory exclusion criteria, prohibited medication, modification to timing of screening and I.V administration details.

Selection of the NI margin

To justify the NI margin of 10%, the MAH refers to two key historical studies. These are Humar et al 2010, and Lowance et al 1999.

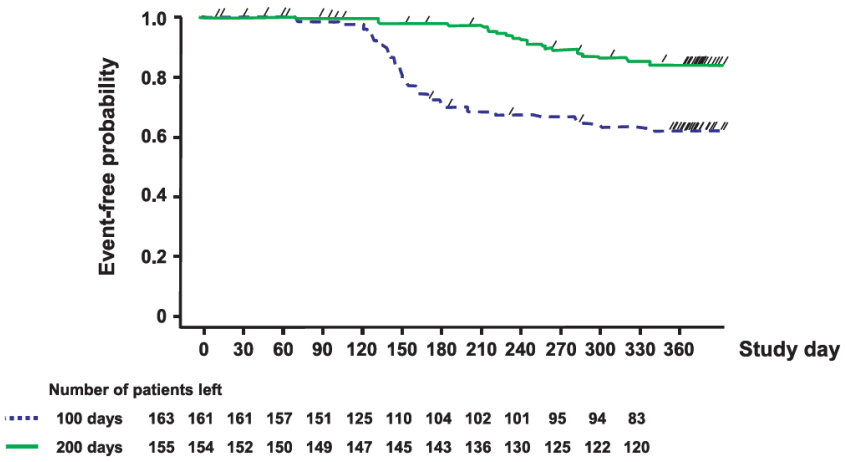
Humar et al describes a multicentre, double-blind, randomized controlled trial which compared the efficacy and safety of 200 days versus 100 days' valganciclovir prophylaxis (900 mg once daily) in 326 high-risk (D+/R−) kidney allograft recipients. The endpoint was CMV disease, which was similarly defined as in the letermovir trial.

In the trial reported by Humar et al, significantly fewer patients in the 200-day group versus the 100-day group developed confirmed CMV disease up to month 12 post-transplant (16.1% vs. 36.8%; p < 0.0001).

Figure 8: Kaplan-Meier plot of time to cytomegalovirus disease up to month 12 posttransplant

Results

Difference	20.7 %
95% CI	11.0687% to 29.7956%
Chi-squared	17.336
DF	1
Significance level	P < 0.0001



This trial would formally support an M1 (as FDA defines it) of 10%, based on the lower 95% CI of the

primary efficacy measure.

There may be concerns that this margin would not be sufficiently conservative given secular trends in outcome, potential differences in the studied population, background immunosuppression or endpoint ascertainment. However, it is notable that the difference in effect between arms in the Humar trial, is despite that patients in both arms were treated with valganciclovir during the first 100 days.

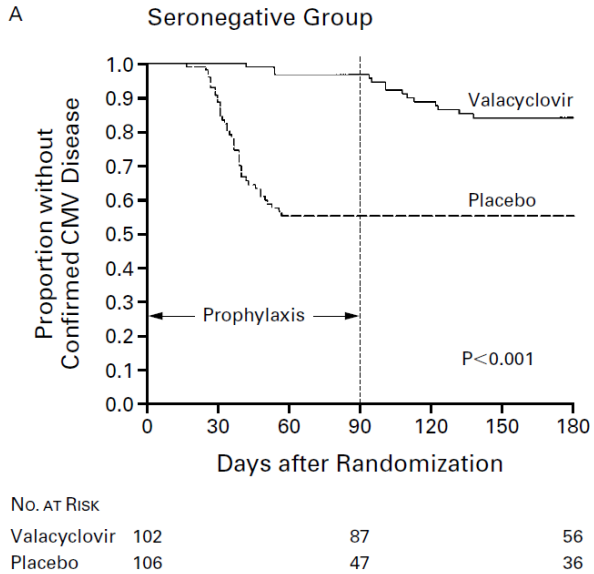
Based on Lowance et al, one may infer that 10% is a rather conservative margin. While this study was performed in the 1990s, it is still of importance as it demonstrates the outcome of a placebo treated group with respect to the risk of CMV disease.

In this study, a total of 208 CMV-negative recipients of a kidney from a seropositive donor and 408 CMV-positive recipients were randomly assigned to receive either 2 g of valaciclovir or placebo orally four times daily for 90 days after transplantation, with the dose adjusted according to renal function. The primary end point was laboratory confirmed CMV disease in the first six months after transplantation.

Among the seronegative patients, the incidence of CMV disease 90 days after transplantation was 45 percent among placebo recipients and 3 percent among valaciclovir recipients.

Results

Difference	42 %
95% CI	31.4043% to 51.6815%
Chi-squared	49.464
DF	1
Significance level	P < 0.0001



It is generally accepted that high dose valaciclovir is not more effective than valganciclovir. Consequently, one may conclude that the efficacy of valganciclovir is considerable in the first 100 days, where patients in both arms of the Humar study received active drugs. Moreover, it is generally agreed that aciclovir at the dose given in the letermovir study arm, will not provide relevant anti-CMV activity.

On this basis, it may be concluded that the 10% NI margin is robustly conservative with respect to indirectly establishing the efficacy of letermovir over no treatment, for the prevention of CMV disease in seronegative recipients.

Study P040

This was a phase III, randomized, placebo-controlled, parallel assignment, multicentre, double-blind, efficacy and safety study evaluating extending LET prophylaxis to 200 days post-transplant in CMV-seropositive recipients (R+) of an allogeneic HSCT who had received LET prophylaxis through Week 14 (~100 days) post-transplant and who were at high risk for CMV infection and/or disease after completion of LET prophylaxis through 100 days post-transplant.

Eligible participants were randomized in a 2:1 ratio to receive LET through Week 28 (LET through 200 days) post-transplant or to receive oral or intravenous placebo once daily through Week 28 (LET through 100 days) post-transplant.

The primary endpoint was clinically significant CMV infection (defined as initiation of pre-emptive therapy [PET] for documented CMV viremia and/or CMV end-organ disease) through week 14 to week 28.

The FAS population were the primary population for efficacy analysis. The FAS population included all randomised participants who received at least one dose of study treatment which is accepted.

To test the primary hypothesis that LET is superior to placebo in the prevention of clinically significant CMV infection when LET prophylaxis is extended from 100 to 200 days post-transplant, the stratum-adjusted Mantel-Haenszel method (with continuity correction) was used to compare the proportion of subjects with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant between the two treatment groups. The primary analysis was stratified by haploidentical donor (yes/no) but not for study centre. This is accepted. Cochran Mantel-Haenszel weights were used to calculate the overall between-group differences across strata. LET was concluded superior to placebo if 1-sided p-value is less than or equal to 0.0249. The statistical methods and handling of missing data were similar as for the P002 study. The prespecified analysis used for the primary endpoint was observed failure approach and a supportive analysis using the Non-Completer=Failure approach was performed at week 28.

The DMC were provided with unblinded descriptive summaries of the efficacy data. Although no formal efficacy analyses were provided, a small amount of alpha ($\alpha = 0.0001$) was allocated for each of these looks. This is accepted.

No method for controlling type I error for secondary endpoints has been specified.

In general, the baseline characteristics were similar between the treatment groups. The proportion of participants with graft-versus-host disease (GVHD) at study entry was higher in the LET group compared with the placebo group. One recipient in the letermovir arm was CMV seronegative at baseline. To be eligible for entering the study participants should have documented positive CMV serostatus (CMV IgG seropositive) for recipient (R+) at the time of transplant. Thus, the patient should not have been included in the study, however, 1/144 patients is negligible given the overall outcome.

The original protocol (dated 03-DEC-2018) was amended twice to limit enrolment of patient who have anti-thymocyte globulin and implement changes related to I.V administration.

It is notable that for the original registrational study P001, the MAH used a conservative NC=F approach to impute outcomes in cases with missing data. For the P002 and P040 studies, the MAH

prespecified an Observed Failure (OF) approach. While it is understood that a non-inferiority study requires different assumptions than a superiority study with respect to what imputations are conservative, the P040 study is a superiority study.

The MAH states that the OF approach was selected partially based on the anticipation that the CMV disease rates would be low and thus the NC=F approach would have overestimated the failure rate and been overly conservative obscuring the true treatment effect. This argument is accepted. Moreover, the sensitivity analyses with NC=F approach for both studies are demonstrating similar results as the analyses of the primary endpoints.

Efficacy data and additional analyses

Study P002

In the phase 3 study P002, LET was demonstrated to be non-inferior to VGCV for the prevention of CMV disease in kidney transplant patients through Week 52 post-transplant; 10.4% vs. 11.8% failures were observed in the LET and VGCV groups respectively (treatment difference -1.4 (95% CI: -6.5, 3.8]).

In the primary analysis missing data was imputed as not considered failures (observed failure approach). A sensitivity analysis with a failure imputation was also performed (non-completer=failure). With a relatively low frequency of actual failures in both treatment arms and a rather high frequency of missing data, both these methods are highly impacted by the amount of missing data. A tipping point analysis exploring the deviation from MAR assumption that would be needed for the conclusion to shift and baseline disease and demographic characteristics provided confirms robustness of the primary non-inferiority analysis.

There is a numerical imbalance between treatment groups in study P002 in the number of patients with end-organ disease, 6 versus 1 patient in the LET and VGCV groups, respectively. Five of the cases in the LET group are CMV end-organ GI disease, of which 4 proven and 1 probable CMV end-organ GI disease. All participants from the LET group experiencing CMV end-organ disease completed more or less the intended duration of treatment (200 days). In almost all cases of CMV end-organ GI disease the onset of symptoms started approximately 1-2 months after completing study intervention (one participant had symptoms approx. 4 months after completing LET). The primary reason for transplant, gender and age varied and no obvious pattern can be discerned. All participants recovered with treatment with either oral valganciclovir and/or iv ganciclovir.

It was noted during the assessment of the pivotal trial P001 in HSCT patients that, despite an on-treatment imbalance between groups in favour of LET, there was an apparent catch-up in cases of CMV end-organ disease in the letermovir group after prophylaxis was discontinued, with 1 patient at week 14 (end of treatment) and additionally 5 patients at week 24, all of whom had GI disease. No risk factors for CMV EOD could be identified from the baseline characteristics, medical history, or concomitant medications for these patients.

The MAH claims that the difference in GI EOD between the treatment arms in P002 is predominantly due to lack of confirmatory endoscopy/tissue-invasive biopsy (required for adjudication confirmed GI EOD) in the majority of investigator reported GI EOD. None (0/16) were performed/documented in the VGCV arm and 5/25 in the LET arm. No risk factors that would increase the likelihood for CMV EOD in these patients have been identified. Baseline characteristics, medical history and concomitant medications were in general comparable with the overall population. All participants with CMV EOD in the LET arm took LET 480 mg daily and did not receive CsA.

The MAH has not provided a satisfactory explanation for the observed imbalance in GI EOD and claims it to be a random finding due to a difference in performed procedures between participants. Moreover, the analysis of the primary endpoint in investigator-reported CMV disease through Week 52 post-transplant also adds support to the efficacy of letermovir.
In summary, this is a likely random finding. Moreover, given the natural history of CMV post-transplant, as well as the nature of the findings, there remains no doubt that letermovir is an effective and useful agent in the proposed treatment niche.

As mentioned above the primary endpoint CMV disease included CMV end-organ disease and "probable CMV syndrome". Leukopenia or neutropenia (criteria 3) or thrombocytopenia (criteria 5) are among the listed criteria which may be counted to fulfil the definition of CMV syndrome. Leukopenia, neutropenia and thrombocytopenia are very common (≥1/10) or common (≥1/100 to <1/10) adverse drug reactions associated with VGCV. Thus, it was questioned whether the number of cases of CMV syndrome in the VGCV arm in study P002 was inflated by the occurrence of cytopenia secondary to VGCV, which would impact the primary efficacy analysis in favour of LET. The prophylaxis treatment period was 28 weeks and the primary efficacy endpoint was assessed at 52 weeks, after a period of off-treatment follow-up. The half-life of VGCV is short (approximately 4 hours) and drug-induced cytopenia is expected to resolve within around a week of stopping. The majority of the CMV syndrome events (24/24 LET and 29/34 VGCV) occurred after cessation of prophylaxis. Most cases of CMV syndrome in the VGCV arm that were confirmed on the basis of criteria 3 or 5 being fulfilled were most likely due to actual CMV syndrome and not an adverse drug reaction associated with VGCV.

The time to onset of CMV disease was comparable between the LET and VGCV groups through Week 52 post-transplant. As mentioned above the majority of CMV disease cases occurred after cessation of treatment. The proportion of CMV disease at 28 weeks post-transplant was 0 vs. 5 participants in the LET and VGCV arms respectively using the OF approach.

It is noted that the proportion of participants with quantifiable CMV DNAemia was lower in the LET group compared to the VGCV group through week 28 and slightly lower also through week 52 post-transplant supporting the efficacy of LET as prophylaxis in this study.

The incidence of CMV disease by intervention group through Week 52 post-transplant was overall comparable across the subgroups of sex, age, race, region and induction therapy.

Viral resistance

Viral resistance testing was performed on samples obtained from participants prior to initiation of CMV treatment or who had suspected or confirmed CMV disease. There were no LET resistance-associated substitutions at a frequency of ≥ 5% in the LET-treated participants with CMV disease or early discontinuation with viremia (n=52). The potential contribution of co-administration of aciclovir with LET in terms of (cross-) resistance to VGCV is not considered likely. The dose of aciclovir used is below the EC50 necessary to treat CMV and would not be expected to exert any selective pressure on the virus to induce potential escape mutants. Moreover, LET was effective in suppressing CMV replication during the prophylaxis period, making the possibility of resistance selection to aciclovir, and possible cross-resistance with VGCV, highly unlikely. Thus, the combination of LET + aciclovir is not likely to compromise the patient's possibilities for receiving adequate treatment in the event of prophylaxis failure.

Study P040

The primary efficacy endpoint of proportion of participants with clinically significant CMV infection from

Week 14 (~100 days) through Week 28 (~200 days) post-transplant (OF approach) was significant with 4/144 (2.8%) vs 14/74 (18.9%) in the LET and placebo groups respectively (difference -16.1 [95% CI; -25.8,-6.5], p-value =0.0005).

In the supportive analysis of the primary efficacy endpoint using NC=F approach 14.6% vs. 24.3% CMV infections at week 28 was observed in the LET and placebo groups, respectively (nominal p-value=0.0505). A total of 16 participants were categorised as "Discontinued from study before Week 28" post-transplant in the LET arm and one in the placebo group. There were no overall trends in the reasons for study discontinuations. In the LET arm, the most common reason for discontinuation was "Withdrawal by Subject" (n=11). Within this category, 4 discontinuations were due to transportation/unable to go to hospital including one also for health issues. Seven discontinuations were due to the participants' desire to not continue participation in the study whereof one was reported due to nausea related to study treatment. Additional reasons for early discontinuation in the LET arm included death (n=1), loss to follow-up (n=1), due to physician decision (n=1), COVID-19 (n=1) or multiple reasons including CMV reactivation and compliance (n=1). It would be expected that these listed reasons for discontinuation would be more or less evenly distributed between the treatment arms, which is not the case. However, with the available data it is not possible to determine if the discontinuations are an effect of letermovir treatment.

Time to onset of clinically significant CMV infection was longer in the LET group and the proportion of participants with PET was lower in the LET group compared to placebo through 28 weeks post-transplant. The results support the effect of letermovir prophylaxis in HSCT for ~200 days.

Proportions of participants with all-cause mortality was a secondary endpoint and was comparable in the treatment groups. From week 14 (~100 days) through week 28 post-transplant there were 2.1% vs. 1.4% in the LET and placebo groups respectively. From week 14 through week 48 post-transplant proportions of participants were 8.3% vs. 8.1% in the LET and placebo groups respectively.

The treatment difference in the incidence of clinically significant CMV infection by treatment group through Week 28 post-transplant across subgroups including age, sex, donor type and immunosuppressive regimen were overall consistent with the outcome of the primary endpoint.

Viral resistance

Overall, 4 participants in the LET group and 1 in the placebo group had detectable resistance-associated amino acid variants (pUL56 gene). In all cases, the LET resistance-associated variants were present at low allele frequencies (≤3%), below the validated assay limit of 5%. Therefore, the clinical significance of these findings is unknown. No known LET resistance-associated variants were detected in the UL51 or UL89 genes in any participant with evaluable sequence data. The SmPC has been updated to include information that no letermovir resistance-associated substitutions were detected above the validated assay limit.

2.4.4. Conclusions on the clinical efficacy

The use of letermovir prophylaxis until 28 weeks post-kidney transplant is effective in preventing CMV disease through 52 weeks post-transplant in seronegative patients receiving kidneys from seropositive donors. This was demonstrated by the non-inferiority of letermovir to the standard of care valganciclovir.

The use of letermovir prophylaxis until 28 weeks post hematopoietic stem cell transplant is effective in postponing CMV reactivation in CMV seropositive patients.

2.5. Clinical safety

Introduction

In support of this application, the MAH presented safety data from the following clinical studies:

Table 35: Summary of clinical studies with LET providing safety information

Study Number (Status) [CTD Location] Number of Study Sites (Countries)	Design (Indication)	Number of Participants by Intervention Group	Study Population (N)
Phase 3 Studies Supporting This Application			
MK-8228-002 (completed) [Ref. 5.3.5.1: P002MK8228] 94 sites (16 countries: Argentina, Australia, Austria, Belgium, Canada, Colombia, France, Germany, Hungary, Italy, Mexico, Poland, New Zealand, Spain, United Kingdom, United States)	Randomized, double-blind, multisite, active comparator-controlled study to evaluate efficacy and safety of LET versus VGCV for prevention of CMV in adult (D+/R-) kidney transplant recipients. Participants were randomized within 7 days post-transplant in a 1:1 ratio to receive LET or VGCV through Week 28. Participants in the LET group also received ACV for HSV and VZV prophylaxis. Each participant was followed until Week 52.	**LET Group:** Randomized: 301 Treated: 292 Completed study intervention: 246 **VGCV Group:** Randomized: 300 Treated: 297 Completed study intervention: 224	Sex: 422 M/167 F Median (range) age: 51 (18 to 82) years
MK-8228-040 (completed) [Ref. 5.3.5.1: P040MK8228] 32 sites in 6 countries (France, Germany, Italy, Japan, United Kingdom, United States)	Randomized, placebo-controlled, parallel-assignment, multisite, double-blind efficacy and safety study of extending LET prophylaxis in CMV seropositive allogeneic HSCT recipients (R+) who had received LET prophylaxis through Week 14 (~100 days) post-transplant and were at risk for late CMV infection and/or disease thereafter. Participants were randomized 2:1 to continue LET uninterrupted for an additional 14 weeks (a total of 200 days of LET post-transplant) or to begin receiving placebo (a total of 100 days of LET post-transplant). Each participant was followed until 48 weeks post-transplant.	**LET (200 days LET):** Randomized: 145 Treated: 144 treated Completed study intervention: 119 **PBO (100 days LET):** Randomized: 75 randomized Treated: 74 Completed study intervention: 56	Sex: 135 M/83 F Median (range) age: 55 (20 to 74) years
ACV=acyclovir; CMV=cytomegalovirus; CTD=common technical document; D+/R-=donor positive/recipient negative; F=female; HSCT=hematopoietic stem cell transplantation; HSV=herpes simplex virus; LET=Letermovir; M=male; PBO=placebo; R+=recipient positive; VGCV=valganciclovir; VZV=varicella zoster virus			

The populations used for the analysis of safety data are APaT population (all randomised participants who received at least one dose of study intervention). Further details of the study designs are summarised above under 2.4.2. *Main studies*.

Power for safety analysis

In Study P002, a power calculation to show the percentage point difference between the treatment arms that could be detected with a 90% probability, given 300 participants in each arm, was geared towards the expectation of superiority of LET over VGCV in terms of the rate of leukopenia AEs. No calculation is provided to show the minimal degree of true inferiority of LET with respect to a given AE rate that can be detected with a reasonable probability in the same study.

In Study P040, if the underlying incidence of a particular AE is 1% (1 of every 100 participants receiving the drug), there is a 52% chance of observing at least one of that particular AE among 72 participants in the placebo (100-day) arm or a 76% chance of observing at least one of that particular AE among 144 participants in the LET (200-day) arm. If no AE of that particular type are observed among the 144 participants in the LET (200-day) arm, this study will provide 95% confidence that the underlying percentage of participants with that particular AE is <2.5% (one in every 40 participants).

2.5.1.1. Study P002 – post-kidney transplant

Patient exposure

A total of 292 participants received at least one dose of LET by any route in study P002. The currently authorised dose of oral LET 480 mg once daily (240 mg when administered with cyclosporin A (CsA)) was administered to 152 participants for >24 to <28 weeks and 98 participants for >28 weeks. The mean duration of exposure to LET (any route of exposure) was longer compared with VGCV (175.6 days vs. 160.7 days).

An amendment was made to study protocol to allow 1:1 randomisation to LET IV 480mg or 240 mg when administered intravenously without CsA. The rationale for this was that popPK simulations using data from the Phase 3 trial in HSCT recipients suggest that a 240 mg IV dose (without CsA) will provide exposures comparable to exposures obtained following administration of a 480 mg PO dose (without CsA).

LET was administered with concomitant ACV for the duration of study treatment. The mean duration of exposure to concomitant ACV was comparable to the duration of exposure to oral LET.

Measurements of Study Intervention Compliance

The proportion of participants with compliance <90% was lower in the LET group (<2%) compared with the VGCV group (>20%).

Adverse events

Overall adverse events

Collection of AEs continued through the treatment phase and 14 days after completion of study intervention. After the treatment phase, only SAEs related to study intervention or resulting in death were collected through week 52 post-transplant.

The overall rate of AEs in each treatment group through 28 weeks post-transplant was generally comparable, with the exception of drug-related AEs (-15.2% (95% CI -22.2, -8.0)) and discontinuation of study intervention due to AEs (-9,4% (95%CI -14.1, -4.9)), including drug-related AEs (-6.0% (95% CI -10.1, -2.4)), which were all lower in the LET group compared with the VGCV group. These differences were primarily due to fewer participants in the LET group with drug-related leukopenia and neutropenia (leukopenia; 11.3% vs 37.0%; neutropenia 2.7% vs 16.5%) through Week 28 post-transplant. There were no notable changes through Week 52 post-transplant for leukopenia or neutropenia.

Common adverse events

The most commonly reported AEs (incidence >10%) for LET were diarrhoea (31.5%), tremor (18.2%), urinary tract infection (14.0%), peripheral oedema (13.4%), hypomagnesemia (12.7%), leukopenia (11.3%), hypertension (11.3%), hypophosphatemia (10.3%) and blood creatinine increased (10.3%).

Table 36: Participants With Adverse Events (P002) (Incidence ≥ 10% in One or More Treatment Groups) Treatment Phase (All Participants as Treated)

	LET Arm		VGCV Arm		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	292		297		589	
with one or more adverse events	271	(92.8)	276	(92.9)	547	(92.9)
with no adverse events	21	(7.2)	21	(7.1)	42	(7.1)
Blood and lymphatic system disorders	**78**	**(26.7)**	**146**	**(49.2)**	**224**	**(38.0)**
Leukopenia	33	(11.3)	110	(37.0)	143	(24.3)
Neutropenia	8	(2.7)	49	(16.5)	57	(9.7)
Cardiac disorders	**33**	**(11.3)**	**47**	**(15.8)**	**80**	**(13.6)**
Gastrointestinal disorders	**153**	**(52.4)**	**144**	**(48.5)**	**297**	**(50.4)**
Diarrhoea	92	(31.5)	85	(28.6)	177	(30.1)
Nausea	25	(8.6)	33	(11.1)	58	(9.8)
General disorders and administration site conditions	**96**	**(32.9)**	**97**	**(32.7)**	**193**	**(32.8)**
Fatigue	18	(6.2)	32	(10.8)	50	(8.5)
Oedema peripheral	39	(13.4)	38	(12.8)	77	(13.1)
Infections and infestations	**131**	**(44.9)**	**146**	**(49.2)**	**277**	**(47.0)**
Urinary tract infection	41	(14.0)	42	(14.1)	83	(14.1)
Injury, poisoning and procedural complications	**66**	**(22.6)**	**73**	**(24.6)**	**139**	**(23.6)**
Investigations	**102**	**(34.9)**	**104**	**(35.0)**	**206**	**(35.0)**
Blood creatinine increased	30	(10.3)	41	(13.8)	71	(12.1)
Metabolism and nutrition disorders	**137**	**(46.9)**	**142**	**(47.8)**	**279**	**(47.4)**
Hyperkalaemia	27	(9.2)	32	(10.8)	59	(10.0)
Hypomagnesaemia	37	(12.7)	39	(13.1)	76	(12.9)
Hypophosphataemia	30	(10.3)	35	(11.8)	65	(11.0)
Musculoskeletal and connective tissue disorders	**57**	**(19.5)**	**64**	**(21.5)**	**121**	**(20.5)**
Nervous system disorders	**104**	**(35.6)**	**81**	**(27.3)**	**185**	**(31.4)**
Tremor	53	(18.2)	52	(17.5)	105	(17.8)
Renal and urinary disorders	**97**	**(33.2)**	**87**	**(29.3)**	**184**	**(31.2)**
Respiratory, thoracic and mediastinal disorders	**44**	**(15.1)**	**58**	**(19.5)**	**102**	**(17.3)**
Skin and subcutaneous tissue disorders	**47**	**(16.1)**	**46**	**(15.5)**	**93**	**(15.8)**
Vascular disorders	**83**	**(28.4)**	**75**	**(25.3)**	**158**	**(26.8)**
Hypertension	33	(11.3)	36	(12.1)	69	(11.7)

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.
MedDRA version 25.0 was used in the reporting of this study.

Drug-related adverse events

The proportion of participants with AEs deemed drug-related by the investigator was lower in the LET group (19.9%) compared with the VGCV group (35.0%), primarily due to fewer participants with drug-

related leukopenia (6.8% vs 22.9%) or neutropenia (2.1% vs 8.1%). Apart from leukopenia and (to a lesser degree) neutropenia, drug-related adverse events were reported at similar rates in both study arms.

Serious adverse events and Deaths

Serious adverse events

The proportion of participants with SAEs through Week 28 post-transplant was generally comparable between the LET group (36.3%) and the VGCV group (38.0%).

The most frequently reported SAEs (incidence >2%) in the LET group were pyrexia, urinary tract infection, blood creatinine increased, acute kidney injury, and lymphocele.

The most frequently reported SAEs (incidence >2%) in the VGCV group were leukopenia, diarrhoea, transplant rejection, cytomegalovirus infection, urinary tract infection, and acute kidney injury.

Apart from the SOC Blood and lymphatic disorders, drug-related serious adverse events were infrequent and reported at similar rates in both study arms.

Table 37: Participants With Drug-Related Serious Adverse Events (P002) (Incidence > 0% in One or More Treatment Groups) Treatment Phase (All Participants as Treated)

	LET Arm		VGCV Arm		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	292		297		589	
with one or more drug-related serious adverse events	4	(1.4)	15	(5.1)	19	(3.2)
with no drug-related serious adverse events	288	(98.6)	282	(94.9)	570	(96.8)
Blood and lymphatic system disorders	**3**	**(1.0)**	**10**	**(3.4)**	**13**	**(2.2)**
Febrile neutropenia	1	(0.3)	3	(1.0)	4	(0.7)
Leukopenia	2	(0.7)	6	(2.0)	8	(1.4)
Neutropenia	2	(0.7)	2	(0.7)	4	(0.7)
Pancytopenia	1	(0.3)	0	(0.0)	1	(0.2)
Cardiac disorders	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.2)**
Atrial fibrillation	1	(0.3)	0	(0.0)	1	(0.2)
Gastrointestinal disorders	**1**	**(0.3)**	**1**	**(0.3)**	**2**	**(0.3)**
Diarrhoea	1	(0.3)	0	(0.0)	1	(0.2)
Nausea	0	(0.0)	1	(0.3)	1	(0.2)
Investigations	**0**	**(0.0)**	**3**	**(1.0)**	**3**	**(0.5)**
White blood cell count decreased	0	(0.0)	3	(1.0)	3	(0.5)
Metabolism and nutrition disorders	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.2)**
Hypophosphataemia	0	(0.0)	1	(0.3)	1	(0.2)

Every participant is counted a single time for each applicable row and column.
Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.
MedDRA version 25.0 was used in the reporting of this study.

Deaths

A total of 5 deaths due to an AE were reported through Week 52 post-transplant. Three deaths in the LET group were due to bacterial sepsis, septic shock, and pulmonary embolism. Two deaths in the VGCV group were due to cardio-respiratory arrest and respiratory failure.

One additional death due to COVID-19 in the VGCV group (not reported as an AE) was reported through Week 52 post-transplant. In addition, 2 deaths (post-transplant lymphoproliferative disorder

and cardio-respiratory arrest) were reported after the last study visit in the LET group. None of the deaths were considered by the investigators to be related to study intervention.

Laboratory findings

Myelotoxicity

AEs of leukopenia, total WBC count <3500 cells/µL, AE of neutropenia, ANC <1000 cells/µL through Week 28 post-transplant were lower in the LET group compared with the VGCV group (-37.9% (95%CI -45.1, -30.3)).

The proportions of participants with Grade 3 or Grade 4 decreases from baseline in leukocytes (2.7% vs 6.6%) or neutrophils (2.1% vs 7.9%) were lower in the LET group compared with the VGCV group respectively. The proportion of participants administered GCSF through Week 28 post-transplant was lower in the LET group (1.7%) compared with the VGCV group (7.1%).

Table 38: Analysis of Participants With Leukopenia or Neutropenia (by Adverse Event Preferred Term or Laboratory Criteria) (P002) Treatment Phase (All Participants as Treated)

	LET Arm		VGCV Arm		Total		Difference in % vs VGCV	
	n	%	n	%	n	%	Estimate (95% CI)[a]	p-value[a]
Participants in population	292		297		589			
With no leukopenia or neutropenia (preferred term or laboratory criteria) events	216	(74.0)	107	(36.0)	323	(54.8)		
With one or more leukopenia or neutropenia (preferred term or laboratory criteria) events	**76**	**(26.0)**	**190**	**(64.0)**	**266**	**(45.2)**	**-37.9 (-45.1, -30.3)**	**<0.0001**
Leukopenia (preferred term)	33	(11.3)	110	(37.0)	143	(24.3)	-25.7 (-32.3, -19.1)	
Leukopenia (WBC <3500 cells/µL)	66	(22.6)	172	(57.9)	238	(40.4)	-35.3 (-42.5, -27.7)	
Neutropenia (preferred term)	8	(2.7)	49	(16.5)	57	(9.7)	-13.8 (-18.7, -9.3)	
Neutropenia (ANC <1000 cells/µL)	12	(4.1)	58	(19.5)	70	(11.9)	-15.4 (-20.7, -10.5)	

[a] Based on Miettinen & Nurminen method.

Source: [P002MK8228: adam-adsl]

Other laboratory findings and vital signs measurements

No meaningful differences or trends in laboratory values over time were observed through Week 28 post-transplant between the LET group and VGCV group, except for leukopenia and neutropenia. No participants had laboratory values that met the predefined criteria for potential DILI.

There were no clinically meaningful findings in vital signs measurements, ECG parameters, or physical examination assessments for either treatment group.

Additional safety findings

Discontinuation due to adverse events

Fewer participants in the LET group (4.1%) discontinued study intervention due to an AE compared with the VGCV group (13.5%). Leukopenia (LET [1.0%] vs. VGCV [5.4%]) and neutropenia (LET [1.4%] vs. VGCV [1.7%]) were the most frequently reported AE leading to study intervention discontinuation in either group. All other adverse events leading to discontinuation occurred at a rate of <1% and mainly as isolated cases.

New-onset diabetes

The proportions of participants with confirmed new onset of diabetes mellitus after transplant through Week 28 (5.9% vs 6.1%) and Week 52 (6.2% vs 6.7%) post-transplant were comparable between the

LET group and the VGCV group.

Renal Graft Rejection, Renal Graft Loss, and Changes in Renal Function

Renal graft rejection, renal graft loss, and changes in renal function are summarised below, and were comparable between the LET group and the VGCV group.

Table 39: Summary of Allograft Dysfunction (Full Analysis Set Population)

	LET Arm (N=289)		VGCV Arm (N=297)	
	n	% (95% CI)	n	% (95% CI)
Allograft Dysfunction and/or Rejection Through Week 28 Post-transplant	**188**	**65.1 (59.2, 70.5)**	**205**	**69.0 (63.4, 74.2)**
≥20% Decline in Post-transplant eGFR from 4 Weeks Post-transplant Through Week 28 Post-transplant[a]	62	21.5 (16.9, 26.6)	72	24.2 (19.5, 29.5)
Biopsy-Proven Acute Renal Graft Rejection Through Week 28 Post-transplant	17	5.9 (3.5, 9.3)	18	6.1 (3.6, 9.4)
Graft Loss Through Week 28 Post-transplant	1	0.3 (0.0, 1.9)	3	1.0 (0.2, 2.9)
eGFR <60 at Week 28 Post-transplant	168	58.1 (52.2, 63.9)	184	62.0 (56.2, 67.5)
Allograft Dysfunction and/or Rejection Through Week 52 Post-transplant	**192**	**66.4 (60.7, 71.9)**	**205**	**69.0 (63.4, 74.2)**
Biopsy-Proven Acute Renal Graft Rejection Through Week 52 Post-transplant	23	8.0 (5.1, 11.7)	20	6.7 (4.2, 10.2)
Graft Loss Through Week 52 Post-transplant	2	0.7 (0.1, 2.5)	6	2.0 (0.7, 4.3)

[a] eGFR is calculated using the MDRD equation. The measurement closest to 4 weeks in the window from 2 to 6 weeks post-transplant is used for the 4 weeks baseline.
eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease.
Note: LET is given concomitantly with acyclovir. VGCV is given concomitantly with a placebo to acyclovir.

Table 40: Creatinine and eGFR in Participants Meeting the Predetermined Criteria Worsening Grade - Treatment Phase (All Participants as Treated)

Criterion[a]	LET Arm n/m	(%)	VGCV Arm n/m	(%)	Total n/m	(%)
Creatinine (mg/dL)						
Grade 1: 1.1 to 1.3 x ULN	20/285	(7.0)	14/293	(4.8)	34/578	(5.9)
Grade 2: > 1.3 to 1.8 x ULN	31/285	(10.9)	20/293	(6.8)	51/578	(8.8)
Grade 3: > 1.8 to < 3.5 x ULN	13/285	(4.6)	14/293	(4.8)	27/578	(4.7)
Grade 4: ≥ 3.5 x ULN	1/285	(0.4)	5/293	(1.7)	6/578	(1.0)
Estimated Glomerular Filtration Rate (mL/min/1.73m2)[b]						
Grade 2: 60 to 90 or 10 to 30% decrease from baseline	6/258	(2.3)	5/277	(1.8)	11/535	(2.1)
Grade 3: 30 to 60 or 30 to 50% decrease from baseline	30/258	(11.6)	36/277	(13.0)	66/535	(12.3)
Grade 4: <30 or ≥50% decrease from baseline	27/258	(10.5)	34/277	(12.3)	61/535	(11.4)

Cardiac events

In study P001, assessed as part of the initial MAA in HSCT, the incidence of Cardiac disorders SOC AEs was higher in participants receiving LET (12.6%) compared with participant receiving placebo (6.3%). Based on the totality of the preclinical and clinical data, it was concluded at that time that there was no evidence for a causal association between the administration of LET and Cardiac disorders SOC AEs.

AEs belonging to the SOC Cardiac Disorders were reported at a frequency comparable with the VGCV arm (AEs: 11.3% vs 15.8%; SAEs: 2.7% vs 3.0%) and also with the previous findings of study P001. Of 33 reported AEs in the LET group, the majority relates to tachyarrhythmias and symptoms thereof, which is similar to the findings in study P001. Apart from this, no patterns can be observed. Most cardiac AEs were mild to moderate in intensity and comparable for both groups. Drug-related cardiac AEs and SAEs were infrequent. None of the cardiac AEs led to discontinuation of study intervention. ECG parameters were comparable between the LET and VGCV groups.

Table 41: Participants with AEs within Cardiac disorders SOC (Incidence >0% in One of More Treatment Groups) Treatment Phase (All Participants as Treated)

	LET Arm		VGCV Arm		Total	
	n	(%)	n	(%)	n	(%)
Cardiac disorders	**33**	**(11.3)**	**47**	**(15.8)**	**80**	**(13.6)**
Cardiac aneurysm	1	(0.3)	0	(0.0)	1	(0.2)
Cardiac arrest	1	(0.3)	0	(0.0)	1	(0.2)
Cardiac failure acute	1	(0.3)	0	(0.0)	1	(0.2)
Cardiac failure congestive	0	(0.0)	2	(0.7)	2	(0.3)
Cardiac hypertrophy	1	(0.3)	0	(0.0)	1	(0.2)
Cardiogenic shock	0	(0.0)	1	(0.3)	1	(0.2)
Cardiomegaly	1	(0.3)	1	(0.3)	2	(0.3)
Coronary artery stenosis	0	(0.0)	2	(0.7)	2	(0.3)
Extrasystoles	1	(0.3)	0	(0.0)	1	(0.2)
Left atrial enlargement	0	(0.0)	1	(0.3)	1	(0.2)
Left ventricular hypertrophy	1	(0.3)	3	(1.0)	4	(0.7)
Mitral valve calcification	1	(0.3)	0	(0.0)	1	(0.2)
Mitral valve incompetence	0	(0.0)	1	(0.3)	1	(0.2)
Myocardial infarction	0	(0.0)	3	(1.0)	3	(0.5)
Myocardial ischaemia	1	(0.3)	1	(0.3)	2	(0.3)
Palpitations	5	(1.7)	6	(2.0)	11	(1.9)
Pericardial effusion	2	(0.7)	0	(0.0)	2	(0.3)
Pericardial rub	0	(0.0)	1	(0.3)	1	(0.2)
Sinus arrhythmia	0	(0.0)	1	(0.3)	1	(0.2)
Sinus bradycardia	0	(0.0)	1	(0.3)	1	(0.2)
Sinus tachycardia	1	(0.3)	1	(0.3)	2	(0.3)
Supraventricular tachycardia	1	(0.3)	2	(0.7)	3	(0.5)
Tachycardia	11	(3.8)	12	(4.0)	23	(3.9)
Ventricular extrasystoles	2	(0.7)	1	(0.3)	3	(0.5)

Other

Rates of re-hospitalizations were lower in the LET group compared with the VGCV group through Week 28 (34.6% vs 40.7%) and Week 52 (43.9% vs 50.8%) post-transplant.

The proportions of participants with select opportunistic infections were comparable between the LET group and the VGCV group through Week 28 (10.4% vs 12.1%) and Week 52 (16.3% vs 17.2%) post-transplant.

The incidence of AEs (reported in ≥2% of the LET group with a risk difference ≥1.4 compared with the VGCV group) by LET exposure (AUC) quartiles were reported. There was no apparent trend of an increase in the incidence of AEs over the range of exposures assessed using LET AUC quartiles.

LET treatment had no observed impact on sex hormone levels (LH, FSH, testosterone, and inhibin b) in male kidney transplant recipients.

2.5.1.2. Study P040 – post-allogenic HSCT

Patient exposure

A total of 144 participants received at least one dose of LET by any route in study P040. The currently authorised dose of oral LET 480 mg once daily (240 mg when administered with cyclosporin A (CsA)) was administered to 68 participants for >12 to 14 weeks and 54 participants for >14 weeks. The mean duration of exposure to LET (any route of exposure) was generally comparable with placebo (88.2 vs. 83.4 days).

All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET), meaning that the actual total duration of exposure to LET in the LET arm was 68 participants for >26 to 28 weeks and 54 participants for >28 weeks, mean duration of exposure to LET (any route of exposure) 188.2 days. As AEs were not collected prior to start of the treatment phase (100 days), the initial LET phase unfortunately does not contribute directly to the safety database.

Measurements of Study Intervention Compliance

All but 5 participants had ≥90% compliance rate which was comparable between the LET and placebo groups. The 5 participants had a compliance rate of ≥75% to <90%.

Adverse events

Overall adverse events

Collection of AEs continued through the treatment phase and through 14 days after completion of study intervention. After the treatment phase, only SAEs related to study intervention or resulting in death were collected through week 48 post-transplant.

The overall rate of AEs, drug-related AEs, SAEs and discontinuations due to AEs in each treatment group were generally comparable.

Common adverse events

Most common adverse events through week 28 post-transplant were reported at similar rates in both study arms and were consistent with the known safety profile in HSCT patients established in study P001, as well as signs and symptoms of the underlying clinical condition.

The most commonly reported AEs (incidence >10%) for LET were GVHD (29.9%), diarrhoea (11.8%) and nausea (11.1%).

Table 42: Participants With Adverse Events (Incidence > 5% in One or More Treatment Groups) Treatment Phase (All Participants as Treated)

	LET (200 days LET)		PBO (100 days LET)		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	144		74		218	
with one or more adverse events	128	(88.9)	69	(93.2)	197	(90.4)
with no adverse events	16	(11.1)	5	(6.8)	21	(9.6)
Blood and lymphatic system disorders	**21**	**(14.6)**	**10**	**(13.5)**	**31**	**(14.2)**
Anaemia	9	(6.3)	2	(2.7)	11	(5.0)
Neutropenia	4	(2.8)	4	(5.4)	8	(3.7)
Eye disorders	**8**	**(5.6)**	**1**	**(1.4)**	**9**	**(4.1)**
Gastrointestinal disorders	**46**	**(31.9)**	**32**	**(43.2)**	**78**	**(35.8)**
Diarrhoea	17	(11.8)	9	(12.2)	26	(11.9)
Nausea	16	(11.1)	13	(17.6)	29	(13.3)
General disorders and administration site conditions	**30**	**(20.8)**	**24**	**(32.4)**	**54**	**(24.8)**
Fatigue	5	(3.5)	4	(5.4)	9	(4.1)
Oedema peripheral	11	(7.6)	5	(6.8)	16	(7.3)
Pyrexia	13	(9.0)	9	(12.2)	22	(10.1)
Immune system disorders	**45**	**(31.3)**	**24**	**(32.4)**	**69**	**(31.7)**
Graft versus host disease	43	(29.9)	23	(31.1)	66	(30.3)
Infections and infestations	**49**	**(34.0)**	**43**	**(58.1)**	**92**	**(42.2)**
Cytomegalovirus infection	0	(0.0)	5	(6.8)	5	(2.3)
Cytomegalovirus infection reactivation	1	(0.7)	6	(8.1)	7	(3.2)
Injury, poisoning and procedural complications	**8**	**(5.6)**	**8**	**(10.8)**	**16**	**(7.3)**
Investigations	**25**	**(17.4)**	**11**	**(14.9)**	**36**	**(16.5)**
Neutrophil count decreased	3	(2.1)	4	(5.4)	7	(3.2)
Metabolism and nutrition disorders	**17**	**(11.8)**	**19**	**(25.7)**	**36**	**(16.5)**
Decreased appetite	6	(4.2)	9	(12.2)	15	(6.9)
Hypokalaemia	5	(3.5)	4	(5.4)	9	(4.1)
Musculoskeletal and connective tissue disorders	**25**	**(17.4)**	**10**	**(13.5)**	**35**	**(16.1)**
Arthralgia	6	(4.2)	5	(6.8)	11	(5.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**21**	**(14.6)**	**7**	**(9.5)**	**28**	**(12.8)**
Acute myeloid leukaemia recurrent	9	(6.3)	1	(1.4)	10	(4.6)
Nervous system disorders	**17**	**(11.8)**	**13**	**(17.6)**	**30**	**(13.8)**
Dizziness	1	(0.7)	4	(5.4)	5	(2.3)
Headache	9	(6.3)	4	(5.4)	13	(6.0)
Psychiatric disorders	**12**	**(8.3)**	**4**	**(5.4)**	**16**	**(7.3)**
Respiratory, thoracic and mediastinal disorders	**20**	**(13.9)**	**15**	**(20.3)**	**35**	**(16.1)**
Cough	7	(4.9)	7	(9.5)	14	(6.4)

Oropharyngeal pain	9	(6.3)	4	(5.4)	13	(6.0)
Skin and subcutaneous tissue disorders	**33**	**(22.9)**	**14**	**(18.9)**	**47**	**(21.6)**
Pruritus	11	(7.6)	2	(2.7)	13	(6.0)
Rash	8	(5.6)	7	(9.5)	15	(6.9)
Vascular disorders	**6**	**(4.2)**	**5**	**(6.8)**	**11**	**(5.0)**

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
LET = Letermovir; PBO = Placebo
Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).
MedDRA version 25.0 was used in the reporting of this study.

Drug related adverse events

The proportion of participants with drug-related AEs was numerically lower in the LET group (2.8%) compared with the placebo group (4.1%).

Serious adverse events, Adverse events of special interest and Deaths

Serious adverse events

Overall, the proportion of participants with SAEs reported during the Treatment Phase were generally comparable between treatment groups (30.6% in the LET group and 33.8% in the placebo group). The most frequently reported SAEs in either treatment group (LET vs placebo) were GVHD (2.8% vs 8.1%), acute myeloid leukaemia recurrent (4.2% vs 0.0%), and pneumonia (2.1% vs 2.7%). No SAEs were considered to be drug-related by the investigator.

Deaths

A total of 14 deaths were reported during the Treatment Phase, 11 (7.6%) in the LET group and 3 (4.1%) in the placebo group. Eight (7 in the LET group and 1 in the placebo group) of the 14 deaths were due to recurrence of the participant's underlying medical condition that necessitated the HSCT (relapse mortality). Non-relapse mortality was comparable between the 2 groups. None of the deaths were considered to be drug-related by the investigator.

Events of Special Interest

Cardiotoxicity

In P040, the frequency of AEs in the Cardiac disorder SOC was comparable between the LET (4.2%) and the placebo groups (4.1%). Most were mild to moderate in intensity. None of the AEs were reported as being drug-related, led to discontinuation of study intervention, or resulted in death.

Hepatotoxicity

The frequency of AEs reported for the Hepatobiliary disorders SOC was lower in the LET group (2.1%) compared with placebo (4.1%). All were mild to moderated in intensity and none of AEs were reported as being related to study intervention or led to discontinuation of study intervention. The patterns of change in liver function test values were comparable between the 2 treatment groups and there was no report of laboratory values that met the protocol-defined ECI criteria for a potential DILI.

Laboratory findings

Myelotoxicity

In this study, the reported incidence of AE terms in the Blood and lymphatic system disorders SOC (LET vs placebo: 14.6% vs 13.5%) were comparable in the 2 treatment groups and lower than the rates reported in study P001 (approximately 26%). Most of these AEs were mild to moderate in intensity and none were reported as being related to study intervention. Reporting rates for individual AEs are comparable with those seen in study P001.

Table 43: Participants With Adverse Events in the Blood and lymphatic system disorders SOC (Incidence > 0% in One or More Treatment Groups) Treatment Phase (All Participants as Treated)

	LET (200 days LET)		PBO (100 days LET)		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	144		74		218	
with one or more adverse events	128	(88.9)	69	(93.2)	197	(90.4)
with no adverse events	16	(11.1)	5	(6.8)	21	(9.6)
Blood and lymphatic system disorders	**21**	**(14.6)**	**10**	**(13.5)**	**31**	**(14.2)**
Anaemia	9	(6.3)	2	(2.7)	11	(5.0)
Anaemia macrocytic	1	(0.7)	0	(0.0)	1	(0.5)
Eosinophilia	1	(0.7)	0	(0.0)	1	(0.5)
Febrile neutropenia	2	(1.4)	0	(0.0)	2	(0.9)
Leukocytosis	1	(0.7)	0	(0.0)	1	(0.5)
Leukopenia	2	(1.4)	1	(1.4)	3	(1.4)
Lymph node pain	1	(0.7)	0	(0.0)	1	(0.5)
Lymphadenopathy	0	(0.0)	1	(1.4)	1	(0.5)
Neutropenia	4	(2.8)	4	(5.4)	8	(3.7)
Pancytopenia	1	(0.7)	0	(0.0)	1	(0.5)
Pure white cell aplasia	1	(0.7)	0	(0.0)	1	(0.5)
Thrombocytopenia	2	(1.4)	0	(0.0)	2	(0.9)
Thrombotic microangiopathy	0	(0.0)	2	(2.7)	2	(0.9)
Warm autoimmune haemolytic anaemia	0	(0.0)	1	(1.4)	1	(0.5)

Every participant is counted a single time for each applicable row and column.
LET = Letermovir; PBO = Placebo
Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).
MedDRA version 25.0 was used in the reporting of this study.

Creatinine

Overall, the central laboratory findings that met predetermined criteria for worsening grade were comparable between treatment groups except for serum creatinine levels, where a numerical imbalance favouring the placebo group was observed for all grades. Most of the worsening grades for creatinine were Grade 1 and 2 abnormalities in both treatment groups. Five participants had Grade 3 and Grade 4 abnormalities; all were in the LET group. Potential causes of increased serum creatinine in these participants include medical history condition that could lead to renal impairment as well as

concomitant use of nephrotoxic drugs. Changes from baseline mean creatinine values over time were, however, similar between treatment groups. It is noted that in the registration study P001, changes to serum creatinine of all grades were reported in both arms, at rates comparable between LET and PBO but generally higher than seen in study P040 (reproduced below).

Table 44: Participants With Central Laboratory Findings That Met Predetermined Criteria Worsening Grade for Creatinine in the Treatment Phase (All Participants as Treated) Study P040

Criterion[a]	LET (200 days LET)		PBO (100 days LET)		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Creatinine (mg/dL)						
Grade 1: 1.1 to 1.3 x ULN	16/143	(11.2)	4/73	(5.5)	20/216	(9.3)
Grade 2: > 1.3 to 1.8 x ULN	20/143	(14.0)	6/73	(8.2)	26/216	(12.0)
Grade 3: > 1.8 to < 3.5 x ULN	4/143	(2.8)	0/73	(0.0)	4/216	(1.9)
Grade 4: ≥ 3.5 x ULN	1/143	(0.7)	0/73	(0.0)	1/216	(0.5)

[a] For graded criteria: participants are counted once per test in the highest grade reported.
For baseline criteria: participants are counted in the '>X-fold Baseline' if the highest test value during treatment fell in this category.
For baseline criteria: participants are counted in the '<X-fold Baseline' if the lowest test value during treatment fell in this category.
For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. Only participants with a worsened grade from baseline were included. A participant was listed with a Grade X event if his/her highest grade during treatment was X.
n = Number of participants with postbaseline test results that met the predetermined criterion.
m = Number of participants with at least one postbaseline test result. For the criteria that involve a comparison to baseline, a baseline value is also required.
ULN = Upper limit of normal range.
Criteria based on Division of AIDS (DAIDS) 2017 Table for Grading the Severity of Adult and Pediatric Adverse Events.
LET = Letermovir; PBO = Placebo
Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).

Table 45: Participants With Central Laboratory Findings That Met Predetermined Criteria Worsening Grade for Creatinine in the Treatment Phase (All Participants as Treated) Study P001

Criterion	Letermovir		Placebo		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Creatinine (mg/dL)						
Grade 1: 1.1 - 1.3 x ULN	4/371	(1.1)	0/191	(0.0)	4/562	(0.7)
Grade 2: >1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above BL	43/371	(11.6)	17/191	(8.9)	60/562	(10.7)
Grade 3: >1.8 - <3.5 x ULN or Increase of 1.5 - <2.0 x BL	102/371	(27.5)	55/191	(28.8)	157/562	(27.9)
Grade 4: ≥3.5 x ULN or Increase of ≥2.0 x Baseline	75/371	(20.2)	31/191	(16.2)	106/562	(18.9)

Additional safety findings

Discontinuation of study intervention due to adverse events

There was a numerical imbalance in the rate of study intervention discontinuation due to AE between LET and PBO arms. Six of the seven AEs leading to discontinuation of the study intervention in the LET group were SAEs. All occurred as isolated cases and no pattern is evident from the data. In the placebo group, 1 participant discontinued study intervention due to GVHD. None of the discontinuations were considered to be drug-related by the investigator.

Table 46: Participants With Adverse Events Leading to Discontinuation From Drug (Incidence > 0% in One or More Treatment Groups) Treatment Phase (All Participants as Treated)

	LET (200 days LET)		PBO (100 days LET)		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	144		74		218	
with one or more adverse events leading to discontinuation from drug	7	(4.9)	1	(1.4)	8	(3.7)
with no adverse events leading to discontinuation from drug	137	(95.1)	73	(98.6)	210	(96.3)
Gastrointestinal disorders	**1**	**(0.7)**	**0**	**(0.0)**	**1**	**(0.5)**
Dyspepsia	1	(0.7)	0	(0.0)	1	(0.5)
General disorders and administration site conditions	**1**	**(0.7)**	**0**	**(0.0)**	**1**	**(0.5)**
Pyrexia	1	(0.7)	0	(0.0)	1	(0.5)
Immune system disorders	**1**	**(0.7)**	**1**	**(1.4)**	**2**	**(0.9)**
Graft versus host disease	1	(0.7)	1	(1.4)	2	(0.9)
Infections and infestations	**2**	**(1.4)**	**0**	**(0.0)**	**2**	**(0.9)**
COVID-19	1	(0.7)	0	(0.0)	1	(0.5)
Lymph node tuberculosis	1	(0.7)	0	(0.0)	1	(0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**(1.4)**	**0**	**(0.0)**	**2**	**(0.9)**
Acute lymphocytic leukaemia recurrent	1	(0.7)	0	(0.0)	1	(0.5)
Post transplant lymphoproliferative disorder	1	(0.7)	0	(0.0)	1	(0.5)

Every participant is counted a single time for each applicable row and column.
LET = Letermovir; PBO = Placebo
Note: All participants received 100 days of LET post-transplant prior to entering the study. Thereafter, they either received an additional 100 days of LET (200 days LET) or 100 days of PBO (100 days LET).
MedDRA version 25.0 was used in the reporting of this study.

Graft versus host disease

The proportion of participants experiencing GVHD was comparable in the LET group and the placebo group through Week 28 post-transplant (29.2% (21.9, 37,3) versus 32.4% (22.0, 44.3)) and through Week 48 post-transplant (38.9% (30.9, 47.4) versus 41.9% (30.5, 53.9)) In both groups, skin was the most frequently reported site for new onset of both acute and chronic GVHD, followed by gastrointestinal tract, at both timepoints. These rates are numerically lower than those seen in both LET and placebo arms through Week 14 and Week 24 in study P001.

2.5.1.3. Safety in sub-populations

In both studies included in the current application, AE profiles by age, sex, race, and ethnicity were evaluated. The safety profile of LET in P002 was generally comparable across subgroups analysed for age, sex, race, and ethnicity. The safety profile of LET in P040 was generally comparable across subgroups analysed for age and sex. Interpretation of the results for race and ethnicity subgroup analyses were limited, as the majority of participants were White and not Hispanic or Latino.

2.5.1.4. Post marketing experience

As of 01-NOV-2022, LET has been registered and approved in 65 countries since it was first approved in Canada (01-NOV-2017). LET is formulated as 240 mg and 480 mg tablets and as a concentrate for solution for infusion (240 mg/12 mL and 480 mg/24 mL). There are no records of any registration being revoked or withdrawn for safety reasons. The benefit-risk information on LET has been summarized in the PSUR submitted on a 3-year cycle to the EMA (and on a 6-month cycle to some regions). Patient exposure estimates were calculated from the MAH's internal distribution data from the WFRS and the Financial Sharing Area database. Total cumulative patient exposure from first licensure (01-NOV-2017) through 01-NOV-2022 was approximately 22,073 patient-years of treatment (11,080 for 240 mg tablets, 10,124 for 480 mg tablets, 603 for 240 mg vial, and 267 for 480 mg vial).

Cumulative post marketing data through 01-NOV-2022 (date of the most recent PSUR) are summarized below. As of 01-NOV-2022, there were 2,818 AE reports containing 7,278 events (3,903 non-serious, 3,375 serious) from spontaneous and non-interventional post marketing study reports in the MAH's global safety database. The distribution of the AEs by SOC is provided in the table below. The most frequently reported SOCs were Injury, poisoning and procedural complications (1,156 reports), General disorders and administration site conditions (1,100 reports), and Immune system disorders (695 reports). The most common PTs in Injury, poisoning and procedural complications SOC were Off label use (332 reports), Product dose omission issue (323 reports), and Product use issue (217 reports). The most common PTs in General disorders and administration site conditions SOC were No adverse event (306 reports), Adverse event (236 reports), and Death (166 reports). The majority of death cases were related to progression of underlying medical conditions. The most common PTs in Immune system disorders SOC were Acute graft versus host disease in skin (370 reports), Acute graft versus host disease in intestine (191 reports), and Chronic graft versus host disease (140 reports). A cumulative analysis of post marketing data as of 01-NOV-2022 did not identify new safety issues for LET.

Table 47: System Organ Classes for Post marketing Adverse Events Reported for LET 01-NOV-2017 to 01-NOV-2022

SOC	# of Cases	% Cases[a]	# of Serious Cases	% Serious Cases*
Injury, poisoning and procedural complications	1156	41.02%	82	4.86%
General disorders and administration site conditions	1100	39.03%	425	25.19%
Immune system disorders	695	24.66%	686	40.66%
Infections and infestations	563	19.98%	503	29.82%
Investigations	407	14.44%	29	1.72%
Gastrointestinal disorders	367	13.02%	62	3.68%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	257	9.12%	257	15.23%
Blood and lymphatic system disorders	209	7.42%	192	11.38%
Renal and urinary disorders	149	5.29%	117	6.94%
Respiratory, thoracic and mediastinal disorders	143	5.07%	94	5.57%
Skin and subcutaneous tissue disorders	109	3.87%	5	0.30%
Nervous system disorders	106	3.76%	59	3.50%
Metabolism and nutrition disorders	100	3.55%	39	2.31%
Surgical and medical procedures	80	2.84%	60	3.56%
Hepatobiliary disorders	68	2.41%	50	2.96%
Cardiac disorders	59	2.09%	51	3.02%
Vascular disorders	44	1.56%	25	1.48%
Musculoskeletal and connective tissue disorders	43	1.53%	5	0.30%
Psychiatric disorders	43	1.53%	14	0.83%
Product issues	40	1.42%	0	0.00%
Reproductive system and breast disorders	16	0.57%	1	0.06%
Eye disorders	13	0.46%	3	0.18%
Social circumstances	7	0.25%	1	0.06%
Ear and labyrinth disorders	4	0.14%	2	0.12%
Endocrine disorders	3	0.11%	3	0.18%
Congenital, familial and genetic disorders	0	0	0	0
Pregnancy, puerperium and perinatal conditions	0	0	0	0
Grand total	**2818**	**100.0%**	**1687**	**100.0%**

LET=letermovir; SOC=System Organ Class

[a] As a case may report more than one AE from the same SOC, the grand total percentage may be greater than 100%.

2.5.2. Discussion on clinical safety

The safety of Prevymis in HSCT patients was previously established based on data from a pivotal Phase 3 study (P001) of up to 14 weeks' LET in 373 HSCT recipients, which was submitted to support the initial marketing authorisation for the indication of prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT) (EMEA/H/C/004536).

In support of the current application, the MAH presented safety data from two completed clinical studies and additionally a summary of available post-marketing data, which build on the existing safety database. The challenging underlying conditions of these patients as well as the transplantation need to be taken into account, and thus the assessment of AEs from the intervention against such a background is a challenge.

Study P002 was a randomized, active-controlled, multi-site, double-blind study to evaluate the efficacy and safety of letermovir (LET) compared with valganciclovir (VGCV) administered for 200 days post-transplant for the prevention of cytomegalovirus (CMV) disease in adult seropositive donor/seronegative recipient (D+/R) kidney transplant recipients. The currently authorised dose of oral LET 480 mg once daily (240 mg when administered with cyclosporin A (CsA)) was administered to 152 participants for >24 to <28 weeks and 98 participants for >28 weeks.

The overall rate of AEs through 28 weeks post-transplant was generally comparable between LET and VGCV, with the exception of drug-related AEs and discontinuation of study intervention due to AEs, which were lower in the LET group compared with the VGCV group. These differences were primarily due to fewer participants in the LET group with leukopenia and neutropenia, which are known adverse effects of VGCV. A total of 5 deaths (LET 3, VGCV 2) due to an AE were reported through Week 52 post-transplant. One additional death due to COVID-19 in the VGCV group (not reported as an AE) was reported through Week 52 post-transplant. In addition, 2 deaths were reported after the last study visit in the LET group. None of the deaths appear to be related to study intervention. There were comparable rates between the LET group and the VGCV group of renal graft rejection through Week 28 (5.9% (3.5, 9.3) versus 6.1% (3.6, 9.4)) and through Week 52 (8.0% (5.1, 11.7) versus 6.7% (4.2, 10.2)).

LET exposure and bioavailability following oral administration in kidney transplant patients appears to be higher than in HSCT patients, but despite this the adverse event profile for LET was generally similar to that seen previously in study P001, with the exception of the rate of leukopenia in study P002, which can reasonably be attributed to the nearly 100% rate of concomitant use of mycophenolate in study P002. Myelosuppression is common (≥1/100) in kidney transplant recipients administered mycophenolate and the rates of leukopenia and neutropenia in the LET arm in study P002 are not over and above what would be expected with mycophenolate alone. Therefore, neither leukopenia nor neutropenia will be added to section 4.8 of the SmPC.

The proportion of participants with leukopenia or neutropenia through Week 28 post-transplant was lower in the LET group compared with the VGCV group. This was a pre-specified but not type-1 error-controlled safety analysis, thus the finding will not be included in the SmPC section 5.1. However, the safety data clearly demonstrate a difference in safety profile for letermovir versus valganciclovir in terms of the rates of leukopenia reported as adverse events in each treatment arm, which represents a clinically relevant advantage of letermovir over alternative. Nevertheless, and in accordance with the SmPC guideline, the CHMP did not support the inclusion of comparative rates of leukopenia in each treatment arm in the text summary for section 4.8 of the SmPC.

In study P001, assessed as part of the initial MAA in HSCT, the incidence of Cardiac disorders SOC AEs was higher in participants receiving LET (12.6%) compared with participant receiving placebo (6.3%). Based on the totality of the preclinical and clinical data, it was concluded at that time that there was no evidence for a causal association between the administration of LET and Cardiac disorders SOC AEs. In study P002, AEs belonging to the SOC Cardiac Disorders were reported at a frequency comparable with the VGCV arm (AEs: 11.3% vs 15.8%; SAEs: 2.7% vs 3.0%) and also with the previous findings of study P001. Of 33 reported AEs in the LET group, the majority relates to tachyarrhythmias and symptoms thereof, which is similar to the findings in study P001. The data from study P002 relating to cardiac disorders is thus considered reassuring against the background conclusions from earlier assessment that there was no evidence for a causal association.

Study P040 was a randomized, placebo-controlled, parallel assignment, multicentre, double-blind, efficacy and safety study evaluating extending LET prophylaxis to 200 days post-transplant in CMV-seropositive recipients (R+) of an allogeneic HSCT who had received LET prophylaxis through Week 14 (~100 days) post-transplant and who were at high risk for CMV infection and/or disease after completion of LET prophylaxis through 100 days post-transplant. The currently authorised dose of oral LET 480 mg once daily (240 mg when administered with cyclosporin A (CsA)) was administered to 68 participants for >12 to 14 weeks and 54 participants for >14 weeks.

Most common AEs through week 28 post-transplant were reported at similar rates in both study arms and were consistent with the known safety profile in HSCT patients up to 100 days as established in study P001, as well as signs and symptoms of the underlying clinical condition. A total of 14 deaths were reported during the Treatment Phase, 11 (7.6%) in the LET group and 3 (4.1%) in the placebo group. Eight (7 in the LET group and 1 in the placebo group) of the 14 deaths were due to recurrence of the participant's underlying medical condition that necessitated the HSCT (relapse mortality). Non-relapse mortality was comparable between the 2 groups. None of the deaths appear to be directly related to study intervention. The rate of GVHD was comparable in the LET group and the placebo group both through Week 28 post-transplant (29.2% (21.9, 37,3) versus 32.4% (22.0, 44.3)) and through Week 48 post-transplant (38.9% (30.9, 47.4) versus 41.9% (30.5, 53.9)). These rates are numerically lower than those seen in both LET and placebo arms through Week 14 and Week 24 in study P001.

A numerical imbalance in the percentage of patients experiencing AEs in the SOC neoplasms was observed between LET 200 days arm (14.6%) versus LET 100 days (placebo) arm (9.5%). This imbalance was partially driven by a higher number of patients who had recurrent acute myeloid leukaemia [9 patients (6.3%) in the LET 200 days arm vs 1 patient (1.4%) in the LET 100 days (placebo) arm]. There appears to be no relationship with duration of treatment with LET. Inspection of Kaplan-Meier plots of time to onset of these events for both arms in both HSCT studies (P040 and P001) did not reveal any recurrent pattern, as no such difference was seen in the P001. The recurrence of AML is not unusual in this population and the observed difference in the P040 study may reflect a random imbalance in a relatively small study.

Adverse events in the Eye disorders SOC were reported more frequently in the LET arm than placebo arm (5.6 vs 1.4%), but much less frequently than seen in either arm in study P001 (16.6 and 16.7%, respectively). The difference is at least partially due to a number of cases of dry eye (4), of which 3 were reported as mild and one as moderate. Review of the cases reveals no pattern and provides no compelling grounds to suspect a causal relationship to LET for any reported PT in the Eye disorders SOC.

In practice, very few participants in either study received IV LET, and those that did continued only for a few days before switching to oral LET, not enabling a meaningful separate analysis of the safety profile for IV administration, including the lower IV dose of 240mg that was added in a protocol amendment to study P002.

2.5.3. Conclusions on clinical safety

The safety profile of letermovir both post-kidney transplant and beyond 100 days post-HSCT is favourable.

2.5.4. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Risk management plan

The MAH submitted an updated RMP version (v4.1, data lock 01-May-2022) with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable.

Safety concerns

No new safety concerns were identified based on the completion of studies P040 in HSCT and P002 in kidney transplant recipients. Therefore, the MAH's proposal to maintain the safety specification unchanged is endorsed.

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

There are no additional pharmacovigilance activities warranted.

Risk minimisation measures

No additional risk minimisation measures are required.

4. Changes to the Product Information

As a result of this group of variations, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

4.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

5. Benefit-Risk Balance

5.1. Introduction

Prevymis (letermovir) is an inhibitor of the viral DNA terminase complex, which plays a key role in cleavage and packaging of viral progeny DNA. The positive B/R of 100 days of letermovir prophylaxis post HSCT has previously been accepted by CHMP.

The data provided in this application are intended to support an indication for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor [D+/R-]. The MAH is also seeking a modification of the current approved posology to extend prophylaxis beyond 100 days post-HSCT. This may be of benefit in some patients at high risk for late CMV reactivation. The safety and efficacy of letermovir use for more than 200 days has not been studied in clinical trials.

Prevymis was designated as an orphan medicinal product in the following indication: Prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk. In the context of the present extension of indication, the MAH wishes to maintain the orphan status of the product. The Committee for Orphan Medicinal Products on the 12 October 2023 was of the view that the scope of this procedure does not raise justified and serious doubts in respect to the fulfilment of the orphan designation criteria.

5.2. Therapeutic Context

5.2.1. Disease or condition

Cytomegalovirus is ubiquitous and generally acquired early in life, with the majority of the adult population being CMV-seropositive in most countries worldwide. Kidney transplant recipients and allogeneic HSCT recipients are immune-compromised, which increases the risk for CMV infection.

In kidney transplant recipients the CMV disease incidence varies by serostatus with the highest incidence among CMV seronegative (R-) kidney recipients with a transplanted kidney from a CMV positive donor.

In HSCT recipients the risk of CMV infection is mostly due to reactivation of latent CMV infection. Hematopoietic stem cell transplant recipients with prior CMV infection (R+) are at highest risk for

developing CMV reactivation and disease, especially during the first 100 days post-transplant (Özdemir 2007).

The risk for CMV infection is reduced after the first 100 days post-transplant as the immune system reconstitutes. However, there are certain HSCT populations who remain at high risk for CMV infection and/or disease beyond 100 days post-transplant due to delayed immune reconstitution, ongoing immunosuppression as a result of treatment for GVHD, or onset of new GVHD when immunosuppression is tapered.

5.2.2. Available therapies and unmet medical need

The current standard of care in kidney transplant recipients is CMV prophylaxis with valganciclovir (VGCV), an orally bioavailable prodrug of ganciclovir. The cumulative rate of CMV disease with no prophylaxis in D+/R- kidney transplant recipients may be inferred to above 50% over 12 months, in the absence of prophylaxis.

VGCV has been shown to be efficacious in reducing the incidence of CMV disease both post solid organ as well as post HSCT. However, VGCV is poorly tolerated, primarily due to myelosuppression and persistent leukopenia and neutropenia. This is a particular problem post HSCT, to the extent that pre-emptive therapy rather than prophylaxis with VGCV is preferred in this setting.

5.2.3. Main clinical studies

In support of this application, the MAH presented data from the following clinical studies:

Study P002MK8228

This was a phase III, randomized, active-controlled, multi-site, double-blind study to evaluate the efficacy and safety of letermovir (LET) compared with valganciclovir (VGCV) administered for 200 days post-transplant for the prevention of cytomegalovirus (CMV) disease in adult seropositive donor/seronegative recipient (D+/R) kidney transplant recipients.

The primary efficacy endpoint was the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant in the FAS population i.e. all randomized participants who received at least one dose of study treatment, are D+/R-, and had no detectable CMV viral DNA (measured by central laboratory) on Day 1. CMV disease included both CMV end-organ disease and CMV syndrome which was defined as CMV viremia together with two or more criteria including specific clinical symptoms or laboratory measures.

This was a non-inferiority study with a non-inferiority margin of 10%.

A dose of 480 mg LET was administered once daily orally and if co-administered with cyclosporine A (CsA), the dosage of LET was decreased to 240 mg once daily. Aciclovir was co-administered with LET at 400 mg orally every 12 hours (total dose 800 mg daily) for prophylaxis of herpes simplex virus (HSV) and varicella zoster virus (VZV). VGCV was administered by two tablets 450 mg once daily. Overall, 601 participants were randomised and 589 received at least 1 dose of study intervention with 292 participants in the LET group and 297 participants in the VGCV group.

Study P040MK8228

This was a phase III, randomized, placebo-controlled, parallel assignment, multicentre, double-blind, efficacy and safety study evaluating extending LET prophylaxis to 200 days post-transplant in CMV-

seropositive recipients (R+) of an allogeneic HSCT who had received LET prophylaxis through Week 14 (~100 days) post-transplant and who were at high risk for CMV infection and/or disease after completion of LET prophylaxis through 100 days posttransplant.

The primary efficacy endpoint was the proportion of participants with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant. Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV PET based on documented CMV DNAemia.

LET was administered orally at a dose of 480 mg once daily and adjusted to 240 mg once daily for participants on CsA, through Week 28 (LET through 200 days) posttransplant. Placebo was administered once daily through Week 28 (LET through 100 days) post-transplant. A total of 220 participants were randomized in a 2:1 ratio, with 144 participants treated in the LET group and 74 participants treated in the placebo group.

5.3. Favourable effects

Study P002MK8228

Letermovir was demonstrated to be non-inferior to valganciclovir, with 10.4% vs. 11.8% of patients with incident cases of CMV disease observed in the LET and VGCV groups respectively. The estimated treatment difference was -1.4 (95% CI: -6.5, 3.8) using the observed failure approach (i.e., participants who discontinue prematurely from the study for any reason are not considered failures).

The number of participants with CMV disease at 28 weeks post-transplant was 0 vs. 5 participants in the LET and VGCV arms respectively using the observed failure approach. The time to onset of CMV disease was comparable between the LET and VGCV groups through Week 52 post-transplant.

The proportion of participants with quantifiable CMV DNAemia was lower in the LET group compared to the VGCV group through week 28 (2.1% vs 8.8%) and slightly lower also through week 52 post-transplant (31.8% vs 37.7%) supporting the efficacy of LET as prophylaxis.

Efficacy was consistently demonstrated across subgroups including sex, age, race, region, and induction therapy through Week 52 post-transplant.

Study P040MK8228

The difference in proportion of participants experiencing clinically significant CMV infection from week 14 through week 28 post-transplant between the LET and placebo group was, -16.1 (95% CI: -25.8, -6.5; one-sided p-value =0.0005) using the observed failure approach.

The proportion of participants with CMV end-organ disease from week 14 through week 28 post-transplant was 0.7% (1/144) in the LET group and 2.7% (2/74) in the placebo group.

The treatment difference in the incidence of clinically significant CMV infection by treatment group through Week 28 post-transplant across subgroups including age, sex, donor type and immunosuppressive regimen were overall consistent with the outcome of the primary endpoint.

5.4. Uncertainties and limitations about favourable effects

Study P002MK8228

The sensitivity analysis using the NC=F approach supported the primary analysis, however, it is noted that the proportion of discontinuations or missing data is relatively high in both treatment arms (19%

and 18% in LET and VGCV respectively) this adds some uncertainty to the relative effect between LET and VGCV.

There is a numerical imbalance between treatment groups in study P002 in the number of patients with end-organ disease, 6 versus 1 patient in the LET and VGCV groups, respectively. Five of the cases in the LET group are CMV end-organ GI disease, of which 4 proven and 1 probable CMV end-organ GI disease. All participants from the LET group experiencing CMV end-organ disease completed more or less the intended duration of treatment (200 days). In almost all cases of CMV end-organ GI disease the onset of symptoms started approximately 1-2 months after completing study intervention (one participant had symptoms approx. 4 months after completing LET). The primary reason for transplant, gender and age varied and no obvious pattern can be discerned. All participants recovered with treatment with either oral valganciclovir and/or iv ganciclovir.

The MAH claims that the difference in GI EOD between the treatment arms in P002 is predominantly due to lack of confirmatory endoscopy/tissue-invasive biopsy (required for adjudication confirmed GI EOD) in the majority of investigator reported GI EOD. No risk factors could be identified. Moreover, the analysis of the primary endpoint in investigator-reported CMV disease through Week 52 post-transplant also adds support to the efficacy of letermovir. This is likely a random finding. The totality of data and the known natural history of CMV post kidney transplantation is compatible with letermovir being an effective and useful treatment alternative, that provides acceptable protection against severe outcomes.

The primary endpoint CMV disease included CMV end-organ disease and "probable CMV syndrome". Leukopenia or neutropenia (criteria 3) or thrombocytopenia (criteria 5) are among the listed criteria which may be counted to fulfil the definition of CMV syndrome. Leukopenia, neutropenia and thrombocytopenia are very common (≥1/10) or common (≥1/100 to <1/10) adverse drug reactions associated with VGCV. Thus, it was questioned whether the number of cases of CMV syndrome in the VGCV arm in study P002 was inflated by the occurrence of cytopenia secondary to VGCV, which would impact the primary efficacy analysis in favour of LET. The prophylaxis treatment period was 28 weeks and the primary efficacy endpoint was assessed at 52 weeks, after a period of off-treatment follow-up. The half-life of VGCV is short (approximately 4 hours) and drug-induced cytopenia is expected to resolve within around a week of stopping. The majority of the CMV syndrome events (24/24 LET and 29/34 VGCV) occurred after cessation of prophylaxis. Most cases of CMV syndrome in the VGCV arm that were confirmed on the basis of criteria 3 or 5 being fulfilled were most likely due to actual CMV syndrome and not an adverse drug reaction associated with VGCV.

Viral resistance testing was performed on samples obtained from participants prior to initiation of CMV treatment or who had suspected or confirmed CMV disease. There were no LET resistance-associated substitutions at a frequency of ≥ 5% in the LET-treated participants with CMV disease or early discontinuation with viremia (n=52). The potential contribution of co-administration of aciclovir with LET in terms of (cross-) resistance to VGCV is not considered likely. The dose of aciclovir used is below the EC50 necessary to treat CMV and would not be expected to exert any selective pressure on the virus to induce potential escape mutants. Moreover, LET was effective in suppressing CMV replication during the prophylaxis period, making the possibility of resistance selection to aciclovir, and possible cross-resistance with VGCV, highly unlikely. Thus, treatment with LET together with aciclovir is not likely to compromise the patient's possibilities for receiving adequate treatment in the event of prophylaxis failure.

Study P040MK8228

In the supportive analysis of the primary efficacy endpoint using NC=F approach 14.6% vs. 24.3% CMV infections at week 28 was observed in the LET and placebo groups, respectively (nominal p-value=0.0505). A total of 16 participants were categorised as "Discontinued from study before Week 28" post-transplant in the LET arm and one in the placebo group. There were no overall trends in the reasons for study discontinuations. With the available data it is not possible to determine if the discontinuations are an effect of letermovir treatment.

5.5. Unfavourable effects

Study P002MK8228

Letermovir when administered to 292 participants at the dose authorised for use post-HSCT and proposed for clinical use post-kidney transplant (480 mg once daily (240 mg when co-administered with cyclosporin A (CsA)) for up to 28 weeks post-kidney transplant (median duration 175.6 days) was associated with a favourable safety profile that was consistent with that characterised from study P001 in HSCT patients at the time of initial marketing authorisation and with the underlying clinical condition. Despite the fact that LET exposure and bioavailability following oral administration in kidney transplant patients appears to be higher than in HSCT patients.

Overall, 92.8% of subjects receiving LET experienced an AE, while 36.3% experienced an SAE, through Week 28 post-transplant. The most commonly reported AEs (incidence >10%) for LET were diarrhoea (31.5%), tremor (18.2%), urinary tract infection (14.0%), peripheral oedema (13.4%), hypomagnesemia (12.7%), leukopenia (11.3%), hypertension (11.3%), hypophosphatemia (10.3%) and blood creatinine increased (10.3%). The most frequently reported SAEs (incidence >2%) in the LET group were pyrexia, urinary tract infection, blood creatinine increased, acute kidney injury, and lymphocele.

The overall rate of AEs in each treatment group through 28 weeks post-transplant were generally comparable between LET and VGCV. Fewer participants in the LET group (4.1%) discontinued study intervention due to an AE compared with the VGCV group (13.5%). Leukopenia (LET [1.0%] vs. VGCV [5.4%]) and neutropenia (LET [1.4%] vs. VGCV [1.7%]) were the most frequently reported AE leading to study intervention discontinuation in either group.

A total of 5 deaths (LET 3, VGCV 2) due to an AE were reported through Week 52 post-transplant. One additional death in the VGCV group was reported through Week 52 post-transplant and 2 deaths were reported after the last study visit in the LET group. None of the deaths appear to be related to study intervention.

There were comparable rates between the LET group and the VGCV group of renal graft rejection through Week 28 (5.9% (3.5, 9.3) versus 6.1% (3.6, 9.4)) and through Week 52 (8.0% (5.1, 11.7) versus 6.7% (4.2, 10.2)).

Study P040MK8228

Letermovir when administered to 144 participants at the dose already authorised for use post-HSCT (480 mg once daily (240 mg when co-administered with cyclosporin A (CsA)) beyond the authorised duration of 14 weeks and up to 28 weeks post-HSCT (median duration 88.2 days) was associated with a favourable safety profile that was consistent with that characterised from study P001 in HSCT patients at the time of initial marketing authorisation.

Overall, 88.9% of subjects receiving LET experienced an AE, while 30.6% experienced an SAE, through

Week 28 post-transplant. The overall rate of AEs, drug-related AEs, SAEs and discontinuations due to AEs were generally comparable between LET and placebo. The most commonly reported AEs (incidence >10%) for LET were GVHD (29.9%), diarrhoea (11.8%) and nausea (11.1%). The most frequently reported SAEs (incidence >2%) in the LET group were GVHD, acute myeloid leukaemia recurrent and pneumonia.

A greater number of participants in the LET group (4.9%) discontinued study intervention due to an AE compared with the placebo group (1.4%). Six of the seven AEs leading to discontinuation of the study intervention in the LET group were SAEs. All occurred as isolated cases and no pattern is evident from the data.

A total of 14 deaths were reported during the Treatment Phase, 11 (7.6%) in the LET group and 3 (4.1%) in the placebo group. Eight (7 in the LET group and 1 in the placebo group) of the 14 deaths were due to recurrence of the participant's underlying medical condition that necessitated the HSCT (relapse mortality). Non-relapse mortality was comparable between the 2 groups. None of the deaths appear to be directly related to study intervention.

The proportion of participants experiencing GVHD was comparable in the LET group and the placebo group through Week 28 post-transplant and on through Week 48 post-transplant (38.9% (30.9, 47.4) versus 41.9% (30.5, 53.9)). These rates are numerically lower than those seen in both LET and placebo arms through Week 14 and Week 24 in study P001.

5.6. Uncertainties and limitations about unfavourable effects

Study P002MK8228

The rate of leukopenia can reasonably be attributed to the nearly 100% rate of concomitant use of mycophenolate as this is not over and above what would be expected with mycophenolate alone. The proportion of participants with leukopenia or neutropenia through Week 28 post-transplant was lower in the LET group compared with the VGCV group, which represents a clinically relevant advantage of letermovir over alternative.

Study P040MK8228

A numerical imbalance in the percentage of patients experiencing AEs in the SOC neoplasms was observed between LET 200 days arm (14.6%) versus LET 100 days (placebo) arm (9.5%), which was partially driven by a higher number of patients who had recurrent acute myeloid leukaemia [9 patients (6.3%) in the LET 200 days arm vs 1 patient (1.4%) in the LET 100 days (placebo) arm]. There appears to be no relationship with duration of treatment with LET neither any recurrent pattern, as no such difference was seen in the P001 study. The recurrence of AML is not unusual in this population and the observed difference in the P040 study may reflect a random imbalance in a relatively small study.

Study P002MK8228 & Study P040MK8228

Given the higher LET exposure and bioavailability following oral administration in kidney transplant patients, a lower intravenous dose of 240mg (without CsA) was added to the study protocol for P002, with a view to potentially investigate a more favourable safety profile of the lower dose. However, in practice, very few participants in either study received IV LET, and those that did continued only for a few days before switching to oral LET. Thus, separate analysis of the safety profile for IV administration, including the lower IV dose of 240mg that was planned in study P002, was not possible.

5.7. Effects Table

Table 48: Effects Table for letermovir as prophylaxis of CMV disease

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Study P002MK8228						
CMV Disease	Proportions through Week 52 post-transplant (observed failure approach). Treatment duration 28 weeks.	N (%)	LET 30/289 (10.4%)	VGCV 35/297 (11.8%)	LET was demonstrated to be non-inferior to standard of care VGCV. Numbers of end-organ disease overall low, however, more cases were observed in the LET group.	Study P002 EMEA/H/C/004536
Study P040MK8228						
Clinically Significant CMV Infection	Proportions from Week 14 (~100 days on LET, then 2:1 randomised to continue LET or start placebo) post-transplant through Week 28 (observed failure approach)	N (%)	LET 4/144 (2.8%)	Placebo 14/74 (18.9%)	Demonstrates clinically relevant statistically significant effect of LET prophylaxis for 200 days.	Study P040 EMEA/H/C/004536
Unfavourable Effects						
Study P002MK8228						
Diarrhoea	Most commonly reported AEs (incidence >10%) for LET Treatment Phase	Incidence (%)	31.5%	28.6%	The rate of leukopenia can reasonably be attributed to the nearly 100% rate of concomitant use of mycophenolate as this is not over and above what would be expected with mycophenolate alone.	Study P002 EMEA/H/C/004536
Tremor			18.2%	17.5%		
Urinary tract infection			14.0%	14.1%		
Peripheral oedema			13.4%	12.8%		
Hypomagnesemia			12.7%	13.1%		
Leukopenia			11.3%	37%		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Hypertension			11.3%	12.1%	The proportion of participants with leukopenia or neutropenia through Week 28 post-transplant was lower in the LET group compared with the VGCV group, which represents a clinically relevant advantage of letermovir over alternative.	
Hypophosphatemia			10.3%	11.8%		
Blood creatinine increased			10.3%	13.8%		
Renal graft rejection	through Week 28 post-transplant	%	5.9% (3.5, 9.3)	6.1% (3.6, 9.4)		
	through Week 52 post-transplant		8.0% (5.1, 11.7)	6.7% (4.2, 10.2)		
Study P040MK8228						
GVHD	Most commonly reported AEs (incidence >10%) Treatment Phase	Incidence (%)	29.9%	31.1%	The percentage of patients experiencing AEs in the SOC neoplasms was higher in the LET 200 days arm (14.6%) versus LET 100 days (placebo) arm (9.5%), which was partially driven by a higher number of patients who had recurrent acute myeloid leukaemia. There appears to be no relationship with duration of treatment with LET neither any recurrent pattern.	Study P040 EMEA/H/C/004536
Diarrhoea			11.8%	12.2%		
Nausea			11.1%	17.6%		

Abbreviations: LET=letermovir; VGCV=valganciclovir; GVHD: Graft versus host disease

5.8. Benefit-risk assessment and discussion

5.8.1. Importance of favourable and unfavourable effects

Study P002MK8228

CMV is a common pathogen that causes infection and disease (i.e., end-organ involvement or CMV syndrome) with substantial morbidity and mortality among kidney transplant recipients. The current standard of care VGCV is associated with poor tolerability including myelotoxicity. The efficacy of LET has been demonstrated by non-inferiority to VGCV at a likely conservative margin of 10%, with regards to proportion of participants with CMV disease.

The safety profile of LET seems favourable in this indication and comparable with that previously established in HSCT patients. The safety data clearly demonstrate a difference in safety profile for letermovir versus valganciclovir in terms of the rates of leukopenia reported as adverse events in each treatment arm, which represents a clinically relevant advantage of letermovir over alternative.

Study P040MK8228

Prophylaxis with Prevymis is currently approved through 100 days post-HSCT. The standard of care for prevention of CMV infection and/or disease after 100 days post-transplant is pre-emptive therapy, meaning that patients need to be monitored for CMV-DNA very frequently, in order to know whether to start valganciclovir pre-emption.

In study P040, the efficacy of LET as prophylaxis through ~200 days against CMV-DNAemia has been demonstrated in HSCT transplanted patients with increased risk of CMV reactivation. Safety was favourable and comparable with that previously characterised for LET during the first 100 days post-HSCT.

5.8.2. Balance of benefits and risks

Even with consideration to the uncertainties on favourable and unfavourable effects, the benefits of letermovir both post-kidney transplant and beyond 100 days post-HSCT outweigh the risks.

5.9. Conclusions

The overall benefit/risk balance of letermovir is positive.

6. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6.a: Extension of indication to include prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor [D+/R-], based on the final results from study P002MK8228; this is Phase III, Randomized, Double-Blind, Active Comparator- Controlled Study to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) Versus Valganciclovir for the Prevention of Human Cytomegalovirus (CMV) Disease in Adult Kidney Transplant Recipients. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted.
In addition, the MAH took the opportunity to introduce minor editorial changes to the product information.

C.I.4: Update of section 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC to reflect a longer duration of treatment recommendation based on the final results from study P040MK8228; this is a Phase 3 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of letermovir (LET) prophylaxis when extended from 100 days to 200 days post-transplant in cytomegalovirus (CMV) seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT). The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted.

The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.