27 February 2025
EMA/CHMP/56610/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on group of extensions of marketing authorisation and an extension of indication variation

Prevymis

International non-proprietary name: Letermovir

Procedure No. EMEA/H/C/004536/X/0037/G

Note

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	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
APaT	all participants as treated
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-24	area under the concentration-time curve for the dosing period (0 to 24 hours)
CI	confidence interval
CL	clearance
CMV	cytomegalovirus
CrCL	creatinine clearance
CsA	cyclosporin A
CS-CMVi	clinically significant CMV infection
CSR	clinical study report
D+	seropositive donors
DAO	data-as-observed
DDI	drug-drug interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiograms
ECI	events of clinical interest
eGFR	estimated glomerular filtration rate
E-R	exposure-response
F	bioavailability
FAS	full analysis set
FSA	financial sharing area
G	gastric
GVHD	graft-versus-host disease
HSCT	hematopoietic stem cell transplant
IA	interim analysis
IBD	international birth date
IV	intravenous
KT	kidney transplantation
LET	letermovir, MK-8228
N	number of participants in a subset of the study
NC=F	non-completer=failure

NCA	noncompartmental pharmacokinetic analysis
NG	nasogastric
NHANES	National Health and Nutrition Examination Survey
OATP	Organic anion transporting polypeptide
OF	observed failure
P	protocol (number)
PAER	periodic adverse experience report
PBPK	physiologically based pharmacokinetics
PET	pre-emptive therapy
PI	prediction interval
PK	pharmacokinetics
PopPK	population pharmacokinetics
PSUR	periodic safety update report
PT	preferred term
QD	once daily
R-	seronegative recipients
R+	seropositive recipients
SAE	serious adverse event
SOC	System Organ Class
ULN	upper limit of normal
US	United States
WFRS	worldwide financial reporting system

1. Background information on the procedure

1.1. Submission of the dossier

Merck Sharp & Dohme B.V. submitted on 11 March 2024 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		**Type**
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	I, IIIB

Extension applications to introduce a new pharmaceutical form (granules in sachet) associated with new strengths (20 and 120 mg) grouped with a type II variation (C.I.6.a) to include treatment of paediatric patients from birth up to 18 years old based on the final results from studies P030 and P031.

Study P030 was a Phase 2b, open-label, single-arm study to evaluate PK, efficacy, safety, and tolerability of LET when used for CMV prophylaxis in pediatric participants from birth to <18 years of age who are at risk of developing CS-CMVi following an allogeneic HSCT.

Study P031 was an open-label, single-dose, four-period, seven-treatment, crossover study designed to evaluate the bioavailability of 2 pediatric formulations of MK-8228 (Formulations A and B) administered alone or in soft food (applesauce and vanilla pudding) compared to a currently marketed tablet formulation.

As a consequence, sections 4.1, 4.2, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.1 of the RMP has also been submitted.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to introduce editorial changes.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

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

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0455/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0455/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0455/2023.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Protocol assistance

The MAH received Protocol assistance from the CHMP on 24 October 2013 (EMEA/H/SA/2616/2/2013/PA/PED/I). The Protocol assistance pertained to non-clinical aspects.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Filip Josephson

The application was received by the EMA on	11 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 June 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	24 June 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 July 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	11 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	13 November 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	12 December 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	27 January 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 February 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	27 February 2025

a marketing authorisation to Prevymis on	
The CHMP adopted a report on similarity of Prevymis with Livtencity on (see Appendix on similarity)	27 February 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Cytomegalovirus (CMV) infection is very common and generally acquired early in life, with the majority of the adult population being CMV-seropositive in most countries. Similar to other herpesviruses, acute infection is generally followed by latent (dormant) 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.

In allogeneic haematopoietic stem cell transplant (HSCT) recipients the risk of CMV infection is mostly due to reactivation of latent CMV infection. Haematopoietic 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.

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.

Letermovir (LET) is currently indicated for the prophylaxis of CMV infection and disease in adult CMV seropositive recipients (R+) of an allogeneic HSCT and for the prophylaxis of CMV disease in adult kidney transplant recipients at high risk (donor CMV seropositive/recipient CMV seronegative [D+/R-].

2.1.2. Epidemiology

Recipients of allogeneic HSCT are immune compromised, which increases the risk for CMV infection (as measured by CMV viremia), primarily due to reactivation of latent CMV infection. Approximately 15% to 22% of allogeneic HSCTs in the U.S. and the EU during 2016-2021 were performed in patients aged ≤18 years of age. It is estimated that nearly 60% of paediatric HSCT recipients are at risk of CMV reactivation (R+ and/or D+).

Reported CMV infection or disease rates vary in kidney transplant recipients, depending on baseline CMV-specific immunity (i.e., donor and recipient CMV immunoglobulin G seropositivity) and the overall state of post-kidney transplant immunosuppression. The risk of CMV disease is highest for D+/R- kidney transplant recipients. Approximately 3% to 4% of kidney transplants in the U.S. and the EU were performed in paediatric patients during 2008-2021.

2.1.3. Biologic features

Antiviral resistance remains an Achilles heel of CMV treatment associated with higher morbidity and mortality. All antiviral agents currently used for treatment of CMV infection/disease target the viral DNA polymerase. Mechanisms of resistance to current anti-CMV drugs include gene mutations in viral genes encoding the UL97 Ser/Thr kinase and UL54 DNA polymerase. The UL97 kinase is involved in phosphorylation of various cellular and viral proteins as well as phosphorylation of the nucleoside analogue ganciclovir which is required for anti-viral activity. Thus, UL97 mutations impairing this phosphorylation (e.g. M460V/I, H520Q, C592G, A594V, L595S and C603W) confer resistance to ganciclovir/valganciclovir. Mutations in UL54 can lead to resistance towards all currently available drugs. Thus, new drugs with a different mode of action are urgently needed.

2.1.4. Clinical presentation

The clinical effects of CMV infection can be divided into direct and indirect effects. Direct effects include the spectrum of CMV disease manifestations. CMV colitis is the most common clinical presentation of CMV disease in the allogeneic HSCT population. While pneumonitis is the most serious manifestation, it has become relatively infrequent with current preventative strategies. Other rare manifestations of CMV disease include hepatitis, retinitis, and encephalitis. The indirect effects of CMV infection include increased risk of opportunistic bacterial and invasive fungal infections, graft-versus-host disease (GVHD), and non-relapse mortality.

2.1.5. Management

Two preventive strategies are used for transplant recipients: (1) antiviral prophylaxis, and (2) PET (pre-emptive therapy, the practice of active surveillance for viral replication and initiating treatment with anti-CMV agents when CMV viremia is detected).

No antivirals are currently approved for the prevention of CMV in paediatric HSCT recipients. Of the 2 preventive approaches, PET is suboptimal because PET is initiated after patients develop CMV, which is associated with an increased risk of overall mortality regardless of initiation of PET. Additionally, currently available anti-CMV agents used for PET (e.g., ganciclovir [GCV], valganciclovir [VGCV], and foscarnet) have significant toxicities, including myelotoxicity, which is particularly relevant in the HSCT setting. Based on these considerations, a safe and efficacious agent for prophylaxis of CMV infection and disease would offer significant advantages over PET in the paediatric HSCT setting.

GCV and its prodrug, VGCV, are currently the only anti-CMV agents approved for prevention of CMV disease in paediatric kidney transplant recipients at high risk. In addition to myelosuppression other limitations of GCV/VGCV prophylaxis in kidney transplant recipients include the need for dose modification based on renal function, which can inadvertently result in underdosing of the antiviral in these patients, increasing the risk of CMV viral breakthrough, CMV disease, and the development of antiviral drug resistance. There is an unmet need for a safe and efficacious drug for CMV prophylaxis in paediatric kidney transplant recipients due to the limitations of current therapies above.

2.2. About the product

Letermovir (also known as MK-8228, Prevymis, LET) has been approved in several markets, including the United States, the European Union, and Japan. LET is a CMV viral DNA terminase complex inhibitor which plays a key role in cleavage and packaging of viral progeny DNA.

The MAH applied for the following indication:

PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult and paediatric CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).

PREVYMIS is indicated for prophylaxis of CMV disease in CMV-seronegative adults and paediatric patients who have received a kidney transplant from a CMV-seropositive donor [D+/R-].

Consideration should be given to official guidance on the appropriate use of antiviral agents.

2.3. Quality aspects

2.3.1. Introduction

The application concerns a line extension of the already approved product Prevymis. Currently approved presentations are Prevymis 240 mg and 480 mg film-coated tablets and Prevymis 240 mg and 480 mg concentrate for solution for infusion.

This application primarily concerns a new pharmaceutical form; granules in sachet, containing 20 mg and 120 mg of letermovir as active substance. The purpose is to support the extension of the adult indications to include paediatric patients from birth to <18 years of age.

Other ingredients in the granules are microcrystalline cellulose (E460), croscarmellose sodium (E468), povidone (E1201), colloidal anhydrous silica (E551), magnesium stearate (E470b), lactose monohydrate, hypromellose (E464), titanium dioxide (E171), triacetin, iron oxide yellow (E172) and iron oxide red (E172).

The product is available in sachets consisting of Polyethylene terephthalate (PET)/Aluminium Foil/Linear low-density polyethylene (LLDPE).

2.3.2. Active Substance

Prevymis granules in sachet contain the same active substance, letermovir, as used to manufacture the already authorised presentations. The same manufacturers as for the approved film-coated tablets and concentrate for solution for infusion are stated in the application form.

As a result of the extension of indication, the already authorised pharmaceutical forms (film-coated tablets and concentrate for solution for infusion) may also be used for paediatric patients. Consequentially, the limit for bacterial endotoxins has been tightened in the active substance specification and in the concentrate for solution for infusion based on possible worst case exposure in the paediatric population.

Other than this change, there is no update to the active substance information in Module 3.

2.3.3. Finished Medicinal Product – granules in sachet

2 . 3 . 3 . 1 . Description of the product and Pharmaceutical Development

Prevymis (Letermovir) Oral Granules are immediate release, film coated granules. Each granule contains 2.5 mg of letermovir. The finished product is presented as beige granules approximately 2

mm in diameter. The granules are filled into sachets containing either 8 or 48 granules to provide strengths of 20 mg or 120 mg, respectively.

The formulation and manufacturing process of the finished product has been based on the marketed tablet formulation, with some adjustments. The applicant has applied some QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product. A risk-based control strategy was developed. Justifications of the suitability of the available and proposed formulations for the paediatric population have been provided.

Two different formulations (A and B) were used in clinical study P031. These formulations differ only in film coating. Batches used in late clinical studies have the same film coating as the intended commercial product. The oral granules used in clinical batches were filled into sprinkle capsules. Due to concerns about unintended consumption of the capsules, the primary packaging has been switched to a sachet for the proposed commercial product. The development of the intended QC method for dissolution testing of granules has been presented and dissolution data for the batches used in clinical studies has been provided to support the proposed acceptance criteria. During the procedure, a major objection was raised as there was a difference observed in dissolution results depending on product strength, and since it is proposed to perform release dissolution testing on bulk samples, the appropriateness of the proposed limit should be justified for both product strengths. In response, the applicant performed further testing on the bulk oral granules or capsules of the relevant clinical batches. Testing has been performed equivalent to the commercial strengths of 20 mg (8 counts) and 120 mg (48 counts), using the analytical method intended for commercial release testing. Average dissolution results were in the range of 89 % to 96 % at 30 minutes. Based on the provided data, the proposed limit of Q=80% in 30 minutes is considered acceptable for both product strengths.

Studies have been performed to demonstrate compatibility with soft foods. Compatibility with nasogastric/gastronomy enteral tubes has been demonstrated.

Manufacturing process development utilised risk assessments, process development knowledge and experience from the Letermovir marketed tablet formulation and similar products, so process parameters that had existing well-developed control strategies or were studied and not found to impact CQAs were not identified as risks for Letermovir Oral Granules.

Clinical studies were performed with an oral granule-in-capsule presentation. Technology transfer development and formal stability study batches were manufactured at the intended commercial site with the intended commercial formulation utilized a granule-in-sachet presentation at varying strengths. A total of six granulation batches were manufactured at the intended commercial site, three of which were used for formal stability studies.

The primary sachet container is constructed of a polyester/aluminium/linear low density polyethylene (PET/Ink/Adhesive/Foil/LLDPE) laminate. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.3.2. Manufacture of the product and process controls

The granules are manufactured by eight main steps: blending, lubrication, roller compaction and milling, lubrication, compression, film coating and sachet packaging. The manufacturing process is regarded as a standard process for the dosage form.

The manufacturing process has been described in sufficient detail. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The number of granules per sachet is essential for correct dosing of both strengths. During the procedure a major objection was raised on the testing frequency and limits for the in-process control of fill count. In response the applicant has tightened limits for the in-process control of fill count for both strengths. The applicant argues that the proposed IPC limits will ensure that the finished product specifications for assay and uniformity of dosage units are consistently met. The lowest patient dose is 40 mg (2 x 20 mg sachets) and the probability of a non-target fill count in both sachets is considered low. The proposed control strategy is considered acceptable and relevant dossier sections have been updated accordingly.

A bulk hold time prior to sachet packaging has been proposed and considered acceptable.

As this is a standard manufacturing process, a formal validation of the complete manufacturing process in the production facility will take place prior to the release to the market. A validation protocol has been provided, including information about tests to be performed and their acceptance criteria, and confirming that three consecutive batches of Prevymis Oral Granules at commercial scale will be evaluated. This was considered acceptable.

2.3.3.3. Product specification, analytical procedures, batch analysis

The proposed finished product specification includes the relevant tests for this type of dosage form: visual description, identification (HPLC, UV), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (HPLC) and microbiological examination (Ph. Eur.).

The specification contains relevant tests for this type of product and the limits have been justified. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

The batch analysis data presented covers clinical and stability batches of products strengths 2.5 mg, 10 mg, 30 mg, 120 mg and 240 mg, in total 17 batches. The batch data presented show that the manufacturing process results in batches of consistent and acceptable quality. It should be noted that dissolution data presented for the clinical batches in the batch analyses section has been obtained using a previous version of the analytical method, and not the intended QC method.

The limits proposed for related substances have been set in accordance with ICH guidelines and are considered acceptable.

The applicant has performed a risk assessment concerning potential elemental impurities in the finished product in accordance with ICH Q3D. Analytical test data confirm levels < 30 % of the PDE. The omission of a test for elemental impurities in the drug product is considered acceptable.

A nitrosamine risk evaluation is generally not necessary when submitting a line extension or variation application. The applicant has confirmed that nitrosamine risk assessments have been previously performed for the commercially approved products. Based on these results, the applicant confirms there is negligible risk of the presence or formation of nitrosamines in Prevymis film-coated tablets and Prevymis concentrate for solution for injection. Additionally, a nitrosamine risk assessment was also performed for Prevymis Oral Granules including the evaluation of the potential risk of nitrosamine formation related to the formulation, manufacturing process, package and storage of the finished product. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The justification presented for not including testing of water activity is considered acceptable.

Reference standards are the same as already used for testing of the marketed tablet formulation.

2.3.3.4. Stability of the product

Three batches of Letermovir Oral Granules were prepared for the formal stability studies. Each granule batch was filled into sachets to obtain batches of product strengths 2.5 mg (1 granule) and 240 mg (96 granules). These strengths bracket the final proposed commercial presentations (20 and 120 mg). The granule batch sizes were > 10 % of the intended production batch size . The applicant states that the sachets used for stability are representative of those used for the commercial products.

Stability studies have been performed in accordance with current ICH guidelines, with one exception: long term stability has been evaluated at 75 %RH, instead of 65 %RH as prescribed in ICH Q1. As a higher relative humidity can be considered worst case for the dosage form, this is acceptable.

Samples were tested according to the shelf life specifications. The analytical procedures used are stability indicating.

Total 36 months' stability data has been provided for the finished product. All results are well within the proposed specifications.

Bulk hold stability data for coated granules has been provided for up to 12 months. The proposed bulk hold time of 12 months is considered acceptable.

Photostability testing has been performed and the coated granules are considered photostable.

The proposed shelf-life of 36 months, without any special storage conditions, is considered acceptable. Stability after mixing with soft foods has been assessed in the development section and reflected in the SmPC.

2.3.3.5. Adventitious agents

The excipient lactose monohydrate (present in the film coating system) has been identified as an ingredient of ruminant origin. The lactose monohydrate is derived from milk certified to originate from healthy animals and is collected in the same manner as milk fit for human consumption. In addition, lactose monohydrate is not prepared with the use of other ruminant materials with the exception of calf rennet. Under these conditions, milk and milk products are considered to be in compliance with the Note for Guidance (EMA/410/01).

Magnesium stearate is derived from purely vegetable origins.

2.3.4. Finished Medicinal Product – concentrate for solution for infusion

As a result of the extension of indication, the already authorised pharmaceutical forms (film-coated tablets and concentrate for solution for infusion) may also be used for paediatric patients.

Consequentially, the limit for bacterial endotoxins has been tightened in the active substance specification and in the concentrate for solution for infusion based on possible worst case exposure in the paediatric population.

In addition, during the procedure a multi-disciplinary major objection was raised on the potential clinical relevance of paediatric exposure to excipient hydroxypropyl betadex (HP-beta-CD). This is discussed in detail under section 2.5.6, 2.5.9 and 2.5.10 below.

2.3.5. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure, major objections were raised on the new presentation relating to the proposed limit for dissolution testing and on the in-process control of the number of granules per sachet. The applicant provided additional information to address the points raised and both were considered to be resolved.

The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

In addition, the limit for bacterial endotoxins has been tightened in the active substance specification and in the concentrate for solution for infusion based on possible worst case exposure in the paediatric population. The clinical relevance of paediatric exposure to excipient hydroxypropyl betadex (HP-beta-CD) is addressed as a clinical/non-clinical issue under sections 2.5.6, 2.5.9 and 2.5.10 below.

2.3.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.7. Recommendation(s) for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

No new non-clinical pharmacology studies have been conducted alternatively old study data or public research studies are being discussed to support the use of letermovir (LET) in the intended paediatric patient population. A short description of the pharmacological dossier information for LET is provided below (derived from the EPAR for Prevymis, approved 2018 for an adult patient indication).

2.4.2. Pharmacology

LET has activity (single-digit nanomolar EC50 values) against laboratory and clinical CMV isolates in cell-culture models of infection. Characterisation of DNA processing, virion maturation, and viral resistance mutations in CMV-infected, LET-treated cells implicate CMV DNA terminase as the target of letermovir. The process of cleaving concatemeric DNA and packaging unit-length genomes into viral capsids is absent in uninfected cells and there are no human homologs of the CMV DNA terminase complex proteins. The mode of action of LET is distinct from that of already approved anti-CMV agents that target CMV DNA replication.

2.4.2.1. Primary pharmacodynamic studies

Not applicable.

2.4.2.2. Secondary pharmacodynamic studies

A number of secondary pharmacodynamics alternative test method studies were conducted to study possible cardiophysiological effects (cardiac inotropy in field stimulated guinea pig left atria, cardiac chronotropy in spontaneous beating guinea pig right atria, aorta rat contractile agonism or antagonism of KCl-induced contractions, ileum guinea pig contractile agonism or antagonism of KCl-induced contractions, trachea guinea pig contractile agonism or antagonism of KCl-induced contractions, portal vein rat contractile agonism or antagonism of KCl-induced contractions) but none exhibited any significant activity (defined as ≥50% change). LET did interact with any off-target protein (out of 63 screened) at 10 micromolar.

2.4.2.3. Safety pharmacology programme

In the safety pharmacology assessment, LET inhibited hERG current with an IC50 of 67 µM (~38,360 µg/L) but in-vivo safety pharmacology studies in dog did not show any indication of cardiophysiological changes (heart rate and blood pressure). There were also no LET-related effects of concern on nervous system, and respiratory functions.

2.4.2.4. Pharmacodynamic drug interactions

Not applicable.

2.4.3. Pharmacokinetics

No new non-clinical pharmacokinetics studies have been conducted alternatively old study data or public research studies are being discussed to support the use of LET in the intended paediatric patient population. A short description of the pharmacological dossier information for LET is provided below (derived from the EPAR for Prevymis, approved 2018 for an adult patient indication).

Following IV administration to Wistar rat and Rhesus monkey, LET exhibited non-linear pharmacokinetics, which is consistent with saturation of its elimination pathways, resulting in greater than dose proportional increase in exposure. At the lowest oral dose tested (1 mg/kg), the bioavailability of LET was 55% in rat and 14% in monkey. Based on studies in bile-duct cannulated rats dosed at 3 mg/kg, the fraction absorbed was estimated to be 83%. The distribution pattern of LET across Wistar, Sprague Dawley and Long Evans rats was similar. LET was rapidly and widely distributed in tissues and highest levels of radioactivity were observed in the gastrointestinal tract, bile duct and liver independent of the route of administration. Low levels of radioactivity in the brain suggested that LET does not readily cross the blood-brain-barrier. In the pigmented rat, the radioactivity in eye tissues was at the level of background after 24 hours, suggesting that LET-related radioactivity does not bind to melanin.

LET showed low (in-vitro) metabolic turnover following incubation with liver microsomes or plated hepatocytes across all species. A total of eight oxidative metabolites were observed in liver microsomes. The metabolism resulted from hydroxylation (M1, M2), O-dealkylation (M3, M4, M5, M6, M11) and oxidative desaturation (M14). In hepatocytes, glucuronidation of LET was the major route of metabolism in all species, including human, forming M7, M8, and M9. In-vivo, LET represented

independent of exposure route the majority of drug-related radioactivity circulating in rat plasma accounting for ~70% of the total plasma AUC. Additionally, an oxidative metabolite (M5) was a circulating constituent of the plasma radioactivity accounting for ~25% of the total plasma AUC. All human metabolites were observed in liver preparations from the safety species. The oxidative metabolite M5, found to circulate in rats, was not observed in human plasma.

The excretion of letermovir was studied in Wistar rats and Rhesus monkeys, as well as in humans. In all species, biliary/faecal excretion was the predominant elimination route, while renal elimination was negligible.

2.4.4. Toxicology

No new non-clinical toxicology studies have been conducted but the MAH has provided a non-clinical overview discussion for the relevance of previously conducted toxicological studies (including a juvenile toxicity study in rat). Only toxicological studies/information of potential relevance/linked to the proposed indication extension are covered below.

2.4.4.1. Repeat dose toxicity

In the original toxicological dossier (Prevymis, 2018), the testis (in rat) was identified as a sensitive target organ for letermovir (LET) in the repeat-dose toxicity studies. Animal-to-human exposure margins were calculated based on AUC-data from humans between 12 and 18 years of age. The 26w rat oral NOAEL was 150 mg/kg/d (~14/5.1-fold relative to clinical adult oral and IV exposures, respectively, in males; and ~18/6.5-fold relative to clinical adult oral and IV exposures, respectively, in females). For 4w IV exposure of rats, the NOAEL was 30 mg/kg/d, the margin for males was 2.9-fold (clinical oral) and 1.1-fold (clinical IV) and for females 18.5-fold (clinical oral) and 6.5-fold (clinical IV). For cynomolgus, the 39w exposure oral NOAEL was established at 100 mg/kg/d (≤1.5-fold relative to clinical oral exposures in males and females; and <1-fold relative to clinical IV exposure). For 4w IV exposure, the NOAEL was also 100 mg/kg/d, corresponding to margin of ~10-11-fold (clinical oral) and 3.6-3.9-fold (clinical IV). The cynomolgus animals at between two and five years of age (roughly corresponding to between 8 and 20 human years of age). No testis toxicity was observed in the juvenile rat toxicity study or in cynomolgus studies. It still remains unclear if the testicular effects are species (rat) specific and the effects are therefore described in section 5.3 of the SmPC.

2.4.4.2. Genotoxicity

Letermovir is non-mutagenic and non-genotoxic.

2.4.4.3. Carcinogenicity

In Type II variation EMEA/H/C/004536/II/0033/G, a 26-week carcinogenicity study in CByB6F1-Tg(HRAS)2Jic hemizygous mice was submitted to support supplemental marketing applications for indications where the duration of continuous treatment duration is longer than 6 months (e.g 200 days). In addition, a WoE-based carcinogenicity risk assessment was provided in accordance with the recently adopted ICH S1B(R1) Addendum to Testing for Carcinogenicity for Pharmaceuticals. The outcome from the 6-month oral carcinogenicity study in CByB6F1 Tg(HRAS)2Jic hemizygous mice was LET-related neoplastic changes 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 at lower doses, or in males at any dose level. The LET-related focal reactive hyperplasia and benign squamous papilloma in the forestomach observed in female mice at 300 mg/kg/day were considered as a likely consequence of persistent local irritation and therefore not of relevance to humans (this was also described in SmPC 5.3).

2.4.4.4. Reproductive and developmental toxicity

In the pre- and post-natal development (PPND) oral exposure rat study, the NOAEL in the F0 generation was 45 mg/kg/d (2.3/<1-fold relative to clinical oral and IV exposures, respectively). There was a possibly minor delay in mean vaginal opening in F1 females (PND 36.7 versus PND 34.5 in controls) but no clear adverse LET-related developmental effects in the F1 generation up to the highest dose tested of 180 mg/kg/d (5.6/2.0-fold relative to clinical oral and IV exposures, respectively). It can be noted that LET was detected in the PND21 plasma of F1 pups (2 hours post-dose 1.56 ng/mL at the maternal NOAEL of 45mg/kg/d), indicating exposure of nursing pups via the milk during the lactation period.

For the juvenile toxicity rat study, LET-exposure was once daily via oral gavage between PND14 and PND27 with doses at 60 or 180 mg/kg/d (n=5 males per experimental group). The study included an assessment of the potential for LET to interfere with the establishment of the blood-testis barrier – although it should be noted that the study design was suboptimal for this purpose as the exposure should have been prolonged to PND40 to fully cover testicular development in rat. In the spleen, there was an increase in haemopoesis in treated animals, characterised by an increase in haemopoetic tissue from all three cell lines within the red pulp. Otherwise, there were no findings in the study except for a slight decrease in body weight gain at 180 mg/kg/d. Oral administration of 60 or 180 mg/kg/d of letermovir to juvenile male rats did not interfere with Sertoli cell proliferation or the germinal epithelium. The juvenile rat NOAEL was set at 180 mg/kg/d but no animal-to-human exposure margins could be estimated due to absence of toxicokinetic measurements.

2.4.4.5. Local tolerance

In the original Prevymis dossier from 2018, local tolerance studies in rabbit were conducted. When LET was dissolved in 20% cyclodextrin (hydroxypropyl betadex) solution, the formulation did not induce signs of local intolerability after IV infusion, intra-arterial or subcutaneous injections of 2.5 or 5 mg/mL.

2.4.5. Ecotoxicity/environmental risk assessment

An updated environmental risk assessment (ERA) has been provided. Previous approved ERA's where part of the original MAA for Prevymis (approved 2018) and a Type II variation (EMEA/H/C/004536/II/0033/G, approved Nov 2023). In the latest ERA assessed, the conclusion was that there was no significant increase in environmental exposure due to further use of LET.

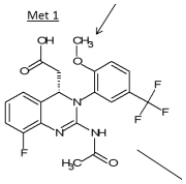
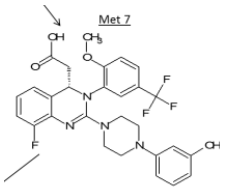
The present updated ERA aims to cover the inclusion of paediatric individuals that are CMV-seropositive recipients [R+] of HSCT or CMV-seronegative recipients who have received a kidney transplant from a CMV-seropositive donor [D+/R-]. In previous ERA's, Log Kow was/is 2.29 (< 4.5, not triggering a PBT assessment) but a Phase IIA assessment was triggered as Phase I PECsw was 2.29 ug/L (>0.01 ug/L and based on a default Phase I calculation with a maximum daily dose of 480 mg LET per day and Fpen 0.01).

DT50 values from the OECD TG308 study were calculated in an SFO model and using Computer Assisted Kinetic Evaluation (CAKE) software for improved curve-fitting. These data were then normalized from 20°C to 12°C using the Arrhenius equation, giving total system DT50 of 47.2 d (Taunton River) and 62.5d (Weweantic River). Letermovir is considered to be slowly degraded in the environment (DT50 > 40d for the total water-sediment system).

Based on the Phase I PECsw, the Phase II PEC/PNEC calculations all resulted in RQ < 1 for all investigated environmental compartments and it is therefore unlikely that LET constitutes an environmental risk.

Table 1: Summary of ERA results

Substance (INN/Invented Name): Letermovir				
CAS-number (if available): 917389-32-3				
PBT screening		Result		**Conclusion**
Bioaccumulation potential log K_{ow}	OECD 107	pH 5: 2.51 pH 7: 2.29 pH 9: 1.01		Potential PBT: N
PBT-assessment				
Parameter	**Result relevant for conclusion**			**Conclusion**
Bioaccumulation	log K_{ow}	1.01-2.51		not B
	BCF	NA		not B
Persistence (OECD 308 derived)	DT50, 12°C Values are derived from the OECD 308 or OECD 307 study below and have been recalculated to 12°C	$DT_{50\ water}$ = 18/24 d $DT_{50sediment}$ = 101/45 d		not P
Toxicity	NOEC or CMR			T/not T
PBT-statement :	Letermovir is considered to be not PBT, nor vPvB			
Phase I				
Calculation	**Value**		**Unit**	**Conclusion**
$PEC_{sw,\ phase\ I,\ default}$	2.4		µg/L	≥ 0.01 threshold: Y
Other concerns	None			N
Phase II Physical-chemical properties and fate				
Study type	**Test protocol**	**Results**		**Remarks**
Adsorption-Desorption Soil 1 = DU Soil (3.8% oc) Soil 2 = RMN Soil (0.81% oc) Soil 3 = MSL Soil (2.0% oc) Soil 4 = CA Soil (0.81% oc) Sludge 1 = Wareham Sludge (32.05% oc) Sludge 2 = New Bedford Sludge (36.8% oc)	OECD 106	$K_{oc,\ soil\ 1}$ = 3.19 L/kg_{oc} $K_{oc,\ soil\ 2}$ = 3.46 L/kg_{oc} $K_{oc,\ soil\ 3}$ = 3.03 L/kg_{oc} $K_{oc,\ soil\ 4}$ = 3.43 L/kg_{oc} $K_{oc,\ sludge\ 1}$ = 2.85 L/kg_{oc} $K_{oc,\ sludge\ 2}$ = 2.49 L/kg_{oc}		
Ready Biodegradability Test	OECD 314B	Half-life: 6.7d Elimination rate constant, ke: 0.1028 d		Two metabolites M1 and M2 were measured in concentrations greater than 10% by Day 28.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = Taunton River (Silt Loam)	OECD 308	Taunton River $DT_{50,\ water,\ 20°C}$ = 8.3d $DT_{50,\ sediment,\ 20°C}$ = 47d days $DT_{50,\ whole\ system,\ 20°C}$ = 22d		Shifting to sediment triggers sediment testing 2 TP (⩾ 10% AR) were observed in some of the chromatograms for the

Sediment 2 = Weweantic River (Sand)		$DT_{50, water, 12°C}$ = 18d $DT_{50, sediment, 12°C}$ = 101d $DT_{50, whole system, 12°C}$ = 47d CO_2 = 0.3 % NER = 57.7% at d100 Weweantic River $DT_{50, water, 20°C}$ = 11d $DT_{50, sediment, 20°C}$ = 21d $DT_{50, whole system, 20°C}$ = 29d $DT_{50, water, 12°C}$ = 24d $DT_{50, sediment, 12°C}$ = 45d $DT_{50, whole system, 12°C}$ = 62d CO_2 = 0.3 % NER = 58.5% at d100 shifting to sediment > 10% Transformation products >10% = Y Taunton River Met-7** max. 10.6% in sediment, Met-1* max. 10% in total system, Weweantic River Met-7** max. 13.9% in sediment, Met-1* max. 12.8% in total system.	Taunton River and Weweantic River samples (Met 1 and 7). Met 1  Met 7 

Phase IIa Effect studies

Study type	Test protocol	Result	Value	Unit	Remarks
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	NOEC LOEC	8.8 >8.8	mg/L	growth rate NOEC is the functional solubility limit.
Daphnia magna, Reproduction Test	OECD 211	NOEC LOEC	1.2 2.4	mg/L	
Fish, Early Life Stage Toxicity Test/*Fathead minnow*	OECD 210	NOEC LOEC	1.0 >1.0	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC / EC_{10}	29.6	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC LOEC	25 50	mg/kg_{dw}	oc=2.5% $NOEC_{oc}$=100 mg/kg

2.4.6. Discussion on non-clinical aspects

Toxicology - Letermovir

In the original toxicological dossier (Prevymis, 2018), the testis (in rat) was identified as a sensitive target organ for letermovir (LET) in the repeat-dose toxicity studies. Animal-to-human exposure margins were calculated based on AUC-data from humans between 12 and 18 years of age/adults.

For long-term oral exposure rat data, a NOAEL of 150 mg/kg/d gives an exposure-margin of ~14/5.1-fold relative to clinical adult oral and IV exposures, respectively, in males; and ~18/6.5-fold relative to clinical adult oral and IV exposures, respectively, in females. For short-term (4w) IV exposure rat data, a NOAEL of 30 mg/kg/d gives a margin for males at 2.9-fold (clinical oral) alternatively 1.1-fold (clinical IV) and for females 18.5-fold (clinical oral) alternatively 6.5-fold (clinical IV). No testis toxicity was observed in the juvenile rat toxicity study or in cynomolgus or mouse studies but some uncertainty still remains whether the testicular effects are species (rat) specific and/or if a younger age-interval may have a different response than adults. It still remains unclear if the testicular effects are species (rat) specific and the effects are therefore described in section 5.3 of the SmPC. Adult non-rat animal studies or clinical trial studies did not indicate any sign of male reproductive toxicity (the clinical data includes measurements of testicular function related biomarkers from adults and one paediatric trial). The experimental juvenile toxicity rat study – while negative in this respect - had some limitations regarding assessment of the testicular toxicity (the exposure duration was between PND14 and PND27 but should have been extended to PND40 to fully cover testicular development in rat). To account for the adult rat toxicity findings, and the uncertainty for younger age groups, a plan for pharmacovigilance monitoring for signs of testicular toxicity is therefore active.

For cynomolgus repeat-dose toxicity, the 39w exposure oral NOAEL was 100 mg/kg/d (≤1.5-fold relative to clinical oral exposures in males and females; and <1-fold relative to clinical IV exposure). For 4w IV exposure, the NOAEL was also 100 mg/kg/d, corresponding to margin of ~10-11-fold (clinical oral) and 3.6-3.9-fold (clinical IV). The cynomolgus animals at between two and five years of age (roughly corresponding to between 8 and 20 human years of age).

No particular toxicological concerns were identified for LET in the developmental toxicity studies of greatest relevance to the proposed extension of the indication (PPND and juvenile toxicity studies in rat). The PPND study (maternal oral exposure) found a possibly minor delay in mean vaginal opening in F1 females (PND 36.7 versus PND 34.5 in controls) but there were no clear adverse LET-related developmental toxicity in the F1 generation up to the highest dose tested of 180 mg/kg/d (5.6/2.0-fold relative to clinical oral and IV exposures, respectively). As LET was detected in the plasma of F1 generation rat pups at PND21, there was likely exposure of nursing pups via the milk during the lactation period. The juvenile study (oral) covered PND14-PND27 exposure, which is less than the age span for testicular development. As such, while the study did not find any signs of male reproductive organ toxicity, some uncertainty remains on the subject of LET testicular effects in a developmental context (non-clinical and clinical).

In the spleen, there was an increase in haemopoesis in treated animals, characterised by an increase in haemopoetic tissue from all three cell lines within the red pulp. There was also a possibly minor delay in mean vaginal opening in F1 females (PND 36.7 versus PND 34.5 in controls). Overall, there was no clear adverse LET-related developmental effects in the F1 generation up to the highest dose tested of 180 mg/kg/d (5.6/2.0-fold relative to clinical oral and IV exposures, respectively). No animal-to-human exposure margins could be estimated due to absence of toxicokinetic measurements.

Toxicology - Excipients

The IV-formulation contains the excipient hydroxypropyl betadex (HP-beta-CD) which belongs to the cyclodextrin class of excipients where, based on CHMP guidance[1], the general safety threshold is set to 20 mg/kg/d for all administration routes (based on non-clinical data) but there is also some clinical experience for up to 250 mg/kg/d over a three-week duration (IV-treated ≥2-year-olds, roughly ≥15 kg BW). Available non-clinical toxicology studies are primarily based on oral exposure but cyclodextrins have poor oral bioavailability, so they cannot easily be considered covered by the oral exposure studies. Toxicological information on HP-beta-CD is provided in SmPC 5.3 including information on ototoxicity in adult rodents. Based on the proposed IV-dosages for paediatric patients under 12 years of age, the daily HP-beta-CD exposure would range between 3600 mg HP-beta-CD (at 480 mg LET solution) down to 150 mg HP-beta-CD (at 20 mg LET solution). A 250 mg/kg/d HP-beta-CD lower limit is used for Prevymis – providing a safety margin of roughly 4x to 8x - under the condition of a recommended maximum treatment period of four weeks, a minimum weight of 5 kg BW, and warnings for (renal impaired) special populations (see SmPC 4.2).

Environmental risk assessment

LET is not a PBT substance and is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

No new non-clinical studies have been submitted. From a toxicological point of view, the pre-existing non-clinical data covers the present indication extension to paediatric patients down to the proposed minimum of 5 kg BW.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies Study ID	**Phase**	**Country/ Region**	**Study Title**	**Study design**	**Dosing regimen**	**Study population**	**Participant exposure**
8228-031 [Ref. 5.3.1.2: P031MK8228]	1	Canada	A Study to Evaluate the Comparative Bioavailability of Two Formulation Batches of MK-8228 Granules Compared to the Adult Formulation in Healthy Adult Subjects Type of Trial: BA Indication: Prophylaxis of	Single-center, open-label, single-dose, randomized, four-period, seven-treatment, twelve-sequence, crossover, comparative bioavailability study	Periods 1-3: Treatment A: A single oral dose of 240 mg letermovir (tablet) Treatment B: A single oral dose of 240 mg letermovir granules) Treatment C: A single oral dose of 240 mg letermovir (granules) Period 4: Treatment W: A single oral dose of 240 mg letermovir	Female subjects Age: 20-55	Letermovir Oral Tablet 240 mg: 24 Letermovir Coated Granules Formulation A: (Treatment B, W, X) 240 mg: 24 Letermovir Coated Granules Formulation B: (Treatment C, Y,

[1] CHMP (2017), "Questions and answers on cyclodextrins used as excipients in medicinal products for human use", EMA/CHMP/495747/2013, 9 October 2017.

			Cytomegalovirus Infection		(granules) in vanilla pudding Treatment X: A single oral dose of 240 mg letermovir (granules) in applesauce Treatment Y: A single oral dose of 240 mg letermovir (granules) in vanilla pudding Treatment Z: A single oral dose of 240 mg letermovir (granules) in applesauce		Z) 240 mg: 24

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Formulation development

A Phase 1 relative bioavailability study of paediatric oral granules administered with and without soft food compared to the approved tablet (240 mg) (P031, see section Absorption below) was conducted to support the selection of the oral granule formulation to be used in the Phase 2b study in paediatric participants from birth to <18 years of age at risk of developing CMV infection and/or disease following allogeneic HSCT (P030). Study P030 also used the approved oral tablet (240 mg) for participants 12 years and older (Age Group 1) who could swallow a tablet, and the approved IV formulation was available for use in all Age Groups as specified in the protocol. All subjects in age group 2 (2 to <12 years) and age group 3 (birth to <2 years) who received oral treatment received the oral granule formulation.

The early formulation of oral granule (Formulation A in P031) was selected as preliminary market formulation (PMF) for further development and used in Phase 2b paediatric study (P030). A beige film-coating system of similar composition to the white film-coating system in formulation A was however selected for the PMF. The intended commercial formulation used the same composition and beige colour film-coating system as the PMF but the primary packaging differs. In the clinical studies, the granules were packaged in capsules: 10 mg (4 oral granules per capsule), 30 mg (12 mg oral granules per capsule) and 120 mg (48 oral granules per capsules) but for commercial use 20 mg (8 granules) and 120 mg (48 granules) will be packed in sachets instead. Compatibility studies have been performed to support the administration of the oral granules in a range of soft-food and the preparation for NG/G tube administration.

The new oral granules formulation can facilitate weight-band dosing in patients <12 years of age but is intended for use in both paediatric and adult patients. The approved tablets are proposed to be used in paediatric patients who receive a dose of 240 or 480 mg QD and are able to swallow tablets and the approved IV formulation is proposed for paediatric patients from birth to <18 years of age.

Methods

Bioanalysis

The determination of letermovir in human plasma was performed using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods (PMRI-1717-17 and PMRI-1769-18).

Pharmacokinetic data analysis

In study P031 (relative BA and food effect study), standard non-compartmental analysis was used.

In study P031, NCA analysis was performed on a subset of the PP population who underwent intensive PK sampling. The popPK analysis included both intensive and sparse PK data, see below.

Evaluation and qualification of models

Introduction

Study MK-8228-030 was a Phase 2b open label, multicentre, single arm study in paediatric recipients of an allogeneic HSCT. The primary endpoint was pharmacokinetics. The MAH has provided popPK report *08HCCH Population Pharmacokinetic Analysis of MK-8228 in Pediatric Hematopoietic Stem Cell Transplant Recipients* with this submission. The population pharmacokinetic (PopPK) analysis objective was to characterise letermovir (LET) pharmacokinetics (PK) in paediatric haematopoietic stem cell transplantation (HSCT) recipients (from study 030) grouped by age. Data from 60 paediatric HSCT recipients across 3 age groups and 8 different body weight (WT) bands receiving intravenous (IV) and/or oral (PO) formulations of LET with and without cyclosporine A (CsA) were used in the analysis.

Dataset

Measurable PK data from the dedicated paediatric study P030 were used in this analysis. In this study, sparse samples were collected throughout the study, and intensive samples were collected typically around Day 7. The paediatric population consisted predominantly of white (68.9%) and male (70.5%) subjects, with an overall median (range) weight of 32.4 (5.14 to 95) kg and median age (range) of 11.0 (0.167 to 17.0) years. Overview of the paediatric dataset prior to exclusions is shown in **Table *5***.

Table 2. Overview of the paediatric popPK Analysis dataset by Age and WT

Age Group	Age Range (years)	WT Limits (kg)		LET Dose (mg)				N of PK Samples/N of Subjects[c]			
				PO (mg)		IV (mg)		PO (mg)		IV (mg)	
				-CsA	+CsA	-CsA	+CsA	-CsA	+CsA	-CsA	+CsA
Total								**193/18**	**187/22**	**57/9**	**66/11**
1	**12 to <18**	**Any WT**		480	240	480	240	88/8	73/12	20/3	23/4
2	**2 to <12**	**≥30**		480	240	240	240	6/1	21/3	13/2	0/0
		18 to <30		240	120	120	120	71/6	7/1	12/2	5/1
		10 to <18		120	60	60	60	16/2	34/2	7/1	24/4
3	**Birth to <2**	**10 to ≤15**		120	60	60	60	4/0	11/1	0/0	6/1
		7.5 to <10	**a**	80	40	40	40	0/0	23/2	0/0	0/0
			b	120	60	60	60	0/0	0/0	0/0	0/0
		5.0 to <7.5	**a**	40	20	20	20	0/0	0/0	0/0	0/0
			b	60	40	40	40	8/1	18/1	5/1	8/1
		2.5 to <5.0	**a**	20	10	10	10	0/0	0/0	0/0	0/0
			b	40	20	20	20	0/0	0/0	0/0	0/0
								Grand Total 503/60			

Source: Reproduced from Protocol number MK-8228-0030-07 and tables-report-poppk-pediatric-letermovir-v4.Rmd

[a] Original dosing regimen proposed in Study P030 for Age Group 3.

[b] Revised dosing regimen for Age Group 3 based on interim analysis for Age Group 3 (implemented through protocol amendment 8).

[c] During the study, some subjects received other doses/formulations than allocated per protocol (based on enrollment WT on Day 1) as dosing may be adjusted based on changing WT, need of CsA, or IV.

Notes: The number of subjects in the table is categorized by their first administered dosing, whereas the number of PK samples is categorized by the regimen received (LET PO or IV with or without CsA) directly prior to the PK sample.

Abbreviations: +/-CsA=with/without CsA coadministration; CsA=cyclosporine A; IV=intravenous; LET=letermovir; N=number; PK=pharmacokinetic; PO=oral; PopPK=population pharmacokinetic; WT=body weight

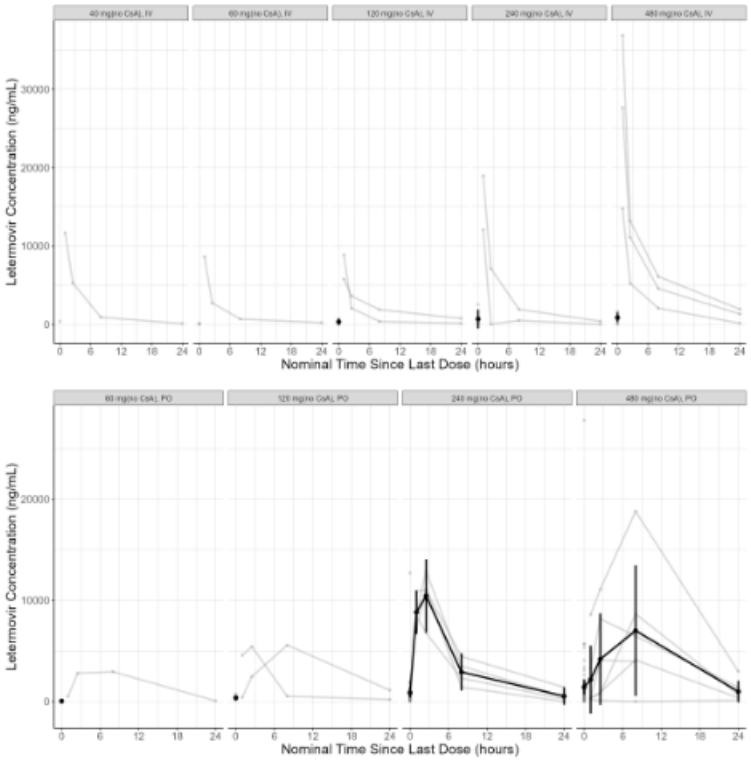
A total of 38 PK observations (which include all PK from 1 subject) were excluded from the analysis. Samples were excluded from the analysis for the following reasons:

- There were 20 BLQ observations after administration of the first dose ("post-treatment BLQ") that were excluded from the analysis. These BLQ observations represent 4.0% of all observations.
- |CWRES| > 5 during model development (6 samples)
- Inconsistent time of dose prior to PK. A flag was included to flag PK samples with imputed time of prior dose. This flag was used to exclude these PK observations from the model run (6 samples).
- One subject (subject ID = 200006) had an aberrant PK profile as identified in the non-compartmental analysis (NCA) of LET PK and the exploratory PopPK data analysis (6 samples).

In summary, the analysis was conducted on a database containing 471 PK observation records and a total of 60 subjects. A total of 38 samples were excluded from the PopPK analysis.

Figure *1* shows individual measurable plasma drug concentration versus time stratified by dose regimen administered without CsA in Study P030.

Figure 1. LET Concentration Versus Time (Nominal Time Since the Last Dose) by Actual Dose Regimen Without CsA in Study P030



Source: eda-poppk-pediatrics-covariates-letermovir-v3.Rmd
Notes: The solid black lines represent the mean concentration, and the solid black bars indicate the confidence intervals. Mean lines and confidence interval are only shown where there are more than 3 PK observations. The gray dots and lines are individual subject PK profiles within each panel.
Abbreviations: CsA=cyclosporine A; IV=intravenous; LET=letermovir; PK=pharmacokinetic; PO=oral

Methods

The software package NONMEM (Version 7.5; ICON Development Solutions, Ellicott City, MD, USA) was used in the PopPK analysis.

PopPK Modeling Strategy

The PopPK of LET has previously been characterised for 2 indications (adult HSCT and kidney transplant [KT]) with a 2-compartment PK model using steady-state observations after PO/IV dosing of 480 mg once daily (or 240 mg with CsA). The HSCT PopPK model included data from adult healthy subjects and adult HSCT recipients. The KT PopPK model included data from adult healthy subjects and adult KT recipients.

Covariates

The previously developed PopPK model in adult HSCT recipients contained various categorical covariates (coadministration of CsA on F1 and CL, Asian effect on Vp, and healthy volunteer [HV] effect on F1 and Ka). Since the paediatric study P030 had 61 subjects in which sampling was relatively sparse and previously identified covariates were extensively evaluated in PopPK models in richly sampled Phase 1 and Phase 3 studies in adult HSCT patients, no formal covariate evaluation was conducted. Key covariates previously found to influence LET exposure were tested and included in the model if supported by the data from P030. **Table *6*** provides a summary of continuous covariates included in the per-protocol PK dataset. None of the continuous covariates evaluated in the PopPK analysis had >30% of missing values. Therefore, all continuous covariates were included as planned in the analysis.

Table 3. Summary of Continuous Covariates

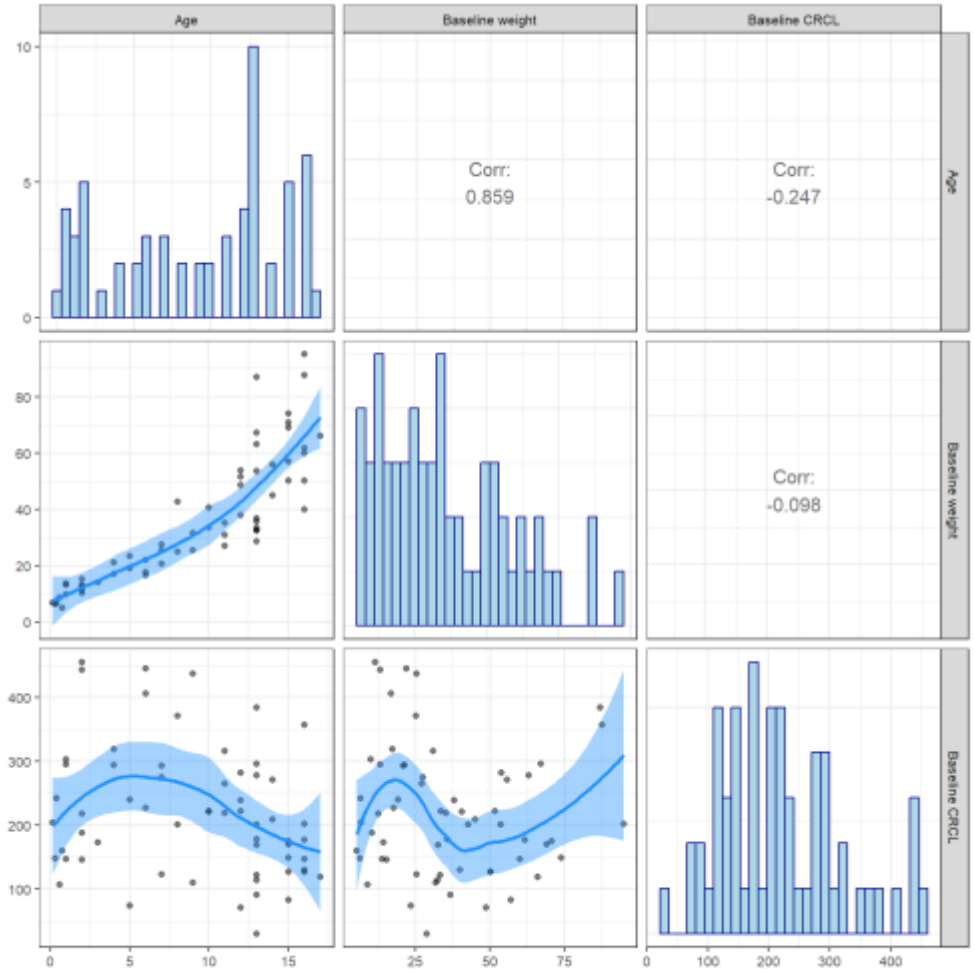
	Age Group 1: Any Weight (N = 28)	Age Group 2: >30 kg (N = 6)	Age Group 2: 18 to 30 kg (N = 10)	Age Group 2: 10 to 18 kg (N = 9)	Age Group 3: 10 to 15 kg (N = 2)	Age Group 3: 7.5 to 10 kg (N = 2)	Age Group 3: 5 to 7.5 kg (N = 4)	Overall (N = 61)
Age (years)								
Mean (SD)	14.1 (1.54)	9.83 (1.17)	6.90 (2.08)	3.22 (1.72)	1.00	0.792	0.417 (0.245)	9.12 (5.41)
Median [min, max]	13.5 [12.0, 17.0]	10.0 [8.00, 11.0]	7.00 [4.00, 11.0]	2.00 [2.00, 6.00]	1.00 [1.00, 1.00]	0.792 [0.583, 1.00]	0.375 [0.167, 0.750]	11.0 [0.167, 17.0]
Baseline body weight (kg)								
Mean (SD)	55.2 (17.7)	35.8 (4.83)	23.7 (2.81)	14.3 (2.61)	13.5	9.35	6.23 (0.744)	36.0 (22.6)
Median [min, max]	53.8 [28.7, 95.0]	34.5 [30.9, 42.7]	24.3 [19.2, 27.5]	14.2 [10.4, 17.7]	13.5 [13.2, 13.7]	9.35 [8.80, 9.90]	6.49 [5.14, 6.79]	32.4 [5.14, 95.0]
Baseline CRCL (mL/min)								
Mean (SD)	183 (84.7)	215 (65.7)	282 (120)	286 (122)	221	205	189 (43.1)	220 (102)
Median [min, max]	173 [31.1, 384]	220 [110, 316]	284 [75.0, 445]	228 [146, 455]	221 [147, 295]	205 [107, 303]	182 [149, 243]	204 [31.1, 455]

Source: tables-report-poppk-pediatric-letermovir-v4.Rmd
Notes: Numeric columns are formatted as mean (SD) and median [range]. SD was not calculated for N < 3.
Age Group 1: 12 to <18 years; Age Group 2: 2 to <12 years; Age Group 3: birth to <2 years
Abbreviations: CRCL=creatinine clearance; max=maximum; min=minimum; N=number of subjects with available information; SD=standard deviation

Coadministration of CsA was the only categorical covariate retained in the model. Asian race comprised 14.8% of the per-protocol P030 population.

Age was not found to be a significant covariate on CL in paediatrics. This is explained by the high correlation of WT and age (**Figure 2**). WT already is in the model as a key covariate utilizing the standard fixed allometric exponents.

Figure 2: Correlations Between Continuous Covariates



Source: tables-report-poppk-japan-letermovir-v4.Rmd
Abbreviations: Corr=correlation; CRCL=creatinine clearance

Maturation functions (MFs) can account for the influence of potential metabolic, elimination, or disposition pathways on PK. Renal elimination was observed to influence LET PK in adults. MF was explored in the model on CL using the following equation:

$$MF = \frac{PMA^{\gamma}}{PMA^{\gamma} + TM_{50}^{\gamma}}$$

where PMA is the postmenstrual age (counted from the last menstruation of the mother) in weeks, TM 50 is the maturation half time, and γ (Hill coefficient) refers to parameters to be estimated.

Estimating the renal function failed while fixing the values to literature values did not decrease the OFV, as allometric scaling already accounted for developmental differences.

Final Model

Table 7 provides a summary overview of the key steps in the model development.

Table 4: Run Record of Key Runs for PopPK Model Development LET in Paediatric HSCT Population (Study P030)

Run	Reference Run	OFV	dOFV	Condition Number	Minimization Status	Description
9001	-	552.176	-	-	Failed	All data; prior Phase 3 HSCT PopPK model; remove covariates except for CsA on CL and F1; remove IOV; use infusion rate instead of bolus IV; add allometric scaling on Vc, Vp, CL, and Q
9002	9001	92.689	-459.00	52.10	Successful	Rich data only
9003	9002	92.689	0.00	48.30	Successful	Rich data only; drop IIV on F1
9005	9004	396.637	-633.00	-	Successful	All data; exclude outliers |CWRES| > 5 (6 observations)
9006	9005	396.636	-0.00	90.10	Successful	All data; drop IIV on Vp
9007	9006	418.402	21.80	28.50	Successful	All data; fix F1 (without CsA) to adult value (0.349)
9008	9007	420.987	2.59	20.70	Successful	All data; fix ALAG to adult value (-0.395)
9009	9008	421.005	0.02	19.80	Successful	All data; fix F1 (with CsA) to adult value (0.849)

Source: runrecord-poppk-pediatrics-letermovir-v3.Rmd
Notes: Run9009 is the final PopPK model.
Abbreviations: ALAG=absorption lag time; CL=clearance; CsA=cyclosporine A; |CWRES| > 5=absolute value of the associated conditional weighted residual is greater than 5; dOFV=difference in OFV; F1=bioavailability; HSCT=hematopoietic stem cell transplantation; IIV=interindividual variability; IOV=interoccasion variability; IV=intravenous; LET=letermovir; OFV=objective function value; PopPK=population pharmacokinetic; Q=intercompartmental clearance; Vc=central volume of distribution; Vp=peripheral volume of distribution

Initial model development resulted in a model with the lowest OFV; however, it had allometrically implausible estimates of CL (with and without CsA). It was also noted that estimates for F with and without CsA were different than those observed in adult HSCT subjects. This is not expected when considering allometric principles. The observed differences in the estimates of F with and without CsA during model development could be explained by the more sparsely sampled PK profiles in the paediatric subjects especially around time to reach maximum concentration. Therefore, estimates for F with and without CsA and lag time on absorption were fixed to adult values.

The previously developed PopPK model in adult HSCT recipients contained various categorical covariates (coadministration of CsA on F1 and CL, Asian effect on Vp, and healthy volunteer [HV] effect on F1 and Ka). However, in the more limited and sparsely sampled paediatric population, the Asian effect on Vp and the HV effect on F1 and Ka were not supported by the data. In the paediatric model, WT effect on CL, intercompartmental CL (Q), central volume of distribution (Vc) and Vp, and CsA effect on F and CL were included in the base structural model. Since BSA and WT are highly correlated, BSA effect on LET PK was not formally evaluated.

During model development, Asian race was not found to influence Vp. This is contrary to previous models in adult HSCT recipients and can be explained by the low number of Asian subjects in Study P030.

The parameter estimates for the final paediatric PopPK model are presented in **Table *8***.

Table 5. LEP popPK Model Parameter Estimates

	Run9009	OFV = 421.005			
Parameter	**Estimate**	**Bootstrap Estimate**	**RSE%**	**95% CI**	**Shrinkage**
Typical values					
Clearance without CsA (L/h)	2.88	2.87	8.30	2.41 – 3.38	
Clearance with CsA (L/h)	2.72	2.72	10.9	2.10 – 3.42	
Central Volume (L)	7.56	8.15	20.3	4.43 – 11.5	
Peripheral Volume (L)	15.1	15.8	19.4	10.6 – 30.1	
Intercompartmental Clearance (L/h)	1.69	1.62	18.9	1.01 – 2.71	
Absorption lag (h)	0.674 Fixed	0.674	n/a	0.674 – 0.674	
Absorption rate (1/h)	0.210	0.220	30.6	0.118 – 0.582	
Bioavailability without CsA	0.346 Fixed	0.346	n/a	0.346 – 0.346	
Bioavailability with CsA	0.849 Fixed	0.849	n/a	0.849 – 0.849	
Covariate effects					
Allometric scaling CL and Q	0.750 Fixed	0.75	n/a	0.750 – 0.750	
Allometric scaling Vc and Vp	1.00 Fixed	1	n/a	1.00 – 1.00	
Between-subject variability (variance)					
On clearance	0.132	0.121	25.8	0.0586 – 0.203	17.5%
On absorption rate	1.78	1.85	35.4	0.774 – 4.56	35.8%
Residual error (variance)					6.60%
Residual exponential error	0.690	0.669	9.38	0.449 – 0.805	
Residual additive error	176	191	33.8	52.2 – 439	

Source: prm-table-poppk-pediatrics-letermovir-v4.Rmd

Notes: F1 with and without the CsA covariate effect was fixed to parameters based on adult HSCT model estimates, and CL with and without the CsA covariate effect was estimated based on pediatric data. Bootstraps were run for the model (run9009), and all the 1000 runs minimized successfully. The condition number was 19.80. The CsA coadministration covariate effect on bioavailability and clearance captures both the drug-drug-interaction of CsA on clearance and bioavailability and the dose nonlinearity between 240 and 480 mg LET. Standard allometric scaling was applied for CL, Q, Vc, and Vp with scalars of 0.75, 0.75, 1, and 1, respectively, with a median weight of 32.4 kg.

Abbreviations: RSE%=percentage of the relative standard error; CI=confidence interval (bootstrap based); CL=clearance; CsA=cyclosporin A; F1=bioavailability; HSCT=hematopoietic stem cell transplantation; LET=letermovir; n/a=not applicable; OFV=objective function value; PopPK=population pharmacokinetic; Q=intercompartmental clearance; Vc=central volume of distribution; Vp=peripheral volume of distribution

Previously, in adult HSCT recipients, IIV was supported on CL, F, Vp, and Ka (17%, 24.5%, 36.7%, and 41.4%, respectively), whereas in paediatric HSCT recipients, only IIV on CL and Ka could be estimated. This is likely explained by the more sparsely sampled PK profiles in paediatric subjects compared to adult subjects. The adult HSCT model also included IOV (15.9%) on F.

The 2-compartmental PopPK model with linear absorption, lag time, standard allometry, and CsA effects on CL and F showed good performance in the pcVPC for P030. Parameter estimates were found to be robust as indicated by the 95% CI from bootstrap runs. The standard WT-based allometry strongly correlated with age, and therefore, including age was not found to be significant. Maturation function was tested but not included in the final model.

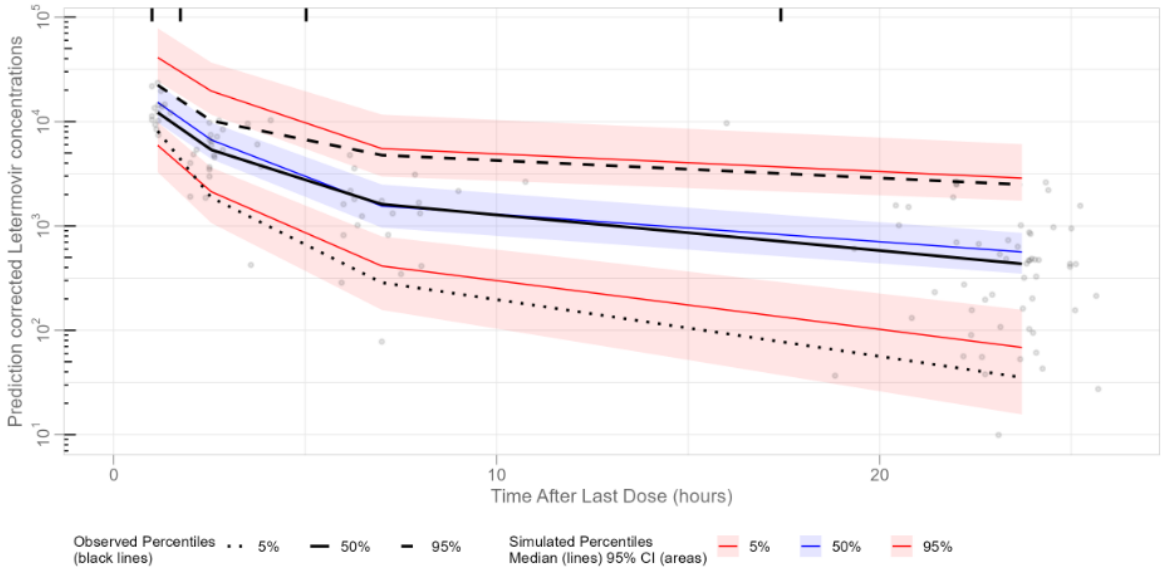
The youngest and lightest dosing group (age 0 to <2 years and WT 2.5 to <5 kg, receiving 20 mg PO with CsA) was a group without observed data, and therefore, their exposure prediction is fully model extrapolated.

Model evaluation

PcVPCs for the paediatric HSCT PopPK model stratified by formulations are shown in Figure 3 and Figure 4. The final paediatric PopPK model was able to predict the observed median, p5, and p95 of observed LET concentrations with adequate accuracy in Study P030, albeit that in some of the dose groups, only limited observed data were available to conclude this. The median concentration was well captured throughout the profiles except for the absorption phase. Observed p5 and p95 were inside the predicted bands over the time course and was predicted. The corresponding pcVPCs by Age Group can be in

Figure 5 and **Figure *6***.

Figure 3: pcVPC for IV PK Profile

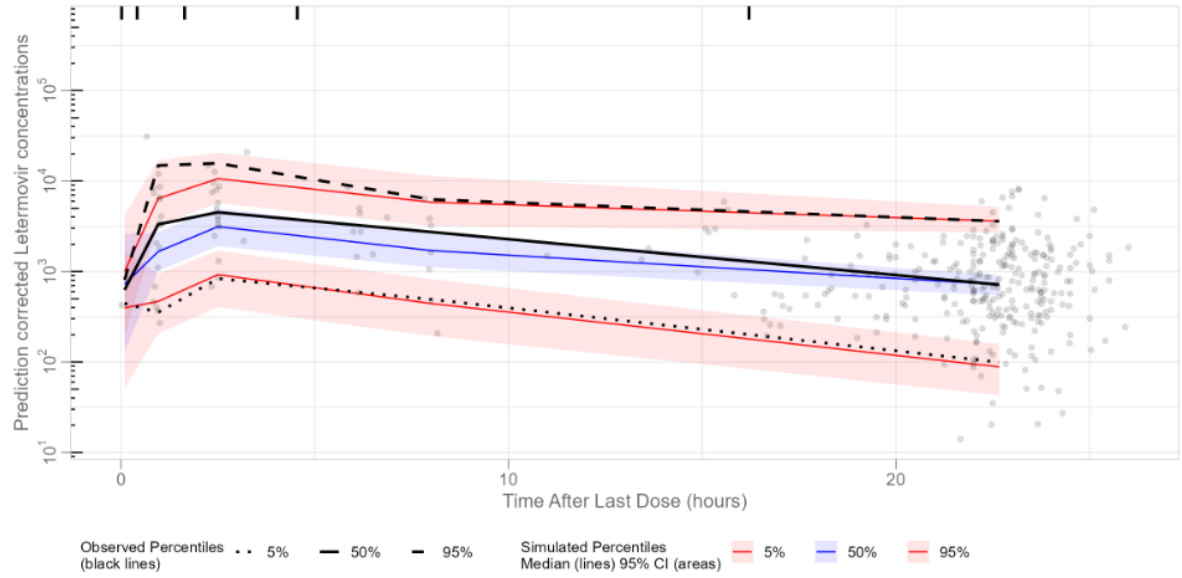


Source: vpc-poppk-final-model-pediatrics-letermovir-v3.Rmd

Notes: The panel shows the pcVPC for the PopPK model. 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. The blue solid line is the median of the simulated medians. The pink areas are the 95% PI of the simulated p5 and p95. The solid red lines are the medians of the simulated p5 and p95 respectively.

Abbreviations: CI=confidence interval; IV=intravenous; p5=5th percentile; p95=95th percentile; pcVPC=prediction-corrected visual predictive check; PI=prediction interval; PK=pharmacokinetic; PopPK=population pharmacokinetic

Figure 4: pcVPC for PO PK Profile

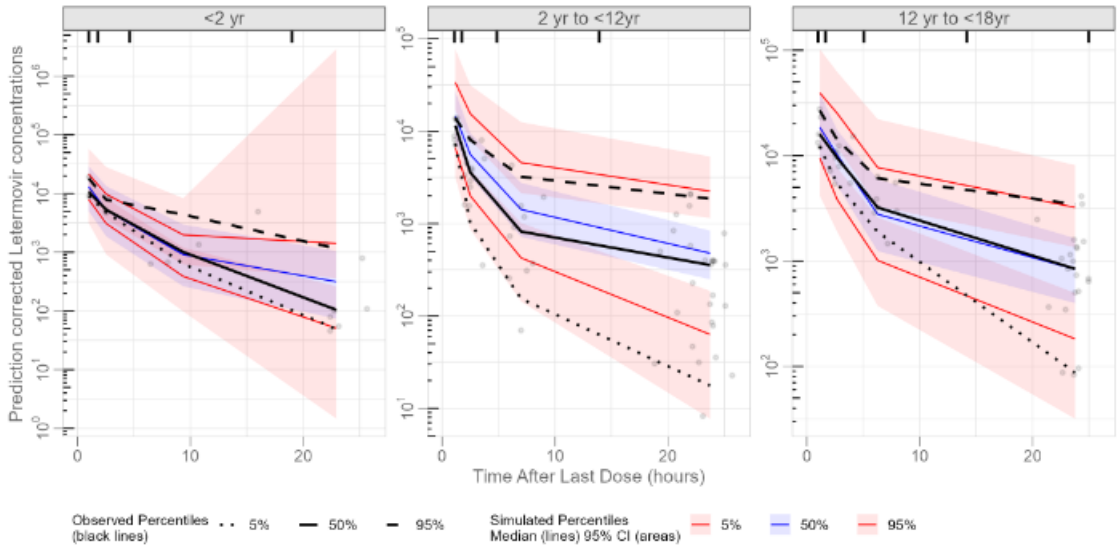


Source: vpc-poppk-final-model-pediatrics-letermovir-v3.Rmd

Notes: The panel shows the pcVPC for the PopPK model. 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. The blue solid line is the median of the simulated medians. The pink areas are the 95% PI of the simulated p5 and p95. The solid red lines are the medians of the simulated p5 and p95 respectively.

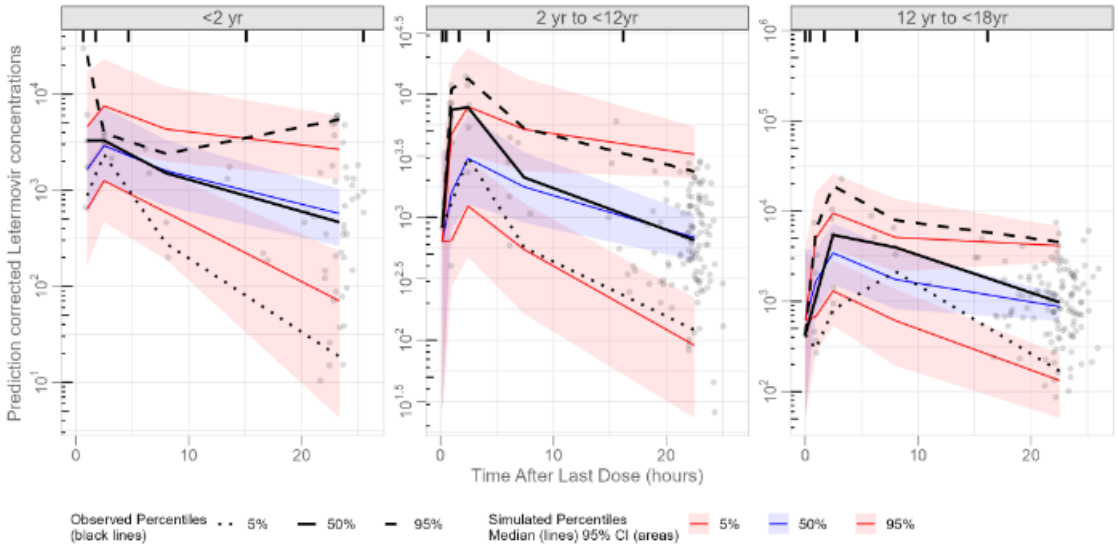
Abbreviations: CI=confidence interval; p5=5th percentile; p95=95th percentile; pcVPC=prediction-corrected visual predictive check; PI=prediction interval; PK=pharmacokinetic; PO=oral

Figure 5. pcVPC on Log Scale: IV stratified on age



Source: vpc-poppk-final-model-pediatrics-letermovir-v3.Rmd
Notes: 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. The blue solid line is the median of the simulated medians. The pink areas are the 95% PI of the simulated p5 and p95. The solid red lines are the medians of the simulated p5 and p95 respectively.
Abbreviations: CI=confidence interval; IV=intravenous; p5=5th percentile; p95=95th percentile; pcVPC=prediction-corrected visual predictive check; PI=prediction interval; yr=year

Figure 6: pcVPC on Log Scale: PO stratified on age



Source: vpc-poppk-final-model-pediatrics-letermovir-v3.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. The blue solid line is the median of the simulated medians. The pink areas are the 95% PI of the simulated p5 and p95. The solid red lines are the medians of the simulated p5 and p95 respectively.
Abbreviations: CI=confidence interval; p5=5th percentile; p95=95th percentile; pcVPC=prediction-corrected visual predictive check; PI=prediction interval; PO=oral; yr=year

Suitability of the final PopPK model was assessed based on goodness-of-fit (GOF) plots, prediction corrected visual predictive checks (pcVPCs), and bootstrap results. The GOF plots of the model show

no appreciable bias. The 2-compartmental PopPK model with linear absorption, lag time, standard allometry, and CsA effects on CL and F showed good performance in the pcVPC for P030. Parameter estimates were found to be robust as indicated by the 95% CI from bootstrap runs. The model was similar in structure to the adult HSCT recipients' model albeit simplified in its statistical model (only IIV on CL and Ka) and included fewer covariates (CsA coadministration and WT).

Absorption

For formulation A of the oral granule formulation (similar to the commercial formulation), t_{max} (median, range) was 1.5 (1.0-3.5) in healthy adult subjects (study P031).

Study MK-8228-031 (P031)

This was a single-center, open-label, single-dose, 4-period, seven-treatment, crossover study in 24 healthy adult female participants designed to evaluate the bioavailability of 2 pediatric oral granule formulations of LET administered alone or in soft food (applesauce and vanilla pudding) compared to the currently approved tablet formulation. Two oral granules formulations were used, formulation A and formulation B . The dose administered in each period was 240 mg. Granules were given either with water or mixed with a small amount (60 g) of soft food. Subjects fasted for at least 10 hours prior to administration of each treatment and then until at least 4 hours post-dose. Blood samples for PK analyses of letermovir were collected pre-dose and up to 72 hours post-dose. The wash-out between treatment administrations was 7 days.

Results are presented in Table 9. Both oral granules formulations had results for C_{max} and AUC_{inf} that were within conventional BE criteria compared to the approved tablet formulation in the fasted state. Formulation A was selected to be used in study P030 following evaluation of the PK profiles and manufacturing considerations of this formulation.

Formulation A mixed with applesauce resulted in a 20% mean increase in LET AUC and 33% mean increase in C_{max}, while when mixed with vanilla pudding resulted in a 13% mean increase in AUC (but 90% CI were within BE acceptance criteria) and 25% mean increase in C_{max}. The MAH concludes that this effect is not clinically relevant.

Table 6: Summary of the Geometric Mean Ratios and 90% CI for LET Plasma PK of AUC0-inf and Cmax Following Administration of a Single Oral Dose of 240¬mg (2x120 mg) LET Coated Granule Formulations A or B administered alone compared With 240 mg Tablet, and granules administered in applesauce, or in vanilla pudding, compared to alone, in Healthy Adult Participants

	GMR and 90% CI	
Oral Granule Comparisons	**AUC0-inf[a]**	**Cmax[a]**
Granules (2 x 120 mg) (n=24) vs Tablet (240 mg) fasting (n=23)		
LET Granules (Formulation A) /LET Tablet	1.00 (0.95, 1.06)	1.05 (0.97, 1.14)
LET Granules (Formulation B) /LET Tablet	0.97 (0.90, 1.03)	0.94 (0.86, 1.04)
Granules (2 x 120 mg) mixed with soft food (n=6) vs Granules alone (2 x 120 mg) (n=24)		
LET Granules (Formulation A) in vanilla pudding/ LET Granules (Formulation A)	1.13 (1.04, 1.22)	1.25 (1.13, 1.39)
LET Granules (Formulation A) (in applesauce)/ LET Granules (Formulation A)	1.20 (1.00, 1.43)	1.33 (1.09, 1.63)
LET Granules in vanilla pudding (Formulation B) / LET Granules (Formulation B)	1.15 (1.04, 1.28)	1.42 (1.26, 1.61)
LET Granules in applesauce (Formulation B)/LET Granules (Formulation B)	1.10 (0.99, 1.23)	1.15 (1.01, 1.31)
AUC0-inf=area under the curve from time 0 to infinity; CI=confidence interval; Cmax=maximum concentration; GMR=least-squares geometric mean ratio between treatments; LET=letermovir; n=number of participants in a subset of the study; PK=pharmacokinetic(s). [a] Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.		

Source: Adapted from [Ref. 5.3.1.2: P031MK8228]

For the approved tablet formulation, it has previously been demonstrated that there is a small effect of concomitant food intake (standard high-fat break-fast) on C_{max} (30% increase) but not on AUC under single-dose conditions in healthy volunteers. The effect is not likely to be clinically relevant and letermovir was administered regardless of food intake in the phase III studies, supporting the SmPC recommendation that the tablets may be taken with or without food.

Distribution

No new data provided.

Elimination

No new data provided.

Dose proportionality and time dependencies

No new data provided.

Intra- and inter-individual variability

According to the population PK analysis in KT patients, inter-individual variability (IIV) was estimated to 25 and 37% for clearance and bioavailability, respectively, while inter-occasion variability (IOV) on bioavailability was estimated to 44%. Previously, in adult HSCT recipients, IIV was supported on CL, F, Vp, and Ka (17%, 24.5%, 36.7%, and 41.4%, respectively), whereas in paediatric HSCT recipients, only IIV on CL and Ka could be estimated (18% and 36 % respectively).

Pharmacokinetics in the target population

Study P030

Study P030 was an open-label, single-arm study to evaluate PK, efficacy, safety and tolerability of LET in paediatric participants from birth to less than 18 years of age at risk of developing CMV infection and/or disease following allogeneic HSCT. The study enrolled participants in 3 age groups:

- Age Group 1: From 12 to <18 years of age (adolescents)
- Age Group 2: From 2 to <12 years of age (children)
- Age Group 3: From birth to <2 years of age (neonates, infants, and toddlers)

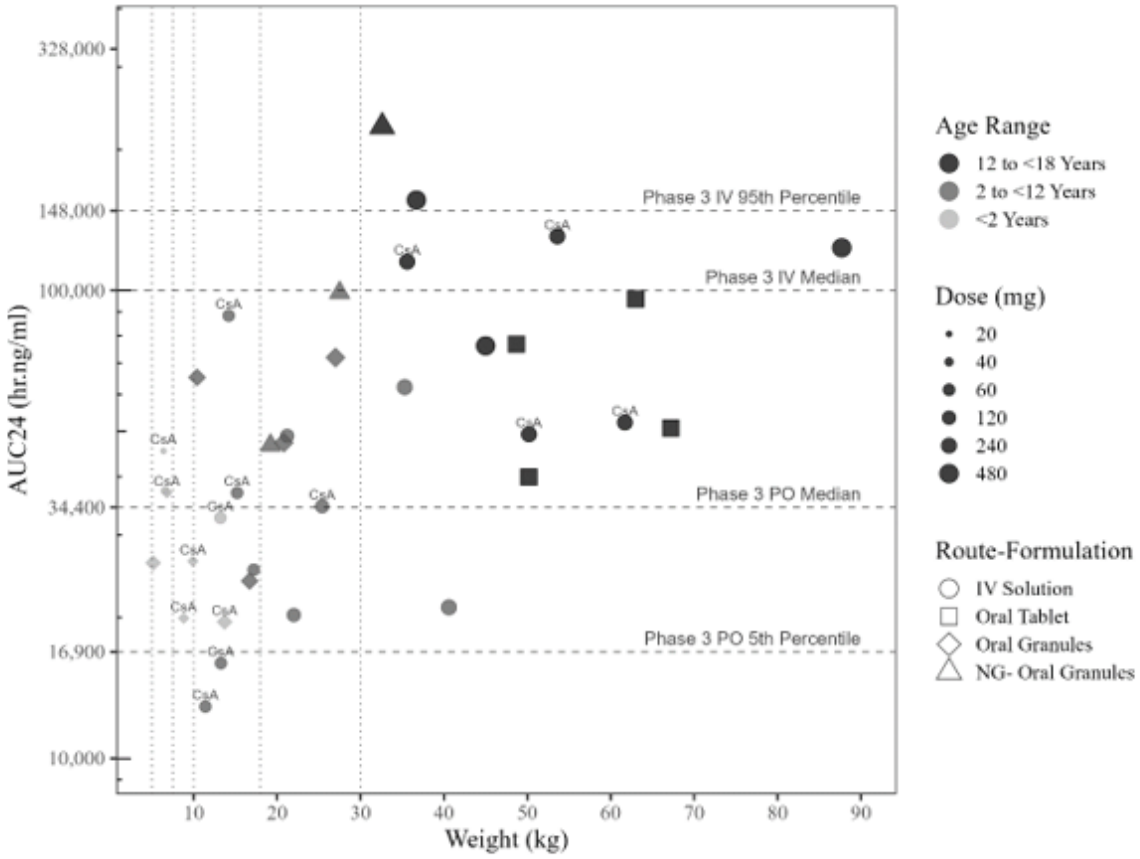
For Age Groups 1 and 2, PK for the first 6 participants (Panel A) was evaluated to confirm dosing before enrolling other participants in the groups (Panel B). For Age Group 3, PK for the first 3 participants was evaluated to confirm or modify dosing, before enrolling the other 5 participants in the group. Participants were to receive LET (oral or IV formulation) from the day of enrollment (Day 1) through Week 14 (~ 100 days) post-transplant. All Panel A participants in Age Groups 1 and 2 were to receive oral LET with no concomitant CsA from Day 1 through Day 7 for intensive PK sampling.

No dose adjustments were made for age groups 1 and 2 based on interim analysis of the first 6 participants (All Panel A participants in Age Group 1 and 2 received oral LET with no concomitant CsA from Day 1 to Day 7 during intensive PK sampling). For age group 3 the LET AUC0-24 from the first 3 participants was compared with the adult reference exposure at the interim analysis and the LET dose was then increased for the remaining 5 participants in Age Group 3.

In age group 1, the approved table formulation was used (preferably) and the oral granules could be used in case of difficulties in swallowing tablets. In age groups 2 and 3, the only oral formulation used was the oral granules. The IV formulation was available for all age groups, in case oral administration was not possible.

A graphical comparison to the target adult reference exposure is provided in **Figure 7**.

Figure 7: Plasma AUC0-24 of LET for Age Groups 1, 2, and 3 Following Once Daily Oral or Intravenous Administration of LET to Pediatric HSCT Recipients; Compared to HSCT Adult Reference Values Following oral or IV LET 480 mg (n=36)



AUC0-24=area under the concentration-time curve for the dosing interval (0 to 24 hours); CsA=cyclosporin.A; HSCT=hematopoietic stem cell transplantation; IV=intravenous; LET=letermovir; n=number of participants in a subset of the study population; NG=nasogastric; Oral=by mouth.
CsA above the symbol indicates CsA was coadministered with the LET dose. Vertical dotted lines show the dosing weight band boundaries for 2 to <12 years (Age Group 2) and <2 years (Age Group 3) (there are no dosing weight boundaries for 12 to <18 years [Age Group 1]).
Source: [Ref. 5.3.5.2: P030V01MK8228: 11]

popPK simulated exposures in paediatric HSCT subjects

Simulations of LET using Monte Carlo simulations to compare paediatric exposure from the paediatric HSCT dosing groups used in Study P030 to the reference range from adult HSCT recipients were conducted. Monte Carlo simulations assuming each age/WT dose regimen of Study P030 and other proposed dosing regimens were used to generate 1000 concentration-time profiles and their derived exposure measures by sampling CL values from the CL-ETA parameter distribution (only IIV term in the paediatric model) and combined with relevant covariates from the NHANES database. Simulations did not include uncertainty on parameters.

LET exposure in paediatric subjects younger than 12 years of age and weighing ≥30 kg corresponding to adult IV dose (480 mg without CsA) were also evaluated. The results are summarised in **Table 10** for PO and **Table 11** for IV dosing. In addition, boxplots are provided in **Figure *8*** and **Figure *9***.

Table 7: popPK derived LET exposure following oral administration, revised weight bands.

Body weight	Oral dose, no cyclosporine	Median (90% prediction interval)*	Oral dose, with cyclosporine	Median (90% prediction interval)*
30 kg and above	480 mg	39,100 (18,700-81,300)	240 mg	49,100 (23,200-104,000)
15 kg to less than 30 kg	240 mg	38,900 (20,200-74,300)	120 mg	51,000 (26,600-98,200)
7.5 kg to less than 15 kg	120 mg	32,000 (16,700-59,300)	60 mg	41,600 (22,300-81,100)
5 kg to less than 7.5 kg	80 mg	30,600 (16,200-55,000)	40 mg	39,000 (20,600-72,000)
* Medians and 90% prediction intervals are based on simulations using the paediatric HSCT population PK model with inter-individual variability.				

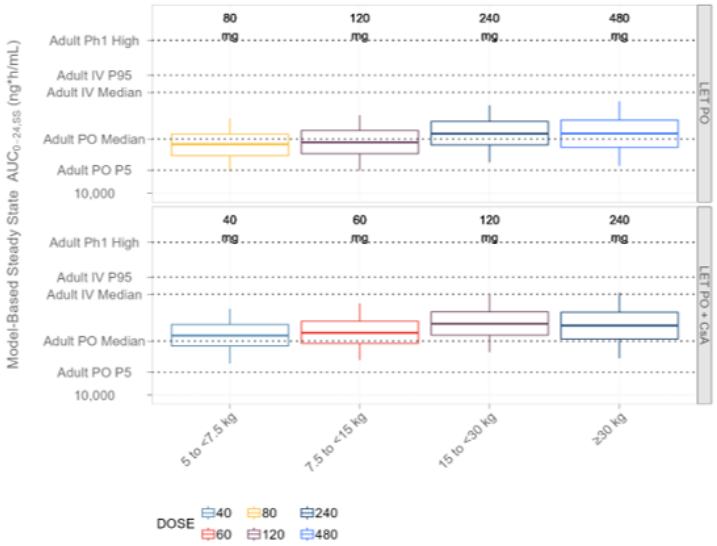
Table 8: popPK derived LET exposure following IV administration, revised weight bands.

Body weight	Intravenous dose, no cyclosporine	Median (90% prediction interval)*	Intravenous dose, with cyclosporine	Median (90% prediction interval)*
30 kg and above	480 mg	111,000 (55,700-218,000)	240 mg	59,800 (28,400-120,000)
15 kg to less than 30 kg	120 mg	57,200 (29,700-113,000)	120 mg	61,100 (29,900-121,000)
7.5 kg to less than 15 kg	60 mg	46,000 (24,300-83,900)	60 mg	49,200 (25,800-93,800)
5 kg to less than 7.5 kg	40 mg	43,400 (24,300-81,000)	40 mg	45,900 (24,900-82,200)
* Medians and 90% prediction intervals are based on simulations using the paediatric HSCT population PK model with inter-individual variability.				

Figure 8: Boxplots simulated AUC, PO administration

Figure 3-1

Model-Predicted Steady State AUC0-24 (ng•hr/mL) Values of Oral LET With and Without CsA in Pediatric HSCT Recipients From Birth to <18 Years of age (Revised Pediatric Weight Bands)



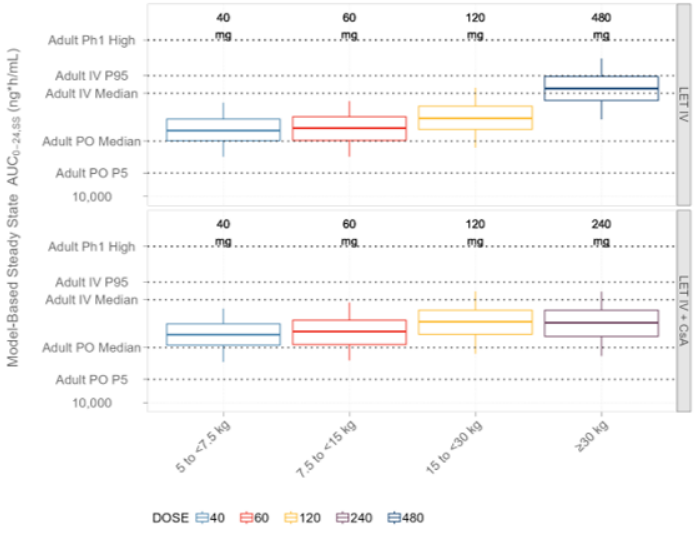
AUC0-24=area under the concentration-time curve for the dosing interval (0 to 24 hours); CsA=cyclosporin.A; HSCT=hematopoietic stem cell transplantation; IV=intravenous; LET=letermovir; PO=by mouth.

A

Figure 9: Boxplots simulated AUC, IV administration

Figure 3-2

Model-Predicted Steady State AUC0-24 (ng•hr/mL) Values of IV LET With and Without CsA in Pediatric HSCT Recipients From Birth to <18 Years of age (Revised Pediatric Weight Bands)



AUC0-24=area under the concentration-time curve for the dosing interval (0 to 24 hours); CsA=cyclosporin.A; HSCT=hematopoietic stem cell transplantation; IV=intravenous; LET=letermovir; PO=by mouth.

The simulated exposures, based upon the final paediatric HSCT PopPK model, support dose recommendations irrespective of weight for patients aged 12 years and older and weight- band dosing

for patients younger than 12 years. The weight-band dosing for patients younger than 12 years of age is largely consistent with the doses evaluated in P030 with the addition of combining some weight bands across age.

Therapeutic window

The initial dose selections used in P030 and the proposed dose recommendation for paediatric HSCT recipients were based on achieving PK exposures in the paediatric population similar to those characterised in adult HSCT recipients; these exposures are expected to result in comparable efficacy and safety in both populations. In adult HSCT recipients the results indicated that the entire range of exposures achieved with LET 480 mg QD, adjusted to 240-mg QD LET with CsA, are efficacious. The pathogenesis of CMV infection (viremia) and disease, and the mechanism of action of LET, are not anticipated to differ in paediatric patients compared to adults. Therefore, the LET PK exposure targets for the paediatric HSCT recipients were the steady state AUC0-24 in adults following oral and IV LET 480 mg (without CsA), respectively. The target adult reference exposure range is 16,900 to 148,000 ng•hr/mL.

Special populations

Based on the initial marketing application for the adult HSCT indication, age, gender, race, and body weight did not have a clinically significant effect on the PK of LET. For the subsequent marketing application for adult KT indication, the covariate intrinsic factors evaluated using PopPK analysis were CrCl post-transplantation and body weight. Based on KT PopPK analysis, there were small increases in LET AUC depending on the degree of renal impairment that was not considered clinically significant. In addition, body weight in the KT recipient population did not have an impact on LET PK.

Since the paediatric study, P030, had 61 participants in which sampling was relatively sparse, no formal full covariate (intrinsic factors) evaluation was conducted. Key covariates previously found to influence LET exposure (healthy adult, adult HSCT and KT recipients) were tested and included in the paediatric HSCT PopPK model and were supported by the data from the P030 study.

The covariate (intrinsic factor) evaluated in the paediatric HSCT PopPK analysis was body weight. The weight-band dosing achieved with the paediatric HSCT PopPK model accounted for the intrinsic factor of body weight. Age, race (Asian)/ethnicity, renal maturation function, and baseline renal function (eGFR and CrCL) were also investigated as potential covariates within the paediatric HSCT PopPK model, but no trends were identified in the paediatric data.

Pharmacokinetic interaction studies

No new in vitro or in vivo DDI studies have been conducted for the paediatric extension of indications. The LET exposures following oral LET in paediatric HSCT recipients are comparable to the exposures that were used to assess the in vitro DDI potential of LET in the initial marketing application. Therefore, the initial DDI assessment remains unchanged in relation to the LET exposure in the paediatric HSCT and KT population.

LET is an OATP1B1/3 substrate, and LET exposure is increased 2- to 3-fold when concomitantly administered with CsA in adults. Information on the ontology of the OATP1B1/3 transporters from birth to <18 years is limited. In the PopPK analysis, the same DDI effect size on LET, due to OATP1B inhibition by CsA, was used for all age groups.

There are no changes to the DDI profile of LET for the paediatric indication.

Pharmacokinetics using human biomaterials

See section above on Pharmacokinetic interaction studies.

2.5.2.2. Pharmacodynamics

There are no new pharmacodynamics data. For clinical virus resistance data see Ancillary analyses under Clinical efficacy.

2.5.3. Discussion on clinical pharmacology

Study MK-8228-030 (P030) was a Phase 2b open label, multicentre, single arm study in paediatric recipients of an allogeneic HSCT. The primary endpoint was pharmacokinetics. The MAH has provided popPK report 08HCCH Population Pharmacokinetic Analysis of MK-8228 in Paediatric Hematopoietic Stem Cell Transplant Recipients with this submission.

Methods

Bioanalytical methods

The bioanalytical methods used for determination of letermovir in plasma were adequately validated and the performance of the analytical methods was satisfactory.

popPK model – paediatric HSCT recipient patients

The VPCs generally support the adequacy of the model but some model misspecifications can be detected, and the variability is not that well predicted. Around the C_{trough}, where most data points have been collected, the model generally predicts the data well. Cmax is not as well characterised, likely due to sparse data available. Based on adult safety data for higher doses and exposure than for the approved dosing, there is no apparent concern with regards to C_{max}. Therefore, it is not considered a major problem that the paediatric model may not describe C_{max} well. AUC is considered satisfactory described and looking at both AUC and C_{trough} can inform on the adequacy of the dosing paediatric HSCT subjects.

The MAH tested maturation function on clearance, but this did not improve the model. The maturation function would increase simulated exposure is the younger subjects. Here, we are mainly worried about a potential lack of efficacy. In adults, doses leading to a 3.2 fold increase in exposure have been studied, without additional safety concerns identified, which support that a slightly higher exposure than for the approved adult dosing is not a major concern.

The popPK model is considered adequate for paediatric HSCT recipient subjects. However, using this model for paediatric KT patients (with no PK data from paediatric KT patients), considering the observed differences in PK between adult HSCT and KT patients, is not agreed with. The MAH proposed that this difference is due to a different bioavailability, however PK data after IV administration for kidney transplant subjects was too sparse to support that it was bioavailability that was different, and it is not known if other parameters such as clearance contribute to the difference in PK.

Studying PK in HSCT paediatric patients follows the PIP for Prevymis (EMEA-001631-PIP01-14-M04). However, due to the finding in adult KT patients regarding difference in PK between HSCT and KT adults (EMEA/H/C/004536/II/0033/G), additional PK data in paediatric KT patients would be needed to be able to select the appropriate dose in paediatric KT patients below 40 kg, and thus support an indication. The adult KT model could be used for paediatric subjects weighing at least 40 kg (body weight range considered covered by the adult indication). The MAH has stated that they have plans to conduct a study in KT children below 40 kg, this plan is fully supported.

Regarding CsA in the model. An effect on clearance was found in HSCT adults but not in paediatric subjects, likely due to the sparse data in paediatric dataset. The proposed dosing in children below 30

kg is the same after IV administration regardless of CsA co-administration, while the dose in different in adults. The MAH conducted a sensitivity analysis. LET clearance with CsA was fixed to 0.7X LET clearance without CsA (the ratio difference estimated in adult HSCT recipients). The Letermovir clearance without CsA was estimated at 3.35 L/hr in the sensitivity analysis model, which is ~16% higher than LET clearance without CsA estimated from the final paediatric model. The simulated AUC for the sensitivity analysis are similar to the LET exposures in adult HSCT recipients following 240 mg with CsA, and thus within the target exposure range. The analysis provides some reassurance that the same IV dose with and without CsA in children, provide adequate exposure.

Absorption

The relative BA study (study P031) was generally performed in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), but some deviations are discussed below. The comparison of granules to tablets was performed in the fasted state, which is acceptable as the tablets can be taken with or without food. The study was performed at a dose of 240 mg (240 mg tablets vs 2x120 mg capsules). As letermovir has non-linear PK with more than dose-proportional increase in exposure with increasing dose (likely due to saturation/autoinhibition of OATP1B1/3), the general recommendation according to the Guideline on the investigation of bioequivalence would be to perform the study with the highest strength. For the granules there is no higher strength than 120 mg but for the tablets the highest strength is 480 mg and this is also the highest recommended dose for the granules. Thus, using a dose of 480 mg would have been preferable, but considering the convincing results at the 240 mg dose it is not considered likely that the results at a higher dose would be significantly different.

In the study, the results for both AUC_{inf} and C_{max} of both granules formulations (A and B) given without soft food were within conventional BE criteria compared to the approved tablet. According to the Guideline on the investigation of bioequivalence, AUC_{0-t} should be the primary PK parameter instead of AUC_{inf} as in the current study (90% CI for AUC_{0-t} not reported). However, the results in the comparison of both granules to the tablet formulation are very well within BE acceptance criteria for AUC_{inf} and it is not considered likely that the results for AUC_{0-t} would be significantly different. Thus, no concern is raised.

Formulation A was chosen for further development. The commercial formulation is very similar to formulation A in the current study, differing only in colour (beige instead of white) and primary packaging (sachets instead of capsules). The granules were taken out from the capsule before administration in the study, just as the commercial granules will be removed from sachets before administration.

The results of the study thus support interchangeability between tablets and oral granules when granules are given without soft food. Administration with a small amount of soft food increased the rate and extent of exposure as further discussed below, but this increase is not considered clinically relevant. The commercial formulation is available in an additional strength of 20 mg which was not included in this study (or in study P030); however, this additional strength contains the same granules only in a lower amount. It is sufficient to study the highest strength.

The tablets can be taken with or without food. For the oral granules, the proposed recommendation is to administer the granules orally mixed with a small amount (1-3 teaspoons) of soft food or mixed with milk, apple juice, formula or water and given via nasogastric or gastric tube. In the paediatric study (study P030), when letermovir was administered as the granule formulation, granules were either given with soft food or as a suspension using G tube/NG tube.

According to the results of study P031, both AUC and C_{max} increased following administration of granules with soft food, especially when given with apple sauce. There was a 20% increase in AUC and

33% increase in C_{max} when mixed with apple sauce compared to administration without soft food. When mixed with vanilla pudding, the point estimate was a 13% increase in AUC (but 90% CI were within BE acceptance criteria) and there was a 25% increase in C_{max} compared to administration without soft food. It is noted that this appears to be a slightly larger effect than that seen on the tablet formulation following administration with a high-fat meal, which was a 30% increase in C_{max} but no effect on AUC (point estimate close to unity, 90% CI within BE acceptance criteria). However, it is agreed that this increase in exposure is not considered clinically relevant and this way of administration is also in line with the use in the paediatric study P030. It is also stated in the SmPC that additional food can be consumed following administration, which is in line with the recommendation for the tablet and acceptable.

For a paediatric patient taking the granules dispersed in soft food (as they were also taken in study P030) and then switching to the tablet formulation, this would instead mean a decrease in exposure. However, for the patient groups where this could be applicable (i.e. children above 15 kg considering that the lowest tablet strength is 240 mg) this decrease in exposure is not considered clinically relevant.

Distribution

No new data on distribution is needed for this application.

Elimination

No new data on elimination is needed for this application.

Dose proportionality and time dependencies

No new data on dose-proportionality and time-dependency is needed for this application.

Therapeutic window / target exposure

PK in adult HSCT and KT patients were different (higher exposure in KT) in adults. The MAH developed separate adult models for HSCT and KT adults and the difference was described by a different bioavailability. In the adult type II variation to extend the indication to adult KT subjects a question was raised. The MAH claimed that biological factors contribute to lower exposures in HSCT recipients which include gastrointestinal mucosal injury induced by chemotherapy and/or radiation therapy and the presence/absence of graft versus host disease. In the end, the issue was not pursued but it was noted in the EPAR that while the MAH maintained the difference was due to different F, it cannot be ruled out that other parameter such as clearance may be affected. The mechanism for the PK difference seen is not understood.

For adults, while LET dosing is the same for HSCT and KT, the resulting exposure is higher for KT patients due to differences in PK. Since the PK/PD relation may differ between HSCT and KT (e.g. due to a higher viral load in the latter case which constitutes a primary infection), the target exposure range for KT is determined by what was actually reached in the relevant adult study. The adult exposure range must be matched for paediatric KT patients, as the efficacy of lower exposures in KT has not been established.

Regarding the upper bound of the therapeutic window correlating to safety, using the highest exposure seen in adults' patients for the approved dosing is considered appropriate for both indications. Also, in adult healthy volunteers, higher doses than the approved dosing have been tested with up to 3.2-fold higher exposure compared to approved dosing, without additional safety concerns. Therefore, slightly higher exposure than from the approved adult dosing may not be a huge concern, but too low exposure would risk lack of efficacy, which is considered problematical.

PK in target population (paediatric patients)

The MAH has simulated exposures in paediatric subjects, divided into different weight cohorts, using the paediatric HSCT popPK model.

The MAH had discussed that AUC correlates well to efficacy, especially considering that this is for prevention. This appears reasonable. The exposure (AUC) generally matches adult exposure well, however for the lower weight group, following oral administration, the simulations suggest slight under exposure compared to adults.

Underexposure would risk lack of efficacy and thus it may be favourable to increase the oral dosing in HSCT subject weighing 2,5-5 kg (no CsA). Underdosing (too low exposure) is problematic but slight over exposure may not be a big issue. Considering this, the lack of data in the lowest body weight, the MAH decided not to pursue an indication below 5 kg.

Special populations

WT was considered an essential covariate effect in the paediatric population and was included in the structural model. WT was implemented as a time-changing variable. Standard allometric scaling was applied for CL, Q, Vc, and Vp with scalars of 0.75, 0.75, 1, and 1, respectively.

No formal full covariate evaluation was conducted but key covariates previously found to influence LET exposure (healthy adult, adult HSCT and KT recipients) were tested and included in the paediatric HSCT PopPK model.

The paediatric dataset, with 61 subjects, does not include sufficient information on some of the covariates included in the adult models. Thus, the strategy for analysing covariates in paediatric patients is considered acceptable (see also subheading Pharmacokinetics in target population).

Interactions

It is agreed that there are no changes to the DDI profile of LET for the paediatric indication

2.5.4. Conclusions on clinical pharmacology

The new oral granules formulation has been sufficiently characterised from a pharmacokinetic perspective. A formulation very similar to the commercial formulation demonstrated similar rate and extent of exposure (results within BE acceptance criteria for AUCinf and Cmax) when comparing granules given without soft food to the approved tablet formulation. There was a slight increase in rate and extent of exposure when administering the granules with soft food, but this increase is not considered clinically relevant.

For adults, LET dosing is the same for HSCT and KT patients, the resulting exposure is higher for KT patients due to differences in PK. Since the PK/PD relation may differ between HSCT and KT (e.g. due to a higher viral load in the latter case which constitutes a primary infection), the target exposure range for KT is determined by what was actually reached in the relevant adult study. The adult exposure range must be matched for paediatric KT patients, as the efficacy of lower exposures in KT has not been established.

Regarding the indication in allogeneic haematopoietic stem cell transplant paediatric patients the indication down to 5 kg is supported.

Regarding the indication in kidney transplant patients, the indication for paediatric patients weighing at least 40 kg, which are covered by the adult body weight range, is supported.

2.5.5. Clinical efficacy

2.5.5.1. Main study

MK 8228-030: A Phase 2b open-label, single-arm study to evaluate pharmacokinetics, efficacy, safety and tolerability of letermovir in paediatric participants from birth to less than 18 years of age at risk of developing CMV infection and/or disease following allogeneic haematopoietic stem cell transplantation (HSCT)

This is a Phase 2b, open-label, single-arm study to evaluate PK, efficacy, safety, and tolerability of LET when used for CMV prophylaxis in paediatric participants from birth to <18 years of age who are at risk of developing CS-CMVi following an allogeneic hematopoietic stem cell transplant (HSCT).

Clinically significant CMV infection is defined as the occurrence of either one of the following outcomes:

- onset of CMV end-organ disease,

  and/or

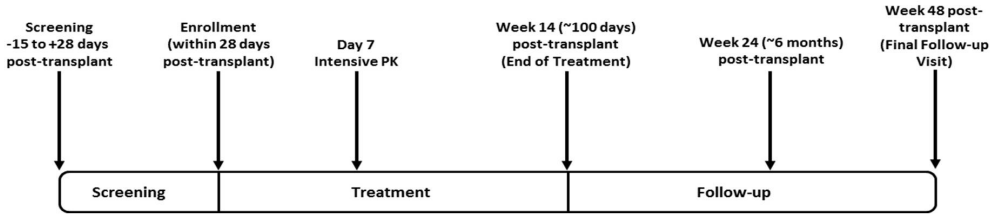
- initiation of anti-CMV PET based on documented CMV viremia and the clinical condition of the participant.

Approximately 60 HSCT recipients will be enrolled in this study. Only R+ participants will be enrolled in the oldest age group (Age Group 1, see below). CMV seroprevalence decreases with decreasing age. Therefore, enrolment criteria for Age Groups 2 and 3 were broadened to include participants with any risk for CMV reactivation (i.e., R+ and/or D+).

The primary endpoint was to evaluate letermovir pharmacokinetics in paediatric patients.

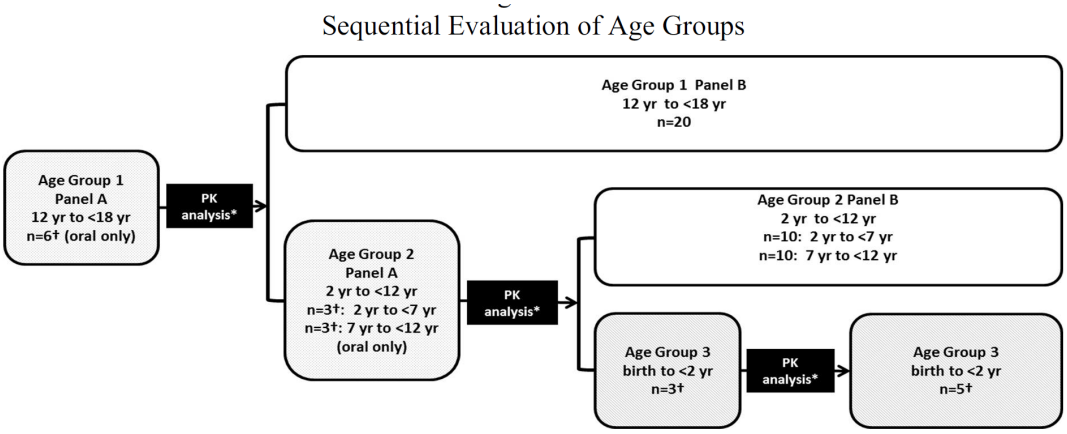
Efficacy was a secondary endpoint, i.e., percent of participants with clinically significant CMV infection (CS- CMVi, defined as initiation of preemptive therapy [PET] for documented CMV viremia and/or CMV disease) through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant.

Figure 10: Study schema



PK=pharmacokinetics.

Figure 11: Study evaluation schema



PK=pharmacokinetics; yr=year.

† n represents number of PK-evaluable participants.

*PK analysis will occur at 3 intervals: when all evaluable participants have completed intensive PK in Age Group 1 Panel A, when all evaluable participants have completed intensive PK in Age Group 2 Panel A, and when the first 3 evaluable participants have completed intensive PK in Age Group 3.

Methods

- **Study Participants**

Inclusion Criteria

Eligible participants were recipients of a first allogeneic HSCT enrolled within 28 days post-transplant with undetectable CMV DNA (plasma or whole blood) within 5 days of enrolment and were aged from birth to <18 years of age at the time of providing documented informed consent/assent. Eligible Age Group 1 participants had documented CMV IgG seropositive status (R+) within 90 days before enrolment. Eligible Age Groups 2 and 3 participants had documented CMV IgG seropositive status within 90 days prior to enrolment and/or had received a transplant from a documented CMV IgG seropositive donor within 1 year prior to enrolment (R+ and/or D+).

Exclusion Criteria

Participants were excluded from the study if they met any of the protocol-specified exclusion criteria. Key exclusion criteria included:

- Previous allogeneic HSCT
- History of CMV end-organ disease within 6 months prior to enrolment

- Evidence of CMV viremia at any time from either providing documented ICF or the HSCT procedure, whichever was earlier, until the time of enrolment
- Severe hepatic insufficiency (defined as Child-Pugh Class C) within 5 days prior to enrolment
- Serum AST or ALT>5 x the ULN or serum total bilirubin >2.5 x ULN within 5 days prior to enrolment
- Received renal replacement therapy or had end-stage renal impairment with a creatinine clearance ≤10 mL/min, within 5 days prior to enrolment
- Moderate hepatic insufficiency AND moderate-to-severe renal insufficiency
- Received ganciclovir, valganciclovir, foscarnet, acyclovir (at doses greater than those recommended for HSV/VZV prophylaxis), valacyclovir (at doses greater than those recommended for HSV/VZV prophylaxis), and famciclovir within 7 days prior to enrollment
- Received cidofovir, CMV immunoglobulin, any investigational CMV antiviral agent/biologic therapy, any investigational CMV antiviral agent/biologic therapy, rifampicin and other strong or moderate inducers within 30 days prior to enrolment
- Received LET at any time prior to enrolment in the study

- **Treatments**

The study interventions are presented in the tables below.

All Panel A participants of Age Groups 1 and 2 received oral LET with no concomitant cyclosporin A (CsA) from Day 1 to Day 7 for intensive PK sampling. Age Group 3 participants received either oral or IV LET with or without concomitant CsA.

Coadministration of LET with CsA (an inhibitor of CYP3A, P-gp, OATP1B1/3, and several other transporters) increases the exposure of LET. Therefore, the adult LET dose of 480 mg is reduced to 240 mg QD when coadministered with CsA. Similarly, the LET dose was reduced for paediatric patients with concomitant CsA treatment, see **Table 12** below.

The dose formulations were: 240 mg tablets; 120 mg, 30 mg, 10 mg granules; 20 mg/mL solution.

Table 9: Study intervention

Letermovir Dosing Table (All Age Groups, Including First 3 Age Group 3 Participants)

Age Group	Age Range	BW limits (kg)	Oral dose LET (mg)	Oral dose LET (mg) with CsA	IV dose LET (mg)	IV dose LET (mg) with CsA
1	12 to <18 years	Any weight	480	240	480	240
2	2 to <12 years	≥30	480	240	240[a]	240[b]
		18 to <30	240	120	120[a]	120[b]
		10 to <18	120	60	60[a]	60[b]
3	birth to <2 years	10 to ≤15	120	60	60[a]	60[b]
		7.5 to <10	80	40	40[a]	40[b]
		5.0 to <7.5	40	20	20[a]	20[b]
		2.5 to <5.0	20	10	10[a]	10[b]

BW=body weight recorded at enrollment (Day 1) was used to determine the initial dosing. Doses were adjusted according to the most recent body weight taken per the SoA; CsA=cyclosporin A; IV=intravenous; LET=letermovir; SoA=Schedule of Activities.

[a] Based on modeling, for Age Group 2 and Age Group 3, the IV dose of LET without CsA was reduced by 50% compared with oral LET in order to maintain target exposures.

[b] No further reduction of IV LET was necessary when coadministered with CsA.

Based on interim analyses results for Age Group 3, doses were increased for the last 5 participants weighing <10 kg.

Table 10: Study intervention dosing table (for last 5 age group 3 participants)

Letermovir Dosing Table (For Last 5 Age Group 3 Participants)

Age Group	Age Range	BW limits (kg)	Oral dose LET (mg)	Oral dose LET (mg) with CsA	IV dose LET (mg)	IV dose LET (mg) with CsA
3	birth to <2 years	10 to ≤15	120	60	60[a]	60[b]
		7.5 to <10	120 [c]	60 [c]	60[c]	60[b,c]
		5.0 to <7.5	60 [c]	40 [c]	40[c]	40[b,c]
		2.5 to <5.0	40 [c]	20 [c]	20[c]	20[b,c]

BW=body weight recorded at enrollment (Day 1) was used to determine the initial dosing. Doses were adjusted according to the most recent body weight taken per the SoA; CsA=cyclosporin A; IV=intravenous; LET=letermovir; SoA=Schedule of Activities.

[a] Based on modeling, the IV dose of LET without CsA was reduced by 50% compared with oral LET in order to maintain target exposures.

[b] No further reduction of IV LET was necessary when coadministered with CsA.

[c] Based on interim analyses results for Age Group 3, doses were increased for the last 5 participants weighing <10 kg.

Concomitant and rescue therapies

The 4 most frequently reported classes of concomitant medications used during the treatment phase included antibacterials for systemic use (96.8%), immunosuppressants (93.7%), antidiarrheals, intestinal anti-inflammatory/anti-infective agents (84.1%), and antivirals for systemic use (84.1%).

A majority (73.0%) of participants received systemic corticosteroids during the treatment phase. Other most frequently used concomitant immunosuppressants during the treatment phase included cyclosporine A (60.3%), mycophenolate (49.2%), tacrolimus (41.3%).

There are no anti-CMV agents approved for the prevention of CMV infection and/or disease in paediatric HSCT recipients. The current preferred approach for preventing CMV disease in paediatric HSCT recipients is pre-emptive therapy (PET), defined as the practice of active surveillance for viral replication and initiating treatment with anti-CMV agents only when CMV viremia is detected.

- **Objectives, Outcomes/endpoints**

Primary Objective:

- To evaluate letermovir PK in paediatric participants grouped by age.

Primary endpoints:

AUC_{0-24}, C_{max} (for participants receiving oral formulation), C_{eoi} (for participants receiving IV formulation), and C_{trough}. For details see PK sections above.

Secondary objectives

- To evaluate the efficacy of letermovir in prevention of clinically significant CMV infection through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant
- To evaluate the safety and tolerability of treatment with letermovir through Week 48 post-transplant based on the proportion of participants with adverse events.
- To evaluate the palatability and acceptability of treatment with letermovir oral granules.

MK-8228 is a descriptive study with no hypotheses. The study was single-armed and no comparative statistical analyses were performed.

Secondary endpoints:

The efficacy endpoints are the proportion and 95% CI of participants with CS-CMVi through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant.

The safety endpoints are: AEs and AEs resulting in study medication discontinuation

The palatability endpoint is: Score on a palatability scale.

Study assessments

CMV viremia

Monitoring for CS-CMVi: Participants had study visits scheduled at weekly intervals during the treatment period. Thereafter, CMV viremia was monitored at biweekly intervals through Week 24 post-transplant. The incidence of CS-CMVi was assessed through Week 24 (~6 months) post-transplant to evaluate the occurrence of late CS-CMVi (between Weeks 14 and 24 post-transplant).

Documented viremia was defined as any detectable CMV viral DNA by PCR obtained immediately prior to (ie, on the day of) the initiation of treatment for CMV disease or PET.

CMV disease

CMV disease was determined using the definitions in the study protocol and confirmed by an independent Clinical Adjudication Committee (CAC). The CAC reviewed clinical, virological, and histopathological data as well as the investigator's assessment for adjudicating all potential cases of end-organ CMV disease. For analysis purposes, the adjudication of cases by the CAC took precedence over the investigator's assessment.

CMV DNA sequence analysis

Analyses were performed on samples from participants who meet the criteria for CS-CMVi at the CMV infection visit. Resistance to LET was assessed by genotypic analysis of the CMV terminase complex genes (UL56, UL89, and UL51) in DNA extracted from plasma samples with detectable CMV viral DNA. Samples were analysed by next generation sequencing technology through an established contract laboratory with validated protocols in place. In participants with multiple CMV-positive samples, the last on-therapy and/or follow-up samples was used for analysis.

Palatability and Acceptance Assessment Endpoint

Acceptability, including palatability, of the oral granule formulation was assessed in participants using the Palatability Acceptance Assessment (PAA).

Study MK-8228-030 was a Phase 2b open label single arm study. The study design is considered acceptable and efficacy is descriptive. The indications in paediatric patients will be supported by extrapolation of efficacy and safety from adults HSCT patients.

Resistance to LET was also be assessed in study MK-8228-030 by genotypic analysis of DNA extracted from plasma samples with detectable CMV viral DNA.

- **Sample size**

A total of at least 26 participants will be enrolled for each of the 2 oldest age groups. The key efficacy objective will be assessed based on the proportion of participants with CS-CMVi through Week 24 (~6 months) post-transplant. The expected rate of participants with CS-CMVi through Week 24 post-transplant is ~18% based on P001 data and assuming LET is expected to be similarly active in adults and paediatric participants. Since the primary missing data approach will be NC=F approach, 25% was added to the expected incidence of CS-CMVi through Week 24 post-transplant with the assumption that higher discontinuation rate will be observed in the more vulnerable paediatric participants than

adults. In terms of estimation with the proposed sample size, with 26 participants, the maximum half-width of the 95% exact confidence interval will be no greater than 21%. The calculation is based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934] and is carried out using SAS v9.4. **Table 14** shows the 95% CIs for CS-CMVi given varying assumptions of number of failures for 8, 26, and 60 participants. Note that the intervals are not symmetric around the point estimate.

Table 11: Two-Sided 95% Confidence Intervals for the Proportion of Participants with Clinically Significant CMV Infection through Week 24 (~6 Months) Post-Transplant (FAS Population)

	Number of Failures[a] (%)	Two-Sided 95% Confidence Interval[b]
N=8	2 (25.0)	(3.2, 65.1)
	3 (37.5)	(8.5, 75.5)
	4 (50.0)	(15.7, 84.3)
N=26	9 (34.6)	(17.2, 55.7)
	10 (38.5)	(20.2, 59.4)
	11 (42.3)	(23.4, 63.1)
	12 (46.2)	(26.6, 66.6)
N=60	19 (31.7)	(20.3, 45.0)
	21 (35.0)	(23.1, 48.4)
	23 (38.3)	(26.1, 51.8)
	25 (41.7)	(29.1, 55.1)
	27 (45.0)	(32.1, 58.4)

[a] Based on Non-Completer = Failure approach.

[b] Based on the two-sided exact confidence interval of a binomial proportion (Clopper and Pearson, 1934).

- **Randomisation and Blinding (masking)**

This was an open-label, single-arm study.

- **Statistical methods and number analysed**

Population analyses

- *PK Analysis Population:* The population for noncompartmental PK analysis was a subset of the per-protocol (PP) population. The PP population included all participants with at least one measurable PK sample and who fulfilled requirements for PK assessment as described in the protocol. This subset included 36 participants who underwent intensive PK sampling and had no missing PK samples on intensive PK sampling days. The PK parameters of interest (AUC_{0-24}, C_{max} for oral, C_{eoi} for IV, C_{trough}) were summarised by age group and dose level, with geometric means and % geometric co-efficient of variation. Plasma concentration of hydroxypropyl betadex in Age Group 3 participants who received IV LET was evaluated in order to characterize hydroxypropyl betadex PK at steady state; individual participant concentration was reported.
- *Efficacy Analysis Population:* The efficacy analyses were based on the full analysis set (FAS) population which consisted of all participants who received study intervention and had no detectable CMV viral DNA on Day 1. The FAS included 56 participants who received ≥1 dose of study intervention and had no detectable CMV viral DNA on Day 1 (day study intervention was initiated). Nine participants were excluded from the FAS population: 7 participants had

detectable CMV viral DNA on Day 1, 1 participant did not receive study intervention, and 1 participant both did not receive study intervention and had detectable CMV viral DNA on Day 1.

- *Safety Analysis Population:* safety analyses were based on the all participants as treated (APaT) population, which included 63 participants who received ≥1 dose of study intervention. Two participants were excluded from the APaT population: both participants did not receive study intervention.
- *Criteria for rescue treatment:* Initiation of anti-CMV PET is based on documented CMV viremia and clinical condition of the participant. Documented viremia is defined as any detectable CMV viral DNA (using a local CMV PCR assay) obtained immediately prior to (i.e., on the day of) the initiation of treatment for CMV disease or PET.

Pharmacokinetic Analyses

The PK parameters of interest (AUC_{0-24}, C_{max}, C_{trough}, C_{eoi}) at Day 7 will be summarised by Age Group and dose level, with geometric means (GMs) and 95% CIs based on natural log-transformed values and the t distribution. Individual AUC_{0-24}, C_{max}, C_{trough}, and C_{eoi} values at Day 7 will be plotted by Age Group and dose level as appropriate.

Population PK analysis will be performed on all participants who undergo PK sampling, while non-compartmental analysis (NCA) will be performed on the subset of participants who undergo intensive PK in Age Groups 1 and 2 Panel A and Age Group 3.

Efficacy Analyses

For the efficacy analysis to estimate the proportion of participants with CS-CMVi through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant, a 95% CI was calculated based on the exact binomial method proposed by Clopper and Pearson (1934). The primary efficacy analysis was performed on the full analysis set (FAS) population.

A sensitivity analysis including those participants who had detectable CMV viral DNA on Day 1 was provided. The primary missing data approach was the Non-Completer= Failure (NC=F) approach. Supportive analyses using different missing data approaches such as observed failure and data-as observed were also conducted.

Safety Analyses

Safety and tolerability were assessed using the APaT population, which consisted of all participants who received ≥1 dose of study intervention. Safety and tolerability were assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements.

Planned subgroup analyses

To assess the consistency of the response across various subgroups, the proportion of participants with CS-CMVi through Week 14 (~100 days) post-transplant and associated 95% CIs will be estimated within each category of the following classification variables:

- Age category (birth to <2 years, 2 years to <12 years, 12 years to <18 years)
- Sex (female, male)
- Race (white, black, Asian, other)
- Donor and/or Recipient Serostatus

The consistency of the response will be assessed descriptively via summary statistics by category for the classification variables listed above. Other clinically relevant variables may be identified for which additional subgroup analyses may be performed.

Changes from protocol-specified analyses

There was one change to the planned PK analysis. Due to the limited number of hydroxypropyl betadex plasma concentrations, the noncompartmental analysis could not be performed.

Data quality assurance

Quality oversight activities implemented at the study investigative site(s) or centrally by the Sponsor are intrinsic to all clinical study-related activities, in accordance with ICH GCP 5.1. For this study, such activities may have included remote and/or on-site monitoring inclusive of SDV, SDR, centralized in-house medical monitoring of clinical study data (including monitoring protocol deviations), and relevant reviews of regulatory submission documents.

Investigative study sites were monitored to assess compliance with the study protocol and with GCP. Study data were reviewed for accuracy, completeness, and consistency and verified versus source documentation according to standard operating procedures.

The Sponsor held investigator meeting(s) before study initiation to review all protocol procedures and investigator responsibilities under GCP.

Quality was also evaluated by independent GCP QA activities, which may have included QA audits of study investigative sites and third-party suppliers. The conduct of QA audits was based on a risk-based approach to assess adherence with the protocol, applicable GCP/GPvP regulations and guidance as well as applicable company policies and procedures.

No serious breaches of GCP or other GCP compliance issues that were assessed as having had a significant impact on the rights, safety, or mental integrity of the study participants and/or the scientific integrity or validity of the study results occurred.

Data quality assurance measures seem adequate.

Results

- **Participant flow**

A total of 84 participants were screened, 65 participants were enrolled, and 63 participants received study intervention. The most common reasons for discontinuation from study intervention were AE and lack of efficacy.

Table 12: Disposition of Participants Through Week 48 (All Randomized Participants)

	12 - <18 Years		2 - <12 Years		<2 Years		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	28		29		8		65	
Participant Study Medication Disposition								
Treated	28	(100.0)	27	(93.1)	8	(100.0)	63	(96.9)
Not Treated	0	(0.0)	2	(6.9)	0	(0.0)	2	(3.1)
Completed Study Medication	17	(60.7)	20	(69.0)	6	(75.0)	43	(66.2)
Discontinued Study Medication	11	(39.3)	7	(24.1)	2	(25.0)	20	(30.8)
Adverse Event	5	(17.9)	2	(6.9)	1	(12.5)	8	(12.3)
Death	0	(0.0)	1	(3.4)	0	(0.0)	1	(1.5)
Lack Of Efficacy	5	(17.9)	2	(6.9)	1	(12.5)	8	(12.3)
Withdrawal By Parent/Guardian	1	(3.6)	2	(6.9)	0	(0.0)	3	(4.6)
Participant Study Disposition								
Completed Study Through Week 24	22	(78.6)	23	(79.3)	6	(75.0)	51	(78.5)
Discontinued Study Prior to Week 24	6	(21.4)	4	(13.8)	2	(25.0)	12	(18.5)
Death	3	(10.7)	1	(3.4)	0	(0.0)	4	(6.2)
Physician Decision	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.5)
Withdrawal By Parent/Guardian	3	(10.7)	3	(10.3)	1	(12.5)	7	(10.8)
Completed Study Through Week 48	21	(75.0)	21	(72.4)	1	(12.5)	43	(66.2)
Discontinued Study Between Week 24 and Week 48	1	(3.6)	2	(6.9)	0	(0.0)	3	(4.6)
Death	0	(0.0)	1	(3.4)	0	(0.0)	1	(1.5)
Physician Decision	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.5)
Withdrawal By Parent/Guardian	0	(0.0)	1	(3.4)	0	(0.0)	1	(1.5)
Continuing in the Study Between Week 24 and Week 48	0	(0.0)	0	(0.0)	5	(62.5)	5	(7.7)
Each participant is counted once for Participant Study Medication Disposition, Participant Study Disposition based on the latest corresponding disposition record.								

- **Recruitment**

The study began on 8th August 2019 (1st participant 1st visit), and was completed on 25th August 2023 (last subject last visit). Database lock took place on 12th September 2023.

A total of 28 clinical investigator study sites in 11 countries enrolled 65 participants of whom 63 received study intervention. Participants were enrolled in Europe and Middle East (54%), Asia Pacific (17.5%), North America (15,9%) and Latin America (12.7%).

- **Conduct of the study**

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

Table 13: Protocol Amendments for MK-8228-030

Document	Date of Issue	Overall Rationale
Amendment 08 (global, including for Spain)	21-OCT-2022	The primary reason for Amendment 08 was Sponsor underwent entity name change and update to the address.
Amendment 07 (global including for Spain)	31-AUG-2021	The primary rationale for the changes in Amendment 07 are as follows: To provide the initial dose of oral and intravenous (IV) letermovir (LET) for Age Group 3, which has been determined by interim pharmacokinetics (PK) analyses using data from participants in Age Group 1 and Age Group 2 of this study. To add a requirement for PK sampling of hydroxypropyl-beta-cyclodextrin (HPCD), an excipient in the IV LET formulation, for Age Group 3 participants receiving the IV formulation for at least 4 consecutive days. In addition, the 10-mg oral capsule of LET is now available for use in Spain. This amendment is intended to merge Amendment 06, a country-specific amendment for Spain, with global Amendment 03, which has been used for all other participating countries, to date. Thus, Amendment 07 will be used globally, including for Spain.
Amendment 06 (country-specific for Spain)	22-NOV-2019	To add information regarding the 30-mg oral capsules of LET granules, which have now been manufactured and made available for use in Spain.
Amendment 05 (country-specific for Spain)	16-OCT-2019	To include all changes from Amendment 02 made in both Amendment 03 (addition of in-line filter and related requirements for administration of the IV formulation of LET and Amendment 04 (removal of the 10-mg and 30-mg oral capsules from the protocol until they become available) in the Summary of Changes table. This country-specific amendment is being released to Spain in lieu of Amendment 03, which was released to the rest of the world. Amendment 04 was not released because the Amendment 04 Summary of Changes inadvertently omitted the changes made in Amendment 03.
Amendment 04 (country-specific for Spain)	17-SEP-2019	The Spanish health authority has required that the protocol be amended to remove the 10-mg and 30-mg oral capsules from the protocol until these capsule potencies have been manufactured and the corresponding quality information has been submitted and authorized. The overall design of the protocol has not changed. Age groups requiring dosing with the 10-mg or 30-mg oral capsules will not be enrolled until a subsequent protocol amendment including these lower potency capsules has been authorized.
Amendment 03	23-AUG-2019	To add the requirement that the IV formulation of 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. 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. This requirement is being implemented to allow for the release of new clinical supplies of IV LET, and, as a precaution, it must be applied regardless of whether the clinical site considers its current clinical supply to be impacted.
Amendment 02	15-MAR-2019	The description of the coating of the oral granule formulation to be used in this study provided in Section 2.2.4 was incorrect in the original protocol. This amendment provides the correct description of the coating of the oral granule formulation being used (Opadry coating without Surelease) and provides the rationale for selection of this oral granule formulation. Additional minor changes have been made to incorporate changes communicated in prior protocol clarification letters.
Amendment 01	24-JAN-2019	Testicular toxicity testing was removed, and creatinine clearance monitoring every 2 weeks was added to the protocol.
Original Protocol (Version 00)	08-OCT-2018	Not applicable

- **Baseline data**

Table 14:Participant Characteristics (All Participants as Treated)

	12 - <18 Years		2 - <12 Years		<2 Years		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	28		27		8		63	
Sex								
Male	15	(53.6)	22	(81.5)	7	(87.5)	44	(69.8)
Female	13	(46.4)	5	(18.5)	1	(12.5)	19	(30.2)
Age (Years)								
12 to <18	28	(100.0)	0	(0.0)	0	(0.0)	28	(44.4)
7 to <12	0	(0.0)	14	(51.9)	0	(0.0)	14	(22.2)
2 to <7	0	(0.0)	13	(48.1)	0	(0.0)	13	(20.6)
1 to <2	0	(0.0)	0	(0.0)	3	(37.5)	3	(4.8)
<1	0	(0.0)	0	(0.0)	5	(62.5)	5	(7.9)
Participants with data	28		27		8		63	
Mean (SD)	14.1 (1.5)		6.6 (3.2)		0.7 (0.3)		9.1 (5.3)	
Median (Range)	13.5 (12 to 17)		7.0 (2 to 11)		0.7 (0 to 1)		11.0 (0 to 17)	
Race								
Asian	6	(21.4)	3	(11.1)	0	(0.0)	9	(14.3)
Black Or African American	3	(10.7)	0	(0.0)	0	(0.0)	3	(4.8)
Multiple	4	(14.3)	2	(7.4)	1	(12.5)	7	(11.1)
American Indian Or Alaska Native, Black Or African American	1	(3.6)	1	(3.7)	1	(12.5)	3	(4.8)
American Indian Or Alaska Native, White	2	(7.1)	1	(3.7)	0	(0.0)	3	(4.8)
Black Or African American, White	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
White	15	(53.6)	22	(81.5)	7	(87.5)	44	(69.8)
Ethnicity								
Hispanic Or Latino	9	(32.1)	4	(14.8)	1	(12.5)	14	(22.2)
Not Hispanic Or Latino	14	(50.0)	21	(77.8)	6	(75.0)	41	(65.1)
Not Reported	4	(14.3)	0	(0.0)	1	(12.5)	5	(7.9)

	12 - <18 Years		2 - <12 Years		<2 Years		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Unknown	1	(3.6)	2	(7.4)	0	(0.0)	3	(4.8)
Baseline Weight (kg)								
Participants with data	28		27		8		63	
Mean (SD)	55.2 (17.75)		24.3 (9.56)		8.8 (3.22)		36.0 (22.31)	
Median (Range)	53.8 (28.7 to 95.0)		23.4 (10.4 to 43.8)		7.8 (5.1 to 13.7)		32.4 (5.1 to 95.0)	
Region								
Asia-Pacific	8	(28.6)	3	(11.1)	0	(0.0)	11	(17.5)
Latin America	5	(17.9)	2	(7.4)	1	(12.5)	8	(12.7)
Europe and Middle East	9	(32.1)	19	(70.4)	6	(75.0)	34	(54.0)
North America	6	(21.4)	3	(11.1)	1	(12.5)	10	(15.9)
Immunosuppressive Regimen Use[a]								
Cyclosporin A	19	(67.9)	16	(59.3)	7	(87.5)	42	(66.7)
Tacrolimus	9	(32.1)	7	(25.9)	1	(12.5)	17	(27.0)
Other	0	(0.0)	4	(14.8)	0	(0.0)	4	(6.3)
CMV DNA on DAY 1 (when study therapy is initiated)[b]								
Not Detected	25	(89.3)	24	(88.9)	7	(87.5)	56	(88.9)
Detected	3	(10.7)	3	(11.1)	1	(12.5)	7	(11.1)
CMV Serostatus								
Recipient positive, donor negative	8	(28.6)	6	(22.2)	4	(50.0)	18	(28.6)
Recipient positive, donor positive	20	(71.4)	18	(66.7)	0	(0.0)	38	(60.3)
Recipient negative, donor positive	0	(0.0)	3	(11.1)	4	(50.0)	7	(11.1)
Donor Type								
Matched related	6	(21.4)	2	(7.4)	1	(12.5)	9	(14.3)
Mismatched related	9	(32.1)	8	(29.6)	2	(25.0)	19	(30.2)
Matched unrelated	9	(32.1)	15	(55.6)	5	(62.5)	29	(46.0)
Mismatched unrelated	4	(14.3)	2	(7.4)	0	(0.0)	6	(9.5)
Stem Cell Source								
Peripheral blood	15	(53.6)	16	(59.3)	4	(50.0)	35	(55.6)

	12 - <18 Years		2 - <12 Years		<2 Years		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Bone marrow	12	(42.9)	10	(37.0)	3	(37.5)	25	(39.7)
Cord blood	1	(3.6)	1	(3.7)	1	(12.5)	3	(4.8)
Conditioning Regimen Use								
Myeloablative	25	(89.3)	24	(88.9)	6	(75.0)	55	(87.3)
Reduced intensity conditioning	3	(10.7)	1	(3.7)	2	(25.0)	6	(9.5)
Non-myeloablative	0	(0.0)	2	(7.4)	0	(0.0)	2	(3.2)
Haploidentical Donor								
Yes	8	(28.6)	8	(29.6)	2	(25.0)	18	(28.6)
No	20	(71.4)	19	(70.4)	6	(75.0)	45	(71.4)
Days from Transplantation to Randomization								
Participants with data	28		27		8		63	
Mean (SD)	9.9 (8.38)		9.0 (8.59)		6.5 (4.07)		9.1 (8.03)	
Median (Range)	7.5 (1.0 to 28.0)		5.0 (1.0 to 27.0)		7.5 (1.0 to 11.0)		7.0 (1.0 to 28.0)	

[a]Participants counted in the cyclosporin A (CsA) row if they received concomitant CsA with or without any other immunosuppressants in the regimen during treatment phase. Tacrolimus containing-regimen included concomitant tacrolimus use with or without any other immunosuppressant use (except CsA). Participants in the Other row received a regimen containing any other immunosuppressants (sirolimus, everolimus, systemic steroids, leflunomide, mycophenolate) except CsA or tacrolimus.

[b]CMV DNA between -7 and +1 day of initiation of study therapy.

Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with CsA.

Medical History and Concurrent Illnesses

The 3 most frequently reported medical history conditions in the "all participants as treated" (APaT) population by SOC were Infections and infestations (66.7%), Blood and lymphatic system disorders (54.0%), and General disorders and administration site conditions (52.4%).

Prior Medications/Treatments/Vaccines

The 3 most frequently reported classes of prior medications in the APaT population included antibacterials for systemic use (100.0%), antimycotics for systemic use (96.8%), immunosuppressants (95.2%), and antiemetics and antinauseants (95.2%).

- **Outcomes and estimation**

The primary endpoint – Pharmacokinetics

See pharmacokinetics section above.

Secondary endpoint - efficacy

Table 15: Proportion of Participants with Clinically Significant CMV Infection Through Week 14 Post-Transplant (NC=F Approach, Full Analysis Set Population)

Parameter	12 - <18 Years (N=25)		2 - <12 Years (N=24)		<2 Years (N=7)		Total (N=56)	
	n (%)	(95% CI)[a]	n (%)	(95% CI)[a]	n (%)	(95% CI)[a]	n (%)	(95% CI)[a]
Failures[b]	**5 (20.0)**	**(6.8, 40.7)**	**4 (16.7)**	**(4.7, 37.4)**	**2 (28.6)**	**(3.7, 71.0)**	**11 (19.6)**	**(10.2, 32.4)**
Clinically significant CMV infection through Week 14[c]	2 (8.0)	(1.0, 26.0)	1 (4.2)	(0.1, 21.1)	1 (14.3)	(0.4, 57.9)	4 (7.1)	(2.0, 17.3)
Initiation of PET based on documented CMV viremia	2 (8.0)	(1.0, 26.0)	1 (4.2)	(0.1, 21.1)	1 (14.3)	(0.4, 57.9)	4 (7.1)	(2.0, 17.3)
CMV end-organ disease	0 (0.0)	(0.0, 13.7)	0 (0.0)	(0.0, 14.2)	0 (0.0)	(0.0, 41.0)	0 (0.0)	(0.0, 6.4)
Discontinued from study before Week 14	2 (8.0)	(1.0, 26.0)	3 (12.5)	(2.7, 32.4)	1 (14.3)	(0.4, 57.9)	6 (10.7)	(4.0, 21.9)
Missing outcome in Week 14 visit window	1 (4.0)	(0.1, 20.4)	0 (0.0)	(0.0, 14.2)	0 (0.0)	(0.0, 41.0)	1 (1.8)	(0.0, 9.6)

[a]Based on the exact binomial method proposed by Clopper and Pearson.

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

[c]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.

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 through week 14 post-transplant visit window.

Table 16: Proportion of Participants with Clinically Significant CMV Infection Through Week 24 Post-Transplant (NC=F Approach, Full Analysis Set Population)

Parameter	12 - <18 Years (N=25)		2 - <12 Years (N=24)		<2 Years (N=7)		Total (N=56)	
	n (%)	(95% CI)[a]	n (%)	(95% CI)[a]	n (%)	(95% CI)[a]	n (%)	(95% CI)[a]
Failures[b]	**6 (24.0)**	**(9.4, 45.1)**	**6 (25.0)**	**(9.8, 46.7)**	**2 (28.6)**	**(3.7, 71.0)**	**14 (25.0)**	**(14.4, 38.4)**
Clinically significant CMV infection through Week 24[c]	2 (8.0)	(1.0, 26.0)	3 (12.5)	(2.7, 32.4)	1 (14.3)	(0.4, 57.9)	6 (10.7)	(4.0, 21.9)
Initiation of PET based on documented CMV viremia	2 (8.0)	(1.0, 26.0)	3 (12.5)	(2.7, 32.4)	1 (14.3)	(0.4, 57.9)	6 (10.7)	(4.0, 21.9)
CMV end-organ disease	0 (0.0)	(0.0, 13.7)	0 (0.0)	(0.0, 14.2)	0 (0.0)	(0.0, 41.0)	0 (0.0)	(0.0, 6.4)
Discontinued from study before Week 24	4 (16.0)	(4.5, 36.1)	3 (12.5)	(2.7, 32.4)	1 (14.3)	(0.4, 57.9)	8 (14.3)	(6.4, 26.2)
Missing outcome in Week 24 visit window	0 (0.0)	(0.0, 13.7)	0 (0.0)	(0.0, 14.2)	0 (0.0)	(0.0, 41.0)	0 (0.0)	(0.0, 6.4)

[a]Based on the exact binomial method proposed by Clopper and Pearson.

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

[c]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.

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 through week 24 post-transplant visit window.

The results of analyses using alternate missing data approaches, the OF and DAO approaches, in the FAS population were consistent with the results of analysis using the NC=F approach.

The results were comparable across the 3 age groups. No cases of CMV end-organ disease were observed.

Secondary endpoint - Palatability and acceptability

Table 17: Summary of Palatability and Acceptability of Treatment With Letermovir Paediatric Oral Granules (All Participants as Treated)

	12 - <18 Years		2 - <12 Years		<2 Years		Total	
	Day 1[a] n (%)	Day 7[b] n (%)	Day 1[a] n (%)	Day 7[b] n (%)	Day 1[a] n (%)	Day 7[b] n (%)	Day 1[a] n (%)	Day 7[b] n (%)
Number of Participants Completing Palatability Questionnaire	4	2	27	23	7	7	38	32
Person Entering the Responses on the Questionnaire								
The patient	1 (25.0)	1 (50.0)	1 (3.7)	1 (4.3)	0	0	2 (5.3)	2 (6.3)
The parent/primary caregiver	1 (25.0)	1 (50.0)	12 (44.4)	11 (47.8)	6 (85.7)	6 (85.7)	19 (50.0)	18 (56.3)
The patient and parent/primary caregiver	2 (50.0)	0	5 (18.5)	5 (21.7)	0	0	7 (18.4)	5 (15.6)
The health care provider[c]	0	0	9 (33.3)	6 (26.1)	1 (14.3)	1 (14.3)	10 (26.3)	7 (21.9)
Taste of Medication								
Very good	0	0	3 (11.1)	3 (13.0)	0	0	3 (7.9)	3 (9.4)
Good	1 (25.0)	1 (50.0)	5 (18.5)	4 (17.4)	3 (42.9)	3 (42.9)	9 (23.7)	8 (25.0)
Neither good nor bad	1 (25.0)	1 (50.0)	8 (29.6)	8 (34.8)	1 (14.3)	4 (57.1)	10 (26.3)	13 (40.6)
Bad	1 (25.0)	0	8 (29.6)	5 (21.7)	3 (42.9)	0	12 (31.6)	5 (15.6)
Very bad	1 (25.0)	0	3 (11.1)	3 (13.0)	0	0	4 (10.5)	3 (9.4)
Problems Taking Medication								
Any problem	2 (50.0)	0	11 (40.7)	8 (34.8)	1 (14.3)	1 (14.3)	14 (36.8)	9 (28.1)

	12 - <18 Years		2 - <12 Years		<2 Years		Total	
	Day 1[a] n (%)	Day 7[b] n (%)	Day 1[a] n (%)	Day 7[b] n (%)	Day 1[a] n (%)	Day 7[b] n (%)	Day 1[a] n (%)	Day 7[b] n (%)
Refusing Medication	0	0	4 (14.8)	5 (21.7)	1 (14.3)	0	5 (13.2)	5 (15.6)
Spitting Out Medication	0	0	3 (11.1)	5 (21.7)	0	0	3 (7.9)	5 (15.6)
Throwing Up/Spitting Up Medication	0	0	4 (14.8)	1 (4.3)	0	0	4 (10.5)	1 (3.1)
Gagging From Medication	1 (25.0)	0	7 (25.9)	3 (13.0)	0	0	8 (21.1)	3 (9.4)
Other Problems Taking Medication	1 (25.0)	0	2 (7.4)	1 (4.3)	0	1 (14.3)	3 (7.9)	2 (6.3)

Percentages are based on number of participants completing palatability questionnaire at first dose of oral granules and again one week later.
[a]Day 1 was the first day the questionnaire was filled out in participants who received granules with soft food.
[b]Day 7 questionnaires were filled out within 7 days and +/- 3 days after Day 1 questionnaire.
[c]Example: physician, nurse, medical assistant or nursing assistant caring for the participants.
All participants listed in the table had at least 1 dose of oral granule reported. One Age Group 1 participant not included in this table, who completed Day 1 and Day 7 questionnaires, gagged and threw up the oral granules on Day 1, and refused to take oral granules on Day 7, resulting in zero doses reported on those days.

Palatability was assessed on Day 1 and Day 7 of treatment with a mixed outcome. Of the participants that completed the questionnaire at Day 7, 40.6% reported the medications as neither good nor bad, 25% reported it as good and 15.6% as bad. None of the participant stopped study treatment due to palatability issues.

The acceptability and palatability of the tablet formulation was not formally assessed in paediatric participants, however a discussion was provided by the MAH. 23 patients aged 12 to 16 years of age received 1x or 2x the 240 mg tablet (size 16.5 mm x 8.5 mm) to achieve a daily dose of 240 mg or 480 mg (depending on ciclosporin coadministration). There was a good spread of patients across this age range with over half of these patients aged 12 or 13 years and over half of these patients taking 2x tablets to achieve a daily dose of 480 mg. No participant in Group 1 Panel A requested the granule formulation (which was available to them) and no palatability AEs directly linked to the study treatment were reported.

Pre-defined and ad hoc important subgroup analyses

No meaningful conclusions could be drawn from subgroup analyses of participants with CS CMVi through Week 14 post-transplant based on participant characteristics (sex, race, and donor and recipient serostatus) due to the small numbers of participants (⩽3) in the subgroups.

- **Ancillary analyses**

Viral Resistance Results

A total of 12 participants had a resistance genotyping attempted on samples collected at the CMV disease visit. Of these, 10 participants had evaluable sequence data available for analysis: 4 in Age Group 1, 4 in Age Group 2, and 2 in Age Group 3. Of these, 2 participants had known LET resistance-associated amino acid substitutions detected in pUL56 at an allele frequency above the validated assay cutoff of 5%. One participant in Age Group 1 had a R369S substitution detected on study Day 54 and 1 participant in Age Group 3, who was positive for CMV DNAemia on Day 1, had a C325W substitution detected on study Day 129. No known LET resistance-associated substitutions were observed in the pUL51 or pUL89 terminase subunits in any participant with evaluable data.

- **Summary of main efficacy results**

The following table summarise the results from the main studies supporting the present application. These summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18: Summary of efficacy for trial MK-8228-030

Title: A Phase 2b open-label, single-arm study to evaluate pharmacokinetics, efficacy, safety and tolerability of letermovir in paediatric participants from birth to less than 18 years of age at risk of developing CMV infection and/or disease following allogeneic haematopoietic stem cell transplantation (HSCT)	
Study identifier	Protocol Number: P030 (MK-8228-030) EudraCT: 2018-001326-25
Design	Phase 2b, open-label, single-arm study to evaluate PK, efficacy, safety, and tolerability of letermovir (LET) when used for cytomegalovirus (CMV) prophylaxis in paediatric participants from birth to <18 years of age who were at risk of developing clinically significant CMV infection (CS-CMVi) following an allogeneic HSCT. The study enrolled eligible participants into 3 age groups (Age Group 1: 12 to <18 years of age, Age Group 2: 2 to <12 years of age, Age Group 3: birth to <2 years of age). Enrollment began with Age Group 1 and moved sequentially to younger age groups. For Age Groups 1 and 2, PK for the first 6 participants (Panel A) was evaluated to confirm dosing before enrolling other participants in the groups (Panel B). For Age Group 3, PK for the first 3 participants was evaluated to confirm or modify dosing before enrolling the other 5 participants in the group. Participants were to receive LET (oral or intravenous [IV] formulation) from the day of enrollment (Day 1) through Week 14 (~100 days) post-transplant. All Panel A participants of Age Groups 1 and 2 were to receive oral LET with no concomitant cyclosporin A (CsA) from Day 1 to Day 7 for intensive PK sampling. Age Group 3 participants received either oral or IV LET with or without concomitant CsA. Any participant who received IV LET for at least 5 consecutive days had intensive PK sampling performed on the fifth day of IV dosing, except for those who had intensive PK sampling for oral LET. CMV viremia was monitored through Week 24 (~6 months) post-transplant.

	Duration of main phase:	First Participant First Visit: 8th August 2019 Last Participant Last Visit: 25th August 2023 Duration of Study: Approximately 48 months
	Duration of run-in phase:	Not applicable
	Duration of extension phase:	Not applicable
Objectives	Primary objective: To evaluate LET PK in paediatric participants grouped by age. Secondary objective: To evaluate the efficacy of LET in prevention of CS-CMVi through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant	
Treatment groups	Age Group 1: 12 to <18 years of age - any weight	Oral dose LET - 480 mg Oral dose LET with CsA - 240 mg IV dose LET - 480 mg IV dose LET with CsA - 240 mg
	Age Group 2: 2 to <12 years of age - ≥30 to 10 kg	Oral dose LET - 480 to 120 mg based on weight Oral dose LET with CsA - 240 to 60 mg based on weight IV dose LET - 240 to 60 mg based on weight IV dose LET with CsA - 240 to 60 mg based on weight
	Age Group 3: birth to <2 years of age - (first 3 participants) - ≤15 to 2.5 kg	Oral dose LET - 120 to 20 mg based on weight Oral dose LET with CsA - 60 to 10 mg based on weight IV dose LET - 60 to 10 mg based on weight IV dose LET with CsA - 60 to 10 mg based on weight
	Age Group 3: birth to <2 years of age - (last 5 participants) - ≤15 to 2.5 kg	Oral dose LET - 120 to 40 mg based on weight Oral dose LET with CsA - 60 to 20 mg based on weight IV dose LET - 60 to 20 mg based on weight IV dose LET with CsA - 60 to 20 mg based on weight
Disposition of participants	Age Group 1: 12 to <18 years of age	28 participants were enrolled, 28 received study interventions, and 21 completed the study
	Age Group 2: 2 to <12 years of age	29 participants were enrolled, 27 received study interventions, and 21 completed the study
	Age Group 3: birth to <2 years of age	8 participants were enrolled, 8 received study interventions, and 6 completed the study

Endpoints and definitions	Primary endpoint	PK	The primary PK endpoints for LET are steady-state plasma area under the concentration-time curve for the dosing period (0 to 24 hours) (AUC0-24), maximum concentration observed (Cmax for participants receiving oral formulation), concentration at the end of infusion (Ceoi for participants receiving IV formulation), and minimum concentration observed before next dose (Ctrough). Additional secondary PK parameters (elimination half-life [t1/2], clearance [CL/F for participants receiving oral formulation], clearance [CL for participants receiving IV formulation], time of maximum concentration (Tmax); apparent volume of distribution during elimination phase [Vd/F for participants receiving oral formulation], and volume of distribution during elimination phase [Vd for participants receiving IV formulation]) were also calculated.
	Secondary endpoint	Efficacy	CS-CMVi (defined as initiation of pre-emptive therapy (PET) for documented CMV viremia and/or CMV end-organ disease) through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant.
Database lock	12-SEP-2023		

Results and Analysis

PK Results

The PK of LET in paediatric (birth to <18 years of age) allogeneic HSCT recipients who received LET within 28 days post-transplant and continued through Week 14 post-transplant indicated:

In Age Group 1 Panel A (n=6), all participants received oral LET with no concomitant CsA from Day 1 to Day 7 during intensive PK sampling. One participant had a higher exposure than the adult reference range. However, it was within the exposure bounds established in the LET Phase 1 program (upper limit of 328,000 ng x h/mL). One participant's PK profile is physiologically implausible for an adolescent participant administered 480 mg of LET, so this participant's PK data were not included because of concerns about the effect on the robustness of the PK assessment based on the participant's comorbidities and concomitant medications. Consequently, only 5 participants were evaluable.

Based on the results observed for this cohort, no dose adjustment was needed for Age Group 2 Panel A and Age Group 1 Panel B. LET exposures for participants in Age Group 1 Panel B (n=7), who received 480 mg IV LET without CsA (n=3) or 240 mg IV LET with CsA (n=4), were comparable with the reference adult exposure.

In Age Group 2 Panel A (n=6), LET exposures at the 240 mg oral dose (n=4) and at the 120 mg oral dose (n=2) were comparable with the reference adult exposure. All Panel A participants in Age Group 2 received oral LET with no concomitant CsA from Day 1 to Day 7 during intensive PK sampling. Based on these results, no dose adjustment was needed for Age Group 3, and Age Group 2 Panel B proceeded as per protocol. LET exposures for participants in Age Group 2 Panel B (n=10), who received IV LET (n=8), were within the reference adult exposure range. LET exposures for 2 participants who received IV LET with CsA were lower than the reference adult exposure.

LET exposures (after dosing of LET with CsA) for the first 3 participants in Age Group 3 trended below the target median adult LET exposure. In the remaining 5 participants, the LET dose was increased for participants weighing <10 kg. The resulting LET exposures for the last 5 participants were comparable with the reference adult exposures.

Efficacy Results

In paediatric (birth to <18 years of age) allogeneic HSCT recipients who received LET within 28 days post-transplant and continued through Week 14 post-transplant (full analysis set [FAS] population, noncompleter=failure [NC=F] approach):

Eleven (19.6%) participants had CS-CMVi through Week 14 post-transplant.

Fourteen (25.0%) participants had CS-CMVi through Week 24 post-transplant.

The percentage of participants with CS-CMVi through Week 14 and Week 24 were generally

Analysis Description	**Primary Analysis (PK)**

Analysis population and time point description	The per-protocol (PP) population was the primary population for the analyses of PK data in the study. The PP population included all participants with at least 1 measurable PK sample and who fulfilled requirements for PK assessment as described in the protocol. The population for noncompartmental PK analysis was a subset of the PP population. This subset included 36 participants who underwent intensive PK sampling and had no missing PK samples on the intensive PK sampling days specified in the protocol. The LET PK exposure targets for the paediatric HSCT population were established using the Phase 3 population PK model predicted steady-state median exposures (AUC0-24) in adult HSCT recipients following oral and IV LET 480 mg without CsA, respectively. The LET AUC0-24 of the paediatric HSCT population (calculated at the interim PK analyses) was compared with the target adult reference exposure range of 16,900 to 148,000 h*ng/mL. The LET PK parameters of interest (AUC0-24, Cmax for oral, Ceoi for IV, Ctrough, Tmax, t1/2, CL [CL/F for oral], and Vd [Vd/F for oral]) are summarised below by age group, weight limits, and dose level, with geometric means and % geometric coefficient of variation.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Study MK-8228-030 was a Phase 2b open label, multicentre, single arm study in paediatric recipients of an allogeneic HSCT. The primary endpoint was pharmacokinetics and efficacy was a secondary endpoint. The efficacy endpoint is similar to the primary endpoint in the adult HSCT study (P001). The paediatric study is a single arm study thus no comparative data are available, this is acceptable.

Study drug was initiated after HSCT (Day 1-28 post-HSCT) and continued through Week 14 post-HSCT. Study drug was administered either orally or IV; the dose of letermovir was based on age, body weight and formulation.

Among the 63 treated subjects the majority were males (69.8 %), white (69.8 %), received cyclosporin A (66.7%) and were recipient positive/donor positive (60.3%).

Efficacy data and additional analyses

Efficacy was a secondary endpoint. The percentage of failures through Week 14 and through Week 24 post-transplant in the FAS population using the NC=F approach was 19.6% and 25.0%, respectively. The percentage of participants with CS-CMVi defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV PET based on documented CMV viremia was 7.1% and 10.7% through Week 14 and Week 24 post-transplant, respectively. The results were comparable across the 3 age groups. No cases of CMV end-organ disease were observed.

Palatability was assessed and of the participants that completed the questionnaire at Day 7, 40.6% reported the medications as neither good nor bad, 25% reported it as good and 15.6% as bad. None of the participant stopped study treatment due to palatability issues. This small dataset indicated no notable acceptability and palatability concerns, but are insufficient for the purposes of fully assessing acceptability and palatability.

Although paediatric patients did not receive the 480 mg tablets, the paediatric dosing means that patients requiring 480 mg (on average around 9 years old) can choose between a single larger tablet or two smaller tablets. As the tablets and granules may be used interchangeably and to provide any of the required paediatric doses, the granule formulation offers a further alternative for any paediatric patient of any age unable to swallow tablets.

The acceptability of the tablet formulation was only assessed in adolescents and, as expected, was overall found acceptable which is the expected outcome for this age group. Tablets were not offered to children from the age of 2 years (Age Group 2) in the paediatric study and therefore acceptability and the risk of choking are not known.

Two 2 participants had known LET resistance-associated amino acid substitutions detected in pUL56 at an allele frequency above the validated assay cutoff of 5%. One participant in Age Group 1 had a R369S substitution detected on study Day 54 and 1 participant in Age Group 3, who was positive for CMV DNAemia on Day 1, had a C325W substitution detected on study Day 129.

There are no clinical data in paediatric kidney transplant patients and the extrapolation from HSCT (adult and paediatric) patients is questioned see PK/efficacy major objection.

For the indication in kidney transplant patients the weight cut-off has been amended to at least 40 kg for all formulations (refer to discussion on clinical pharmacology). This is agreed.

For the indication in HSCT patients the weight cut-off has been amended for the IV and granule formulation to at least 5 kg (refer to discussion on clinical pharmacology). This is agreed.

2.5.7. Conclusions on the clinical efficacy

The indications in paediatric HSCT and kidney transplant recipients is based on extrapolation of efficacy and safety from adult HSCT patients in study P001. The efficacy data in study P030 is considered supportive. For HSCT patients, comparable exposure has been established in patients weighing at least 5kg, thus letermovir is expected to be effective also in paediatric HSCT patients.

In paediatric kidney transplant patients, no dose in patients below 40kg can be justified by bridging to adult data. However, the adult KT model can be used for paediatric population weighing at least 40 kg (body weight range considered covered by the adult dataset), therefore this weight cut-off is considered acceptable.

2.5.8. Clinical safety

The paediatric clinical safety data come from a single open-label, single-arm Phase 2b study (P030) of 65 participants to evaluate the PK, efficacy, safety, and tolerability of LET when used for CMV prophylaxis in paediatric participants who were at risk of developing CS-CMVi following an allogeneic HSCT. Enrolment began with Age Group 1 (12 to <18 years)) and moved sequentially to younger age groups 2 (2 to <12 years) and 3 (birth to <2 years) following re-evaluation of appropriateness of the dose in the first 6 participants (panel A).

Safety and tolerability were assessed as secondary objectives in P030 using the All Participants as treated (APaT) population (n=63), which consisted of all participants who received ≥1 dose of study intervention. The safety and tolerability of LET were evaluated by clinical review of all relevant parameters including AEs, clinical laboratory assessments, vital signs, and ECG measurements. AEs and laboratory tests were collected through 28 days after the last dose of study intervention

(treatment phase). Thereafter, only drug related SAEs and AEs with a fatal outcome were collected through Week 48 post-transplant (follow-up).

2.5.8.1. Patient exposure

Table 19: Extent of Exposure to Letermovir by Route of Administration, Study P030 (Safety Population = All Participants as Treated)

Letermovir	≤ 2wks	> 2wks to 4wks	> 4wks to 6wks	> 6wks to 8wks	> 8wks to 10wks	> 10wks to 12wks	> 12wks to 14wks	> 14wks	Total Participants	Duration Range	Mean Duration	Median Duration
Any route of administration	6	5	3	3	2	15	23	6	63	3 to 102 days	71.5 days	84 days
12 - <18 Years	3	1	2	2	2	5	11	2	28	5 to 102 days	71.2 days	83 days
2 - <12 Years	3	3	1	0	0	9	8	3	27	3 to 101 days	70.4 days	84 days
<2 Years	0	1	0	1	0	1	4	1	8	20 to 99 days	76.5 days	88 days
IV	9	12	3	0	0	0	0	0	24	2 to 32 days	17.7 days	20 days
12 - <18 Years	4	4	2	0	0	0	0	0	10	2 to 32 days	17.3 days	21 days
2 - <12 Years	5	5	1	0	0	0	0	0	11	7 to 31 days	16.5 days	16 days
<2 Years	0	3	0	0	0	0	0	0	3	20 to 26 days	23.7 days	25 days
Oral	8	3	1	4	9	17	13	6	61	1 to 102 days	66.9 days	76 days
12 - <18 Years	3	2	0	2	5	6	7	2	27	5 to 102 days	67.4 days	75 days
2 - <12 Years	5	1	1	0	4	10	3	3	27	1 to 101 days	63.7 days	76 days
<2 Years	0	0	0	2	0	1	3	1	7	45 to 99 days	77.3 days	87 days

Each participant who received Letermovir is counted once on the "Any route of administration" row in the column that reflects the total duration of exposure to Letermovir.
Participants may be counted in multiple rows if they received different routes of administration. On each applicable specific age group row, the participant is counted once in the column that reflects the duration of exposure to that specific route of administration.
IV = intravenous

Participants were predominantly male, Caucasian and not Hispanic or Latino, and from the Europe and the Middle East region. The CMV serostatus for most recipients was positive (R+) (56/63, 88.9%), and 7 (11.1%) participants had detectable CMV DNA (D+) on the day of enrolment (Day 1). The most common reasons for HSCT were acute myeloid leukaemia (17.5%) and aplastic anaemia (9.5%). The 4 most frequently reported classes of concomitant medications used during the treatment phase included antibacterials for systemic use (96.8%), immunosuppressants (93.7%), antidiarrheals, intestinal anti-inflammatory/anti-infective agents (84.1%), and antivirals for systemic use (84.1%). A majority (73.0%) of participants received systemic corticosteroids during the treatment phase. Other most frequently used concomitant immunosuppressants during the treatment phase included cyclosporine A (60.3%), mycophenolate (49.2%), tacrolimus (41.3%).

There are no data from letermovir treatment for longer than 100 days in paediatric HSCT patients, which was the maximum treatment duration in the study.

Compliance with the study intervention regimen was high and generally comparable across the 3 age groups; mean compliance (SD) was 99.0% (2.2%).

2.5.8.2. Adverse events

AEs were reported for all participants during the treatment phase.

Table 20: Summary of Adverse Events (Safety Population = All Participants as Treated, Treatment Phase)

	12 - <18 Years			2 - <12 Years			<2 Years			Total		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	28		28	27		27	8		8	63		63
with one or more adverse events	28	(100.0)	(87.7, 100.0)	27	(100.0)	(87.2, 100.0)	8	(100.0)	(63.1, 100.0)	63	(100.0)	(94.3, 100.0)
with no adverse event	0	(0.0)	(0.0, 12.3)	0	(0.0)	(0.0, 12.8)	0	(0.0)	(0.0, 36.9)	0	(0.0)	(0.0, 5.7)
with drug-related[b] adverse events	9	(32.1)	(15.9, 52.4)	8	(29.6)	(13.8, 50.2)	3	(37.5)	(8.5, 75.5)	20	(31.7)	(20.6, 44.7)
with serious adverse events	12	(42.9)	(24.5, 62.8)	17	(63.0)	(42.4, 80.6)	6	(75.0)	(34.9, 96.8)	35	(55.6)	(42.5, 68.1)
with serious drug-related adverse events	2	(7.1)	(0.9, 23.5)	0	(0.0)	(0.0, 12.8)	0	(0.0)	(0.0, 36.9)	2	(3.2)	(0.4, 11.0)
who died	3	(10.7)	(2.3, 28.2)	1	(3.7)	(0.1, 19.0)	0	(0.0)	(0.0, 36.9)	4	(6.3)	(1.8, 15.5)
discontinued drug due to an adverse event	5	(17.9)	(6.1, 36.9)	2	(7.4)	(0.9, 24.3)	1	(12.5)	(0.3, 52.7)	8	(12.7)	(5.6, 23.5)
discontinued drug due to a drug-related adverse event	2	(7.1)	(0.9, 23.5)	0	(0.0)	(0.0, 12.8)	0	(0.0)	(0.0, 36.9)	2	(3.2)	(0.4, 11.0)
discontinued drug due to a serious adverse event	2	(7.1)	(0.9, 23.5)	2	(7.4)	(0.9, 24.3)	1	(12.5)	(0.3, 52.7)	5	(7.9)	(2.6, 17.6)
discontinued drug due to a serious drug-related adverse event	1	(3.6)	(0.1, 18.3)	0	(0.0)	(0.0, 12.8)	0	(0.0)	(0.0, 36.9)	1	(1.6)	(0.0, 8.5)

[a] Based on the exact binomial method proposed by Clopper and Pearson.
[b] Determined by the investigator to be related to the drug.

Source: [P030V01MK8228: adam-adsl; adae]

Table 21: Participants With Adverse Events, Study P030 (Incidence ≥ 10% in One or More Age Groups) (Safety Population = All Participants as Treated, Treatment Phase)

	12 - <18 Years		2 - <12 Years		<2 Years		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	28		27		8		63	
with one or more adverse events	28	(100.0)	27	(100.0)	8	(100.0)	63	(100.0)
with no adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood and lymphatic system disorders	8	(28.6)	15	(55.6)	1	(12.5)	24	(38.1)
Anaemia	1	(3.6)	7	(25.9)	0	(0.0)	8	(12.7)
Febrile neutropenia	3	(10.7)	4	(14.8)	0	(0.0)	7	(11.1)
Lymphopenia	1	(3.6)	3	(11.1)	0	(0.0)	4	(6.3)
Neutropenia	2	(7.1)	8	(29.6)	1	(12.5)	11	(17.5)
Thrombocytopenia	5	(17.9)	9	(33.3)	0	(0.0)	14	(22.2)
Cardiac disorders	7	(25.0)	4	(14.8)	0	(0.0)	11	(17.5)
Tachycardia	4	(14.3)	3	(11.1)	0	(0.0)	7	(11.1)
Endocrine disorders	1	(3.6)	0	(0.0)	2	(25.0)	3	(4.8)
Adrenal insufficiency	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Hypothyroidism	1	(3.6)	0	(0.0)	1	(12.5)	2	(3.2)
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Eye disorders	5	(17.9)	3	(11.1)	0	(0.0)	8	(12.7)

Gastrointestinal disorders	27	(96.4)	27	(100.0)	5	(62.5)	59	(93.7)
Abdominal pain	11	(39.3)	6	(22.2)	1	(12.5)	18	(28.6)
Constipation	4	(14.3)	3	(11.1)	0	(0.0)	7	(11.1)
Diarrhoea	12	(42.9)	12	(44.4)	0	(0.0)	24	(38.1)
Gastrointestinal inflammation	1	(3.6)	3	(11.1)	0	(0.0)	4	(6.3)
Nausea	12	(42.9)	6	(22.2)	0	(0.0)	18	(28.6)
Oesophagitis	0	(0.0)	3	(11.1)	0	(0.0)	3	(4.8)
Stomatitis	8	(28.6)	9	(33.3)	0	(0.0)	17	(27.0)
Teething	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Vomiting	14	(50.0)	20	(74.1)	3	(37.5)	37	(58.7)
General disorders and administration site conditions	16	(57.1)	18	(66.7)	4	(50.0)	38	(60.3)
Asthenia	1	(3.6)	3	(11.1)	0	(0.0)	4	(6.3)
Mucosal inflammation	0	(0.0)	4	(14.8)	1	(12.5)	5	(7.9)
Pyrexia	11	(39.3)	13	(48.1)	3	(37.5)	27	(42.9)

	12 - <18 Years		2 - <12 Years		<2 Years		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Hepatobiliary disorders	5	(17.9)	3	(11.1)	0	(0.0)	8	(12.7)
Immune system disorders	15	(53.6)	13	(48.1)	4	(50.0)	32	(50.8)
Acute graft versus host disease	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Drug hypersensitivity	1	(3.6)	3	(11.1)	0	(0.0)	4	(6.3)
Graft versus host disease	10	(35.7)	11	(40.7)	3	(37.5)	24	(38.1)
Graft versus host disease in skin	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Infections and infestations	21	(75.0)	18	(66.7)	5	(62.5)	44	(69.8)
BK virus infection	4	(14.3)	1	(3.7)	0	(0.0)	5	(7.9)
Bacteraemia	3	(10.7)	2	(7.4)	1	(12.5)	6	(9.5)
Cytomegalovirus infection reactivation	2	(7.1)	0	(0.0)	1	(12.5)	3	(4.8)
Device related bacteraemia	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Device related infection	1	(3.6)	3	(11.1)	2	(25.0)	6	(9.5)
Epstein-Barr virus infection reactivation	2	(7.1)	0	(0.0)	2	(25.0)	4	(6.3)
Febrile infection	1	(3.6)	0	(0.0)	1	(12.5)	2	(3.2)
Nasopharyngitis	1	(3.6)	2	(7.4)	1	(12.5)	4	(6.3)
Rhinitis	2	(7.1)	2	(7.4)	1	(12.5)	5	(7.9)

Streptococcal infection	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Injury, poisoning and procedural complications	6	(21.4)	8	(29.6)	1	(12.5)	15	(23.8)
Contusion	0	(0.0)	1	(3.7)	1	(12.5)	2	(3.2)
Investigations	13	(46.4)	13	(48.1)	2	(25.0)	28	(44.4)
Alanine aminotransferase increased	5	(17.9)	4	(14.8)	1	(12.5)	10	(15.9)
Aspartate aminotransferase increased	4	(14.3)	1	(3.7)	1	(12.5)	6	(9.5)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Epstein-Barr virus test positive	0	(0.0)	1	(3.7)	1	(12.5)	2	(3.2)
Metabolism and nutrition disorders	12	(42.9)	14	(51.9)	4	(50.0)	30	(47.6)
Decreased appetite	3	(10.7)	8	(29.6)	0	(0.0)	11	(17.5)
Hypercholesterolaemia	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Hypoalbuminaemia	3	(10.7)	5	(18.5)	0	(0.0)	8	(12.7)
Hypokalaemia	4	(14.3)	4	(14.8)	1	(12.5)	9	(14.3)
Hypomagnesaemia	4	(14.3)	3	(11.1)	1	(12.5)	8	(12.7)
Neonatal diabetes mellitus	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)

	12 - <18 Years		2 - <12 Years		<2 Years		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Metabolism and nutrition disorders	12	(42.9)	14	(51.9)	4	(50.0)	30	(47.6)
Sodium retention	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Musculoskeletal and connective tissue disorders	6	(21.4)	3	(11.1)	0	(0.0)	9	(14.3)
Pain in extremity	3	(10.7)	1	(3.7)	0	(0.0)	4	(6.3)
Nervous system disorders	13	(46.4)	5	(18.5)	1	(12.5)	19	(30.2)
Headache	6	(21.4)	3	(11.1)	0	(0.0)	9	(14.3)
Neurotoxicity	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Tremor	4	(14.3)	0	(0.0)	0	(0.0)	4	(6.3)
Psychiatric disorders	3	(10.7)	2	(7.4)	0	(0.0)	5	(7.9)
Renal and urinary disorders	14	(50.0)	8	(29.6)	0	(0.0)	22	(34.9)
Acute kidney injury	3	(10.7)	0	(0.0)	0	(0.0)	3	(4.8)
Dysuria	6	(21.4)	3	(11.1)	0	(0.0)	9	(14.3)
Haematuria	4	(14.3)	2	(7.4)	0	(0.0)	6	(9.5)
Renal impairment	3	(10.7)	3	(11.1)	0	(0.0)	6	(9.5)
Reproductive system and breast disorders	3	(10.7)	3	(11.1)	0	(0.0)	6	(9.5)

Respiratory, thoracic and mediastinal disorders	13	(46.4)	8	(29.6)	0	(0.0)	21	(33.3)
Cough	4	(14.3)	4	(14.8)	0	(0.0)	8	(12.7)
Epistaxis	1	(3.6)	3	(11.1)	0	(0.0)	4	(6.3)
Hypoxia	3	(10.7)	0	(0.0)	0	(0.0)	3	(4.8)
Oropharyngeal pain	5	(17.9)	2	(7.4)	0	(0.0)	7	(11.1)
Rhinorrhoea	3	(10.7)	0	(0.0)	0	(0.0)	3	(4.8)
Skin and subcutaneous tissue disorders	12	(42.9)	17	(63.0)	2	(25.0)	31	(49.2)
Alopecia	1	(3.6)	3	(11.1)	0	(0.0)	4	(6.3)
Dry skin	1	(3.6)	2	(7.4)	1	(12.5)	4	(6.3)
Eczema	0	(0.0)	1	(3.7)	1	(12.5)	2	(3.2)
Erythema	1	(3.6)	3	(11.1)	0	(0.0)	4	(6.3)
Macule	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)

	12 - <18 Years		2 - <12 Years		<2 Years		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	12	(42.9)	17	(63.0)	2	(25.0)	31	(49.2)
Nail pigmentation	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Palmar erythema	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Pruritus	6	(21.4)	3	(11.1)	0	(0.0)	9	(14.3)
Rash	4	(14.3)	4	(14.8)	0	(0.0)	8	(12.7)
Rash erythematous	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Rash macular	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Vascular disorders	10	(35.7)	11	(40.7)	2	(25.0)	23	(36.5)
Flushing	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Hypertension	7	(25.0)	9	(33.3)	0	(0.0)	16	(25.4)
Hypotension	3	(10.7)	2	(7.4)	0	(0.0)	5	(7.9)
Venoocclusive disease	0	(0.0)	1	(3.7)	1	(12.5)	2	(3.2)

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.
MedDRA version 25.1 was used in the reporting of this study.

2.5.8.3. Serious adverse event/deaths/other significant events

Adverse Events of Special Interest

One Event of clinical interest was pre-specified for this study:

"*An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol -specified laboratory testing or unscheduled laboratory testing.*"

Two participants (both in Age Group 1) had laboratory values that met the protocol defined ECI criteria for potential DILI events. Potential DILI was defined as an elevated AST or ALT laboratory value ≥3X the ULN and an elevated total bilirubin laboratory value ≥2X the ULN and, at the same time, an alkaline phosphatase laboratory value <2X the ULN.

For the first participant, the ECI criteria were met during the screening period before administration of the study medication. For the second participant, the ECI was due to an (eventually fatal) SAE (hepatosplenic candidiasis) which is a confounding (and more likely alternative) cause of the observed liver injury.

Serious adverse events (SAEs)

Table 22: Participants With Serious Adverse Events (Incidence > 0% in One or More Age Groups) (All Participants as Treated, Treatment Phase

	12 - <18 Years		2 - <12 Years		<2 Years		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	28		27		8		63	
with one or more adverse events	12	(42.9)	17	(63.0)	6	(75.0)	35	(55.6)
with no adverse events	16	(57.1)	10	(37.0)	2	(25.0)	28	(44.4)
Blood and lymphatic system disorders	**1**	**(3.6)**	**1**	**(3.7)**	**0**	**(0.0)**	**2**	**(3.2)**
Febrile neutropenia	1	(3.6)	1	(3.7)	0	(0.0)	2	(3.2)
Cardiac disorders	**1**	**(3.6)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.6)**
Atrial fibrillation	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(1.6)**
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Gastrointestinal disorders	**1**	**(3.6)**	**2**	**(7.4)**	**0**	**(0.0)**	**3**	**(4.8)**
Rectal haemorrhage	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
Stomatitis	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Vomiting	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
General disorders and administration site conditions	**4**	**(14.3)**	**2**	**(7.4)**	**0**	**(0.0)**	**6**	**(9.5)**
Multiple organ dysfunction syndrome	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Pyrexia	3	(10.7)	2	(7.4)	0	(0.0)	5	(7.9)
Immune system disorders	**2**	**(7.1)**	**2**	**(7.4)**	**1**	**(12.5)**	**5**	**(7.9)**
Acute graft versus host disease	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Graft versus host disease	1	(3.6)	1	(3.7)	1	(12.5)	3	(4.8)
Haemophagocytic lymphohistiocytosis	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
Transplant rejection	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Infections and infestations	**7**	**(25.0)**	**8**	**(29.6)**	**3**	**(37.5)**	**18**	**(28.6)**
BK virus infection	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
Bacteraemia	0	(0.0)	1	(3.7)	1	(12.5)	2	(3.2)
Bronchitis	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
Bronchitis bacterial	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Campylobacter gastroenteritis	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Candida infection	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Cystitis viral	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)

Infections and infestations	**7**	**(25.0)**	**8**	**(29.6)**	**3**	**(37.5)**	**18**	**(28.6)**
Cytomegalovirus infection reactivation	1	(3.6)	0	(0.0)	1	(12.5)	2	(3.2)
Device related infection	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Epstein-Barr virus infection reactivation	0	(0.0)	0	(0.0)	2	(25.0)	2	(3.2)
Febrile infection	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Gastroenteritis	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
Gastroenteritis clostridial	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
Hepatosplenic candidiasis	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Human herpesvirus 6 infection	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
Klebsiella bacteraemia	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Pneumonia klebsiella	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Sepsis	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Septic shock	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
Staphylococcal bacteraemia	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Injury, poisoning and procedural complications	**2**	**(7.1)**	**2**	**(7.4)**	**0**	**(0.0)**	**4**	**(6.3)**
Engraft failure	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
Humerus fracture	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
Transfusion reaction	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Transplant failure	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Investigations	**1**	**(3.6)**	**1**	**(3.7)**	**1**	**(12.5)**	**3**	**(4.8)**
Alanine aminotransferase increased	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
Blood bilirubin increased	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Epstein-Barr virus test positive	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Metabolism and nutrition disorders	**1**	**(3.6)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(1.6)**
Hypokalaemia	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**(7.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(3.2)**
Acute myeloid leukaemia recurrent	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Post transplant lymphoproliferative disorder	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Nervous system disorders	**1**	**(3.6)**	**1**	**(3.7)**	**1**	**(12.5)**	**3**	**(4.8)**
Neurotoxicity	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)
Polyneuropathy	0	(0.0)	1	(3.7)	0	(0.0)	1	(1.6)
Posterior reversible encephalopathy syndrome	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Respiratory, thoracic and mediastinal disorders	**3**	**(10.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(4.8)**
Hypoxia	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Pneumonitis	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Respiratory distress	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.6)
Vascular disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(1.6)**
Venoocclusive disease	0	(0.0)	0	(0.0)	1	(12.5)	1	(1.6)

Every participant is counted a single time for each applicable row and column.
MedDRA version 25.1 was used in the reporting of this study.

Source: [P030V01MK8228: adam-adsl; adae]

SAEs were reported for 35 (55.6%) participants during the treatment phase, predominantly in the youngest age group (<2 years of age). The 2 most frequently reported SAEs were pyrexia (7.9%) and GVHD (4.8%), which are commonly encountered in the clinical setting of HSCT. Other reported Preferred Terms were diverse and mainly the subject of single reports.

Fatal adverse events

There were 4 (6.3%) fatal SAEs during the treatment phase.

Three deaths occurred for Age Group 1 participants due to the following: (1) candida infection and multiple organ dysfunction syndrome; (2) post-transplant lymphoproliferative disorder and hepatosplenic candidiasis; and (3) acute myeloid leukaemia recurrent. The fourth death was due to septic shock (Age Group 2).

Two participants had AEs with a fatal outcome after the treatment phase; 1 in Age Group 1 (acute lymphocytic leukaemia recurrent) and 1 in Age Group 2 (thrombotic microangiopathy).

2.5.8.4. Laboratory findings

Disturbances in haematological parameters were common amongst paediatric HSCT patients in the study. This reflects the underlying condition and transplant procedure as well as concomitant treatment regimens that are known to be myelotoxic.

Disturbances in liver function tests were also common paediatric HSCT patients in the study, and this is not unexpected. ADRs of ALT and AST increased are already listed for letermovir in the authorised SmPC. On review, neither of the two cases that met the protocol defined ECI criteria for potential DILI events (of which one occurring before the treatment period) could be attributed to study treatment.

2.5.8.5. Safety in special populations

Female participants who were pregnant and/or lactating were excluded from enrolment in the study. No pregnancies were reported during the study. Therefore, there are no new data to further inform the risk assessment for the use of LET during pregnancy and lactation.

2.5.8.6. Immunological events

AEs relating to hypersensitivity were reported in 6.3% (see section of Adverse events above). On review of the data, the concomitant use of multiple other classes of drug in HSCT patients generally precludes direct attribution to letermovir.

2.5.8.7. Safety related to drug-drug interactions and other interactions

No new DDI studies were conducted in the paediatric population.

One on-treatment drug-related (investigator assessment) adverse event of drug interaction with tacrolimus, moderate, requiring no interruption of study treatment, and resolved, was reported in a single female patient aged 12 years.

2.5.8.8. Discontinuation due to adverse events

A total of 51 participants completed the study through Week 24 post-transplant and 43 participants completed the study through Week 48 post-transplant. There were 8 (12.7%) discontinuations of study drug due to an adverse event during the treatment phase. On review of the case narratives, particularly given that prior and concomitant polypharmacy was administered in all patients in the paediatric study, no case could be identified where the AE leading to discontinuation of study drug can be directly attributed to treatment with LET.

2.5.8.9. Post marketing experience

The MAH's safety database was queried for valid, spontaneous, and non-interventional study reports in patients <18 years of age. Between 01-NOV-2017 to 01-OCT-2023 (i.e. since first worldwide authorisation in adults), a total of 136 reports with 276 events were identified. Of the 276 events; 51 were considered serious and 225 were non serious. The median age was 11 years (range: 3 months – 17 years). Notably, a large proportion of reported events concerned off-label use in the paediatric population rather than a clinical sign or symptom per se. Otherwise, the reports fall largely under SOC Gastrointestinal disorders, Immune system disorders, Infections and infestations and Investigations, which is not unexpected for the population or for the product.

2.5.9. Discussion on clinical safety

The safety of Prevymis in adult HSCT patients was previously established from data from a pivotal Phase 3 study P001 of up to 14 weeks' LET in 373 HSCT recipients, which was submitted to support 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/004536/0000).

The MAH presents in this submission safety data from Study P030, a single open-label, single-arm Phase 2b study to evaluate the PK, efficacy, safety, and tolerability of LET when used for CMV prophylaxis in paediatric participants who were at risk of developing CS-CMVi following an allogeneic HSCT. This was primarily a PK study. Additional reassurance regarding clinical safety is provided in the form of exposure-matching to the exposure demonstrated to be effective and safe in adult HSCT patients.

The approach to collection of safety data in study P030 was reasonable overall for the study design and overall authorisation strategy for this direct acting antiviral, namely extrapolation of efficacy and safety from adult data. The small size (n=63) and open-label, single arm nature of this study limit interpretation of the data for the purposes of independently establishing clinical safety in paediatric patients. Specifically, the study is not comparative and not large enough to detect new events specific to the paediatric population occurring at a frequency lower than around 1 in 20 (applying the 3/X rule). Moreover, the investigator's assessment of treatment-relatedness is unavoidably impacted by the single-arm, open-label design and as such these attributions are to be interpreted with caution.

Patients with pre-existing severe hepatic or renal insufficiency, or simultaneous moderate hepatic and renal insufficiency, were excluded from the paediatric study. This is already reflected in warning statements in section 4.2 of the authorised SmPC, whereby the product is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment, moderate hepatic impairment combined with moderate or severe renal impairment or ESRD. There are no clinical safety data for letermovir treatment beyond 100 days in paediatric HSCT patients. The paediatric study was limited to HSCT patients, and no data are available from paediatric kidney transplant patients.

Early non-clinical studies (in rat) identified testicular toxicity as a potential safety concern for letermovir. However, based on the totality of non-clinical data in other species as well as adult clinical data to date, and following re-discussion with regulatory authorities, specific clinical safety indicators for testicular toxicity were not followed in the paediatric clinical study.

Compliance with the study intervention regimen was high (99.0%). Most participants (61/63, 96.8%) received oral study intervention (tablets or oral granules) for a median duration (range) of 76 days (1 to 102 days). The 24 participants who received IV study intervention did so for a median duration (range) of 20 days (2 to 32 days).

Treatment-emergent adverse events were reported for all study participants. The 6 most frequently reported AEs during the treatment phase were vomiting (58.7%), pyrexia (42.9%), diarrhoea (38.1%), GVHD (38.1%), abdominal pain (28.6%), and nausea (28.6%). These non-specific adverse events are common in the clinical setting of HSCT in both adult and paediatric patients and may also occur secondary to underlying and/or concomitant medications. All of these terms, with the exception of pyrexia and GVHD which occur secondary to the disease and associated complications, are listed as ADRs in the Prevymis SmPC. The observed rates of GVHD and CMV infection/ reactivation are in line with that previously seen in adults post-HSCT in study P001, which is reassuring.

The paediatric safety database is too small to permit meaningful comparison of the AE profile by age subgroup, sex, race, and ethnicity etc.

SAEs were reported for 35 (55.6%) participants during the treatment phase, predominantly in the youngest age group (<2 years of age). The 2 most frequently reported SAEs were pyrexia (7.9%) and GVHD (4.8%), which are commonly encountered in the clinical setting of HSCT. Other reported Preferred Terms were diverse and mainly the subject of single reports.

All four reported fatal adverse events are consistent with the clinical context and underlying disease. None of these can be reasonably attributed to the study drug. Review of the case narratives for study deaths reveals nothing to indicate that adverse effects or lack of efficacy of LET contributed to deaths.

Even high-level comparison with clinical safety data from the previously completed study P001 in adult HSCT during the first 100 days of letermovir is hampered by the small size, open-label design, and lack of placebo arm in the paediatric study P030 and concomitant (and toxic) polypharmacy administered across all clinical studies in HSCT. Importantly, both the underlying reasons for HSCT and the treatment regimens administered concomitantly with LET differ between the paediatric and adult populations. Therefore, observed numerical discrepancies may represent differences in background rate of non-LET-treatment-related complications in the paediatric population rather than a difference in safety profile of letermovir per se (e.g. abdominal pain is a very frequent, non-specific complaint in the paediatric population). The current ADR profile described in SmPC section 4.8 is considered to already adequately inform the prescriber on potential risks of letermovir relevant to the paediatric population, and no changes to the already agreed frequency categories are deemed necessary. In summary, it is agreed that no new ADRs for letermovir are identified for the paediatric HSCT population based on the clinical safety data generated in the paediatric study P030.

The MAH was asked to discuss in further detail the clinical safety of an excipient (hydroxypropyl betadex (cyclodextrin)) specific to the IV formulation and known to confer a risk of renal toxicity, for which the proposed doses overstep the general safety threshold of 20 mg/kg/d. A total of 24/63 participants in Study P030 (of which 10 were >12 years of age, 11 were 2 to <12 years of age, and 3 were <2 years of age) received intravenous LET with a median duration of exposure of 20 days. Thus, the clinical safety data that can support safety of the intravenous formulation in paediatric patients, particularly in the youngest age subset, is very limited and furthermore confounded by the initial choice of administration route being inextricably linked to patient clinical status, so as to make interpretation difficult in the absence of a placebo arm. Whilst acknowledging these limitations, it can be agreed that the incidence of renal or extrarenal adverse events, including laboratory abnormalities, was numerically comparable in participants who received the IV formulation and those who received the oral formulation only.

The authorised SmPC text plus agreed updates, such as the update in section 5.3 on potential hearing loss in animal studies (refer to discussion on non-clinical aspects), including warnings specific to the potential risks of hydroxypropyl betadex used in the intravenous formulation and a recommended maximum IV treatment duration of 4 weeks, adequately reflects safety aspects for letermovir in the

paediatric population.

2.5.10. Conclusions on the clinical safety

No new safety concerns have been identified beyond what has already been established for letermovir in adult HSCT. The paediatric safety database is small, however exposure-matching to adult HSCT patients also provides reassurances.

The agreed updates to the SmPC, including wording specific to the potential risks of hydroxypropyl betadex used in the intravenous formulation and a recommended maximum IV treatment duration of 4 weeks, ensure that the information adequately reflects safety aspects for letermovir specific to the paediatric population.

2.6. Risk Management Plan

2.6.1. Safety concerns

None.

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

None.

2.6.4. Conclusion

The CHMP considered that the risk management plan version 6.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

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.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Cytomegalovirus infection is very common and generally acquired early in life, with the majority of the adult population being cytomegalovirus-seropositive in most countries. Similar to other herpesviruses, acute infection is generally followed by latent (dormant) infection. Among individuals with intact immune systems, reactivation of cytomegalovirus infection is uncommon and is generally asymptomatic. However, cytomegalovirus reactivation in immunocompromised patients, such as immunosuppressed transplant recipients, can cause significant morbidity and mortality.

In allogeneic haematopoietic stem cell transplant recipients, the risk of cytomegalovirus infection is mostly due to reactivation of latent cytomegalovirus infection. Haematopoietic stem cell transplant recipients with prior cytomegalovirus infection are at highest risk for developing cytomegalovirus reactivation and disease, especially during the first 100 days post-transplant.

In kidney transplant recipients the cytomegalovirus disease incidence varies by serostatus with the highest incidence among cytomegalovirus seronegative kidney recipients with a transplanted kidney from a cytomegalovirus positive donor.

Letermovir is currently indicated for the prophylaxis of cytomegalovirus infection and disease in adult cytomegalovirus seropositive recipients of an allogeneic haematopoietic stem cell transplant and for the prophylaxis of cytomegalovirus disease in adult kidney transplant recipients at high risk (donor cytomegalovirus seropositive/recipient cytomegalovirus seronegative).

3.1.2. Available therapies and unmet medical need

Two preventive strategies for cytomegalovirus are used for transplant recipients: (1) antiviral prophylaxis, and (2) pre-emptive therapy, the practice of active surveillance for viral replication and initiating treatment with anti- cytomegalovirus agents when cytomegalovirus viremia is detected.

No antivirals are currently approved for the prevention of cytomegalovirus in paediatric haematopoietic stem cell transplant recipients. Of the 2 preventive approaches, pre-emptive therapy is more complicated since initiation of treatment is based on viral load monitoring with treatment initiated only as viral replication is detected. Additionally, currently available anti-cytomegalovirus agents used for pre-emptive (for example, ganciclovir, valganciclovir, and foscarnet) have significant toxicities, including myelotoxicity.

Ganciclovir and its prodrug, valganciclovir, are currently the only anti-cytomegalovirus agents approved for prevention of cytomegalovirus disease in paediatric kidney transplant recipients at high risk. In addition to myelosuppression other limitations of ganciclovir/valganciclovir prophylaxis in kidney transplant recipients include the need for dose modification based on renal function, which can inadvertently result in underdosing of the antiviral in these patients, increasing the risk of cytomegalovirus viral breakthrough, cytomegalovirus disease, and the development of antiviral drug resistance.

3.1.3. Main clinical study

Study MK-8228-030 was a Phase 2b, open label, single arm study to evaluate pharmacokinetics, efficacy, safety, and tolerability of letermovir when used for cytomegalovirus prophylaxis in paediatric participants from birth to <18 years of age who are at risk of developing clinically significant cytomegalovirus infection following an allogeneic haematopoietic stem cell transplant. The primary endpoint was to evaluate pharmacokinetics and efficacy was a secondary endpoint.

3.2. Favourable effects

Letermovir efficacy has been established in adult haematopoietic stem cell transplant and kidney transplant recipients. As comparable exposure has been established, letermovir is expected to be effective also in paediatric patients considering the weight cut-offs from 5 kilograms in paediatric haematopoietic stem cell transplant recipients and from 40 kilograms in paediatric kidney transplant recipients.

In study P030 the percentage of participants with clinically significant cytomegalovirus infection defined as the occurrence of either cytomegalovirus end-organ disease, or initiation of anti-cytomegalovirus pre-emptive therapy based on documented cytomegalovirus viremia was 7.1% and 10.7% through Week 14 and Week 24 post-transplant, respectively. The results were comparable across the 3 age groups (12 to less than 18 years, 2 to less than 12 years, and less than 2 years). No cases of cytomegalovirus end-organ disease were observed.

3.3. Uncertainties and limitations about favourable effects

There are no clinical data in paediatric kidney transplant patients and extrapolation from haematopoietic stem cell transplant patients to kidney transplant paediatric patients was applied. For adults, while letermovir dosing is the same for haematopoietic stem cell transplant and kidney transplant, the resulting exposure is higher for kidney transplant patients due to differences in pharmacokinetics. Since the pharmacokinetics/pharmacodynamics relation may differ between haematopoietic stem cell transplant and kidney transplants (for example, due to a higher viral load in the latter case which constitutes a primary infection), the target exposure range for kidney transplant is determined by what was actually reached in the relevant adult study. The adult exposure range must be matched for paediatric kidney transplant patients, as the efficacy of lower exposures in kidney transplant has not been established.

The population pharmacokinetics model is considered adequate for paediatric haematopoietic stem cell transplant recipient subjects down to 5 kilograms. However, using this model for paediatric kidney transplant patients (with no pharmacokinetics data from paediatric kidney transplant patients), considering the observed differences in pharmacokinetics between adult haematopoietic stem cell transplant and kidney transplant patients, is not straightforward. The adult kidney transplant model

can be used for paediatric population weighing at least 40 kilograms (body weight range considered covered by the adult dataset).

3.4. Unfavourable effects

Amongst 63 paediatric haematopoietic stem cell transplant patients treated with letermovir up to 100 days in a single open-label, single-arm Phase 2b pharmacokinetics and safety study, the most frequently reported adverse events during the treatment phase were vomiting (58.7%), pyrexia (42.9%), diarrhoea (38.1%), graft-versus-host disease (38.1%), abdominal pain (28.6%), and nausea (28.6%).

Serious adverse events were reported for 35 (55.6%) participants during the treatment phase, predominantly in the youngest age group (<2 years of age). The 2 most frequently reported Serious adverse events were pyrexia (7.9%) and graft-versus-host disease (4.8%). Other reported Preferred Terms were diverse and mainly the subject of single reports.

There were no fatal serious adverse events during the treatment or follow-up phases attributable to letermovir treatment.

There were 8 (12.7%) discontinuations of study drug due to an adverse event during the treatment phase.

3.5. Uncertainties and limitations about unfavourable effects

Interpretation of the clinical safety data from study P030 is limited by the small size (n=63), in particular with respect to detection of adverse events occurring with a frequency lower than approximately 1 in 20 (applying the 3/X rule).

High-level comparison with clinical safety data from the previously completed study P001 in adult haematopoietic stem cell transplant during the first 100 days of letermovir is hampered by the open-label design, and lack of placebo arm in the paediatric study P030 and concomitant (and toxic) polypharmacy administered across all clinical studies in haematopoietic stem cell transplant. Importantly, both the underlying reasons for haematopoietic stem cell transplant and the treatment regimens administered concomitantly with letermovir differ between the paediatric and adult populations. Therefore, observed numerical discrepancies may represent differences in background rate of non-letermovir-treatment-related complications in the paediatric population rather than a difference in safety profile of letermovir per se.

The intravenous-formulation contains the excipient hydroxypropyl betadex and recommended safety thresholds are not met in the proposed dosages. The incidence of renal or extrarenal adverse events, including laboratory abnormalities, was numerically comparable in participants who received the intravenous formulation and those who received the oral formulation only, however the total amount of safety data is limited. Agreed updates to the Summary of the Product Characteristics therefore include warnings specific to the potential risks of hydroxypropyl betadex used in the intravenous formulation and a recommended maximum intravenous treatment duration of 4 weeks.

Patients with pre-existing severe hepatic or renal insufficiency, or simultaneous moderate hepatic and renal insufficiency, were excluded from the paediatric study, in line with earlier adult studies.

There are no clinical safety data from letermovir treatment for longer than 100 days in paediatric haematopoietic stem cell transplant patients.

There are no clinical safety data from paediatric kidney transplant patients.

The Committee for Medicinal Products for Human Use considered that these uncertainties can be adequately managed with routine pharmacovigilance.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Given the limitations of pre-emptive therapy and lack of tolerable cytomegalovirus prophylaxis there is an unmet medical need in paediatric haematopoietic stem cell transplant and kidney transplant patients. Letermovir has favourable efficacy and safety profiles in adults and therefore if comparable exposures can be achieved in paediatric haematopoietic stem cell transplant and kidney transplant patients, letermovir is expected to be effective and safe also in these populations.

A key issue is that due to differences in letermovir bioavailability and clearance depending on medical condition, adult exposure was higher in kidney transplant patients than post- haematopoietic stem cell transplant. The mechanism behind this is unknown. It is also unknown whether the same difference will be seen in paediatric patients (there are no data in paediatric kidney transplant patients). Moreover, the cytomegalovirus infection in haematopoietic stem cell transplant is a reactivation of the patient's chronic, latent cytomegalovirus, whereas that in kidney transplant is a primary infection from the graft. This is anticipated to result in different viral dynamics, which means that the exposure necessary for effective treatment may not be similar and may be higher in the kidney transplant setting.

The population pharmacokinetic model is considered adequate to support the dose in paediatric haematopoietic stem cell transplant recipient subjects down to 5 kilograms.

Since the pharmacokinetic/pharmacodynamic relation may differ between haematopoietic stem cell transplant and kidney transplant, the target exposure range for kidney transplant is determined by what was actually reached in the relevant adult study. The adult exposure range must be matched for paediatric kidney transplant patients, as the efficacy of lower exposures in kidney transplant has not been established. The adult kidney transplant model could be used for adolescents weighing at least 40 kilograms. However, using only the popPK model for paediatric kidney transplant patients (with no kidney transplant data from paediatric kidney transplant patients), considering the observed differences in pharmacokinetics between adult haematopoietic stem cell transplant and kidney transplant patients, is not straightforward. Thus, for kidney transplant paediatric subjects below 40 kilograms, no dose can currently be justified for bridging to adult data.

Notwithstanding the described uncertainties regarding the paediatric clinical safety database, the observed safety profile was generally in line with what has previously been characterised in adult haematopoietic stem cell transplant patients and is described in the authorised Product Information. No new adverse drug reactions for letermovir are identified for the paediatric haematopoietic stem cell transplant population based on the clinical safety data generated in the paediatric study P030. Exposure-matching to exposures established as efficacious and safe in adult haematopoietic stem cell transplant patients provides additional reassurance regarding clinical safety. Agreed updates to the Summary of the Product Characteristics include warnings specific to the potential risks of hydroxypropyl betadex used in the intravenous formulation and a recommended maximum intravenous treatment duration.

3.6.2. Balance of benefits and risks

Regarding the indication in an allogeneic haematopoietic stem cell transplant patients, the benefit/risk is considered positive for paediatric patients weighing at least 5 kilograms.

Regarding the indication in kidney transplant patients, the benefit/risk is considered positive for paediatric patients weighing at least 40 kilograms.

3.7. Conclusions

The overall benefit/risk balance of Prevymis is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Prevymis is not similar to Livtencity within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Prevymis is favourable in the following indications:

Film-coated tablets

> *PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult and paediatric patients weighing at least 15 kg who are CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).*
>
> *PREVYMIS is indicated for prophylaxis of CMV disease in CMV-seronegative adult and paediatric patients weighing at least 40 kg who have received a kidney transplant from a CMV-seropositive donor [D+/R-].*
>
> *Consideration should be given to official guidance on the appropriate use of antiviral agents.*

Concentrate for solution for infusion and granules in sachets

> *PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult and paediatric patients weighing at least 5 kg who are CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).*
>
> *PREVYMIS is indicated for prophylaxis of CMV disease in CMV-seronegative adult and paediatric patients weighing at least 40 kg who have received a kidney transplant from a CMV-seropositive donor [D+/R-].*
>
> *Consideration should be given to official guidance on the appropriate use of antiviral agents.*

The CHMP therefore recommends the extension(s) of the marketing authorisation for Prevymis subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0455/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
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, IIIA and IIIB

Extension applications to introduce a new pharmaceutical form (granules in sachet) associated with new strengths (20 mg and 120 mg) grouped with a type II variation (C.I.6.a) to include treatment in paediatric allogeneic haematopoietic stem cell transplant patients weighing at least 5 kg (concentrate for solution for infusion and granules in sachet) or 15 kg (film-coated tablets), and in paediatric kidney transplant patients weighing at least 40 kg (all pharmaceutical forms) based on the final results from studies MK-8228-030 and MK-8228-031.

Study MK-8228-030 was a Phase 2b, open-label, single-arm study to evaluate PK, efficacy, safety, and tolerability of letermovir when used for cytomegalovirus (CMV) prophylaxis in paediatric participants from birth to <18 years of age who are at risk of developing CS-CMVi following an allogeneic HSCT. Study MK-8228-031 was an open-label, single-dose, four-period, seven-treatment, crossover study designed to evaluate the bioavailability of 2 paediatric formulations of letermovir (Formulations A and B) administered alone or in soft food (applesauce and vanilla pudding) compared to a currently marketed tablet formulation.

As a consequence, sections 4.1, 4.2, 4.5, 4.8, 4.9, 5.1 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.0 of the RMP has also been approved. In addition, the MAH took the opportunity to introduce editorial updates throughout the Product Information and to update the list of local representatives in the Package Leaflet.