EU RISK MANAGEMENT PLAN (RMP) FOR LETERMOVIR

Oral tablet, 240 mg

Oral tablet, 480 mg

Concentrate for Solution for Infusion, 20mg/mL, 240 mg

Concentrate for Solution for Infusion, 20mg/mL, 480 mg

RMP version to be assessed as part of this application:

RMP Version number: 4.1

Data lock point for this RMP: 01-MAY-2022

Date of final sign off: 06-Dec-2022

Rationale for submitting an updated RMP:

This RMP is being revised to support the following:

Use of letermovir for the prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant through 200 days (P040).

Use of letermovir for the prophylaxis of CMV disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]) (P002).

Removal of missing information from non-clinical safety concerns for letermovir.

Summary of significant changes in this RMP:

RMP Section	Summary of Changes
PART I: PRODUCT(S) OVERVIEW	Use of letermovir in kidney transplant population added to the indication. Duration of letermovir extended from 100 days to 200 days in participants at risk for late CMV infection and disease under dosage.
PART II: MODULE SI- EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)	Epidemiology information on extended use of letermovir through 200 days updated. Epidemiology information on the kidney transplant population updated.
PART II: MODULE SII- NON-CLINICAL PART OF THE SAFETY SPECIFICATION	Table SII.1 Updated with results from the 6-month carcinogenicity in rasH2 transgenic mice, and information from clinical trials P002 and P040. Table SII.2 Removed missing information of "Abnormal findings in rat fertility studies with an unknown significance to male patients"
PART II: MODULE SIII- CLINICAL TRIAL EXPOSURE	Updated with exposure data from P002 and P040
PART II: MODULE SIV- POPULATION NOT STUDIED IN CLINICAL TRIALS	Updated with information from P002 and P040
PART II:MODULE SV- POST-AUTHORIZATION EXPERIENCE	Exposure data updated with data lock point of 01-MAY-2022

Other RMP versions under evaluation: Not applicable

RMP Version number: Not applicable

Submitted on: Not applicable

Procedure number: Not applicable

Details of the currently approved RMP:

Version number:3.1

Approved with procedure: EMEA/H/C/004536/R/0027

Date of approval (opinion date): 24-AUG-2022

QPPV name*:* Guy Demol, MD

QPPV signature: see signature page

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Experience
ATC	Anatomical Therapeutic Chemical classification system
ATMP	Advanced Therapy Medicinal Product
BID	Twice A Day
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human
CT	Computed Tomography
DUS	Drug Utilization Study
ECG / EKG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPITT	European Pharmacovigilance Issues Tracking Tool
EU	European Union
HGB	Hemoglobin
HLGT	High Level Group Term
HLT	High Level Term
HSCT	Haematopoietic Stem Cell Transplant
ICH	International Conference on Harmonization
IM	Intramuscular(ly)
INN	International Nonproprietary Name
IV	Intravenous(ly)
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
PAES	Post-authorization Efficacy Study
PASS	Post-authorization Safety Study
PO	Oral(ly)
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term

QD	Once Daily
QOD	Every Other Day
QPPV	Qualified Person for Pharmacovigilance
QWK	Weekly
RMP	Risk Management Plan
SC	Subcutaneous
SOC	System Organ Class
SmPC	Summary of Product Characteristics
TIW	Three Times Per Week
VGCV	Valganciclovir
WBC	White Blood Cell Count

PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) **(INN or Generic name)**	Letermovir
Pharmacotherapeutic group(s) (ATC Code)	Antiviral (J05AX18)
Marketing Authorisation Holder	Merck Sharp & Dohme LLC.
Number of medicinal products to which this RMP refers	1 product with 2 formulations (oral tablets and concentrate for solution for infusion)
Invented name(s) in the European Economic Area (EEA)]	PREVYMIS® Oral tablets, 240 mg and 480 mg. PREVYMIS®. Concentrate for solution for infusion 240 mg and 480 mg (20mg/mL)
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: CMV viral DNA terminase complex inhibitor
	Summary of mode of action: Letermovir inhibits the CMV DNA terminase complex, which is required for viral DNA replication
	Important information about its composition: Letermovir Concentrate for solution for infusion contains hydroxypropyl β-cyclodextrin (also called hydroxypropylbetadex)
Hyperlink to the Prescribing Information	The current version of the Prescribing Information (PI) was approved on 4-Jan-2022 via procedure EMEA/H/C/004536/ R/0027 and is available at the following hyperlink: https://www.ema.europa.eu/en/documents/product-information/prevymis-epar-product-information_en.pdf
Indication(s) in the EEA	Current: PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).
	Proposed: PREVYMIS is indicated for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor [D+/R-].

Table I.1: Product Overview

Dosage in the EEA	Current: PREVYMIS is available as oral tablets and concentrate for solution for infusion (240mg and 480mg). PREVYMIS tablets and concentrate for solution for infusion may be used interchangeably at the discretion of the physician, and no dose adjustment is necessary. The recommended dosage of PREVYMIS is 480mg once daily. PREVYMIS should be started after HSCT. PREVYMIS may be started on the day of transplant and no later than 28 days post-transplant. PREVYMIS may be started before or after engraftment. Prophylaxis with PREVYMIS should continue through 100 days post-transplant. The safety and efficacy of letermovir use for more than 100 days has not been studied in clinical trials. Prolonged letermovir prophylaxis beyond 100 days post-transplant may be of benefit in some patients at high risk for late CMV reactivation (see section 5.1). Use of letermovir prophylaxis for greater than 100 days requires a careful assessment of the benefit-risk balance.
	Dosage adjustment ▪ If PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily (see sections 4.5 and 5.2). ▪ If cyclosporine is initiated after starting PREVYMIS, the next dose of PREVYMIS should be decreased to 240 mg once daily. ▪ If cyclosporine is discontinued after starting PREVYMIS, the next dose of PREVYMIS should be increased to 480 mg once daily. ▪ If cyclosporine dosing is temporarily interrupted due to high cyclosporine levels, no dose adjustment of PREVYMIS is needed.
	Proposed: *HSCT (revision to use post 100 days is proposed as follow):* Prolonged PREVYMIS prophylaxis beyond 100 days post-HSCT may be of benefit in some patients at high risk for late CMV reactivation (see section 5.1). The safety and efficacy of PREVYMIS use for more than 200 days has not been studied in clinical trials. *Kidney Transplant (addition of subsection on dosing in kidney transplant patients is proposed):* PREVYMIS should be started on the day of transplant and no later than 7 days post-kidney transplant and continued through 200 days post-transplant.

Table I.1: Product Overview

Pharmaceutical form(s) and strengths	Current: **Film-coated tablet (tablet):** PREVYMIS 240mg film-coated tablets Each film-coated tablet contains 240mg of letermovir. Yellow oval tablet of dimensions 16.5mm x 8.5 mm, debossed with "591" on one side and MSD logo on the other side. PREVYMIS 480mg film-coated tablets Each film-coated tablet contains 480mg of letermovir. Pink oval, bi-convex tablet of dimensions 21.2mm x 10.3mm, debossed with "595" on one side and MSD logo on the other side. **Concentrate for solution for infusion (sterile concentrate):** PREVYMIS 240 mg concentrate for solution for infusion Each vial contains 240mg (12mL per vial) of letermovir. Each mL contains 20mg of letermovir. PREVYMIS 480mg concentrate for solution for infusion Each vial contains 480mg (24mL per vial) of letermovir. Each mL contains 20mg of letermovir. Clear, colourless liquid pH between 7 and 8
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

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

Incidence: Cytomegalovirus (CMV) is ubiquitous and generally acquired early in life, with the majority of the adult population being CMV-seropositive in most countries worldwide. Allogeneic HSCT recipients are immune-compromised, which increases the risk for CMV infection (as measured by CMV viremia), mostly due to reactivation of latent CMV infection. PREVYMIS prophylaxis in the first 100 days post-HSCT has been shown to be effective in preventing CMV infection and disease following HSCT [Ref. 5.4: 085RKS]. However, after completion of prophylaxis with PREVYMIS, clinically significant late CMV infection (i.e., CMV infection and or disease occurring beyond day 100 post-transplantation) can occur in some patients.

Among allogeneic HSCT recipients who are CMV seropositive (R+), 80% of recipients develop CMV reactivation, and 20% to 35% of this population progress to CMV disease in the absence of preventive measures [Ref. 5.4: 03RRN9]. The highest risk period for developing CMV infection (as defined by detectable CMV DNA) is during the first 100 days post-transplant [Ref. 5.4: 03RTB5].

Prevalence: In 2019, the median HSCT rate (TR) per 10 million in Europe was 144 [Ref. 5.4: 07YS3Z]). According to available studies, adult HSCT recipients who have evidence of prior CMV infection (R+) are at risk for CMV reactivation and disease post-HSCT [Ref. 5.4: 03RRN9, 04HYZL, 04HYZR, 04J8SK]. In the review of three studies from the USA and Sweden, [Ref. 5.4: 07YS42] a CMV seropositive rate of 55.9% (2114/3780) was reported in all-HSCT; 13% of the seropositive patients developed CMV disease versus 1.7% of CMV seronegative recipients. Thus, the CMV-seropositive recipients had ninefold higher odds of CMV disease than the CMV-seronegative recipients (OR 9.12, 95% CI 6.19–13.43, $p < 0.0001$).

Demographics of the population in the authorized indication and risk factors for the disease:

From 2006 to 2012, approximately 400,000 allogeneic HSCTs were reported by 1,516 transplant centers in 75 countries [Ref. 5.4: 04J8SG], including approximately 10,000 subjects in the U.S. The numbers from the US remain the same annually for more recent years (2013-2019) [Ref. 5.4: 05N82D]. In Europe, 19,800 allogeneic HSCTs were performed in 30 European and 11 non-European countries in 2019 [Ref. 5.4: 07YS3Z]. From 2006 to 2012, in Southeast Asia and Western Pacific region, there were (on average) approximately 6,400 allogeneic HSCTs performed annually [Ref. 5.4: 04J8SG]. According to one large retrospective study of over 28,000 HSCTs, patients were on average 43 years old (interquartile range: 31 to 53 years) and were more often male (55% male vs 45% female)

[Ref. 5.4: 04L9MF]. There is no evidence demonstrating regional or gender differences in CMV infection or disease among HSCT patients.

The main existing treatment options:

There are currently two approaches to preventing CMV infection or disease in HSCT recipients:

1) Prophylaxis with PREVYMIS, and 2) pre-emptive therapy (PET), which refers to the practice of active surveillance for viral replication and initiating treatment with anti-CMV agents when CMV viremia is detected [Ref. 5.4: 03RT9X].

Prior to PREVYMIS, all available anti-CMV agents, whether used for prophylaxis or PET, are nucleoside analogues which have toxicities, including myelosuppression and nephrotoxicity, that limit their clinical utility. The most widely used agents, ganciclovir (GCV) and valganciclovir (VGCV), are associated with myelosuppression, which is problematic in the HSCT setting. The use of foscarnet, a second-line agent, is often associated with nephrotoxicity. Cidofovir, typically used as a third-line agent, is associated with both myelosuppression and renal impairment. High doses of acyclovir or valacyclovir are sometimes used for prophylaxis, but their role in the management of CMV is questionable and they are not approved as anti-CMV therapy [Ref. 5.4: 03V285, 03RSYS].

In patients at high risk for late CMV infection or disease after 100 days post-transplant, PET has been a standard approach. However, PET may be suboptimal for several reasons, including:

- PET is initiated after patients develop CMV viremia. A recent study concluded that CMV viremia is associated with an increased risk of overall mortality regardless of the initiation of PET [Ref. 5.4: 04HYZH].

- Given the toxicities associated with anti-CMV agents, it is important not to initiate PET unless it is clear that the benefit outweighs the risks. However, there is no universally accepted viral load threshold for the initiation of PET to guide clinicians when to initiate PET [Ref. 5.4: 04JBHN].

- PET requires frequent monitoring for CMV viremia, which is both burdensome and costly [Ref. 5.4: 04JBGP].

Based on the limitations of PET for late CMV infection or disease, a safe and efficacious prophylaxis strategy represented a significant advantage. Thus, there was an unmet medical need for an effective and well-tolerated antiviral agent for the prevention of CMV infection and disease in HSCT recipients [Ref. 5.4: 04JBGP, 04JBHS, 04HYZL]. Such an agent fulfills the need to prevent the direct and indirect effects of CMV viremia. A recent study has also found that extending PREVYMIS use beyond week 14 (~100 days) post-allogeneic HSCT led to reduced CMV reactivation and could be warranted in patients at high risk of developing late-onset CMV disease [Ref. 5.4: 085RL2].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The highest risk period for developing CMV infection is during the first 100 days post HSCT [Ref. 5.4: 03RTB5]. Risk factors that can further increase probability of CMV infection (defining a subset of "high risk" patients) include: older age of recipient, CMV positivity of the donor (D+) and transplant-related factors including use of high dose corticosteroids, T-cell depletion, use of mismatched or unrelated donor and graft-versus-host disease (GVHD), use of T cell depleting agents (antithymocyte globulin, fludarabine, and alemtuzumab), use of CD 34+ selected (T cell depleted) transplant, and total body irradiation for conditioning in preparation of HSCT transplantation, GVHD, a low CD4 count, and undetectable CMV-specific T-cell immunity [Ref. 5.4: 04LLX2, 03W7QK, 04J8SD]. The clinical effects of CMV infection can be divided into direct and indirect effects [Ref. 5.4: 03RT9X, 03RVMQ].

The direct effects, which have been extensively described, include the spectrum of CMV disease manifestations. CMV gastroenteritis is a common clinical presentation in this population. While pneumonia is the most serious manifestation, it has become relatively infrequent with current pre-emptive therapy strategies for CMV disease [Ref. 5.4: 03RVMQ, 03RVMS]. Other rarer manifestations of CMV disease include hepatitis, retinitis, and encephalitis [Ref. 5.4: 03RT9X, 03RVMQ]. The indirect effects of CMV infection include increased risk of opportunistic bacterial and invasive fungal infections, GVHD, and non-relapse mortality as well as all-cause mortality [Ref. 5.4: 03RVN2, 03RVN6, 03RTB5, 03RVN7, 03RVN8, 03RVNB, 03RVNC, 04J8SD, 04HYZH].

Important co-morbidities:

Of the 118,782 allogeneic HSCTs reported to have been performed globally from 2006 to 2010, 85,550 (72%) were associated with underlying leukemias, 17,427 (15%) with lymphoproliferative disorders, 14325 (12%) with non-malignant disorders, 722 (<1%) with solid tumors and 758 (<1%) had other underlying conditions for receiving HSCT [Ref. 5.4: 04J8SG].

In the U.S., acute leukemias (AML, ALL) and MSD accounted for 76% of allo-HSCTs [Ref. 5.4: 05N82D]. Similarly in Europe, the main indications for allo-HSCT in 2019 were myeloid malignancies (98%) with AML accounting for 38% [Ref. 5.4: 07YS3Z].

HSCT recipients receive cytotoxic antineoplastic agents as components of the pre-HSCT conditioning regimen and thereafter experience a prolonged and profound period of neutropenia between HSCT and engraftment, during which the HSCT recipient is at high risk for infectious post-procedure complications (i.e., bacterial, fungal and/or viral infections). HSCT recipients also require immunosuppressive agents such as CsA and tacrolimus to prevent rejection and are at risk for GVHD requiring treatment with systemic corticosteroids (see SI.2).

HSCT recipients are at increased risk of post-transplant complications including: cardiovascular disease [Ref. 5.4: 04M5Z2]; liver disease, including hepatic complications due to chronic graft versus host disease [Ref. 5.4: 04M5YV]; renal dysfunction

[Ref. 5.4: 04M5YV]; diabetes/metabolic syndrome due to the use of corticosteroids and/or calcineurin inhibitors [Ref. 5.4: 04M5YH]; and infectious complications, including those due to CMV in CMV seropositive HSCT recipients [Ref. 5.4: 04M5Z8, 04M5YM].

Indication: PREVYMIS is indicated for the prophylaxis of CMV disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]).

Incidence: D+/R- kidney transplant recipients may acquire CMV infection and disease if the virus is transmitted by the transplanted organ to a recipient who does not carry the virus [Ref. 5.4: 085JLC].

Among all kidney transplant recipients, 64% developed CMV infection and 24% progressed to CMV disease in the absence of prophylaxis [Ref. 5.4: 085JLC]. Even with the use of current preventive strategies, the incidence of CMV infection and disease may range between 17%-92% and 0%-37%, respectively [Ref. 5.4: 085RKW]. The subgroup at highest risk of post-transplant complications is D+/R- recipients, who have a 28% higher risk of graft loss, 36% higher risk of all-cause mortality, and eight times the risk of mortality from viral infection compared to that of D-/R- recipients (i.e., patients who receive CMV-negative blood or leukocyte-depleted blood products during and after transplantation) [Ref. 5.4: 085JLC, 085RKW].

Prevalence: In 2016, the kidney transplantation rate in Europe ranged from 17.8 per million people in non-EU member states to 38.1 per million people in EU member states [Ref. 5.4: 085RLF]. Prevalence was higher in the U.S., where there were 678 kidney transplant recipients per million people in 2018 [Ref. 5.4: 085RLJ]. CMV disease occurrence was nearly three times higher (56% versus 20%) in D+/R- recipients compared to the D-/R+ and D+/R+ subgroups [Ref. 5.4: 04GCTW]. Based on a prior study of 20,000 transplanted patients in the US, D+/R- recipients may account for at least 18% of the total kidney transplant population [Ref. 5.4: 085JLC].

Demographics of the population in the authorized Indication and risk factors for the disease:

Based on a study conducted in Norway, kidney transplant recipients who developed CMV infection were more likely to have D+/R- CMV IgG antibody status (60.8%) and to be of older age (mean age of 50.2 years (standard deviation of 15.0 years)) relative to recipients who did not develop CMV infection [Ref. 5.4: 085RLB]. Other risk factors for CMV infection across multiple studies included the presence of acute rejection episodes; older donor age; use of CsA, antilymphocyte antibodies, or other immunosuppressive drugs; and impaired transplant function [Ref. 5.4: 085RLB, 085RKW].

The main existing treatment options:

There is currently one approach to preventing CMV infection and disease in D+/R- kidney transplant recipients: prophylaxis, which involves the administration of VGCV to D+/R- kidney transplant recipients starting within 10 days post-transplant and continuing for 3-6

months or for 1-3 months after treatment with antilymphocyte antibodies or high-dose steroids [Ref. 5.4: 085RKW, 085JLC].

VGCV is a nucleoside analogue that has toxicities limiting its clinical utility.

Based on the high occurrence of drug-related toxicity associated with prophylaxis, a safe and efficacious preventive strategy would represent a significant advantage over the existing treatment option. Thus, there is an unmet medical need for an effective and well-tolerated antiviral agent for the prevention of CMV infection and disease in D+/R- kidney transplant recipients [Ref. 5.4: 04JBGP, 04JBHS, 04HYZL, 085RKW]. Such an agent fulfills the need to prevent the direct and indirect effects of CMV viremia and could be used prophylactically.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The subgroup of kidney transplant recipients at highest risk of developing CMV infection and disease includes D+/R- patients [Ref. 5.4: 085JLC]. In addition to CMV IgG antibody status, risk factors that can increase the probability of CMV infection are older age of the recipient, older age of the donor, presence of acute rejection episodes, exposure to immunosuppressive drugs, and impaired transplant function [Ref. 5.4: 085RLB, 085RKW]. The clinical effects of CMV infection can be divided further into direct and indirect effects [Ref. 5.4: 03RT9X, 03RVMQ, 085JLC].

The direct effects, which have been extensively described, include the spectrum of CMV disease manifestations. CMV gastroenteritis is a common clinical presentation in this population. While pneumonia is the most serious manifestation, it has become relatively infrequent with current PET strategies for CMV disease [Ref. 5.4: 03RVMQ, 03RVMS]. Other manifestations of CMV disease include hepatitis, pancreatitis, retinitis, encephalitis, and invasive disease in other tissues [Ref. 5.4: 03RT9X, 03RVMQ, 085JLC]. The indirect effects of CMV infection include increased risk of opportunistic bacterial and invasive fungal infections, GVHD, and non-relapse mortality as well as all-cause mortality [Ref. 5.4: 03RVN2, 03RVN6, 03RTB5, 03RVN7, 03RVN8, 03RVNB, 03RVNC, 04J8SD, 04HYZH, 085JLC].

In a series of prospective studies of a large Norwegian cohort of kidney transplant recipients who did not receive universal prophylaxis or PET, both CMV infection and disease were associated with several post-transplant complications. CMV infection may increase the risk of new-onset post-transplant diabetes through reduced insulin secretion. In a subgroup analysis, the incidence of new-onset diabetes was four times higher in kidney transplant recipients with CMV infection relative to those without CMV infection (26% versus 6%) [Ref. 5.4: 04GCTW]. CMV occurrence was a significant risk factor for clinical acute allograft rejection during the first 100 days post-transplantation [Ref. 5.4: 04GCTW]. Relative to no CMV infection, asymptomatic CMV infection and disease were independent risk factors for overall renal recipient mortality more than 100 days after transplantation and significantly reduced graft survival when deaths with functioning grafts were included [Ref. 5.4: 04GCTW]. CMV disease was also a significant predictor of biopsy-verified acute

tubulointerstitial rejection and has been associated with an increased risk of long-term mortality across several studies [Ref. 5.4: 04GCTW].

Important co-morbidities:

Patients eligible for kidney transplantation typically have end stage renal disease (ESRD) with an estimated glomerular filtration rate of $\leq$ 20 ml/min per 1.73 m^2 [Ref. 5.4: 085RLJ]. Among kidney transplant recipients in the U.S. in 2019, half had either diabetes mellitus (30%) or hypertension (20%) as the listed cause of ESRD, whereas glomerulonephritis (18%) and cystic kidney disease (13%) were less common [Ref. 5.4: 085RLJ].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

An extensive nonclinical safety pharmacology and toxicological program was conducted to support the filing and registration of letermovir. This program included safety pharmacology studies in both in vitro and in vivo test systems to assess potential effects on main physiological functions, in vitro and in vivo genetic toxicity studies, oral and IV acute toxicity studies in rats and mice, repeat-dose oral toxicity studies (up to 3, 6, and 9 months in duration in mice, rats, and monkeys, respectively), 4-week intravenous dose toxicity studies in rats and monkeys, local IV tolerability studies in rats and rabbits, and a 6-month carcinogenicity study in rasH2 transgenic mice. In addition, a series of reproductive and developmental studies in rats and rabbits, and a juvenile male toxicity study in rats were conducted.

The important nonclinical safety findings are summarized in Table SII.1. In this document, the nonclinical/clinical exposure (AUC) and Cmax ratios are calculated based on the clinical AUC for letermovir of 99,960 ng•hr/mL and Cmax of 21,570 ng/mL achieved at 480 mg IV in HSCT patients, which is the most conservative approach for safety margin calculation as this regimen resulted in the highest exposures in patients. The projected IV exposure of LET in the kidney transplant population is comparable to the IV exposure in HSCT recipients (see [Sec. 2.7.2.3.1.1]).

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety findings (from non-clinical studies)	Relevance to human usage
Single and repeat-dose toxicity:	In controlled Phase 3 P001 clinical trial in HSCT patients, the most commonly reported gastrointestinal adverse events in the letermovir group were diarrhea (26.0%), nausea (26.5%), and vomiting (18.5%). In Phase 3 P040 clinical trial in HSCT patients, nausea, diarrhea and vomiting were reported (11.1%, 11.8% and 4.2%, respectively). The overall rate for these adverse events was generally similar to or lower than the rate observed in the placebo group in both studies. In Phase 3 P002 clinical trial in kidney transplant patients, the most frequently reported gastrointestinal adverse events were also nausea (8.6%), diarrhea (31.5%) and vomiting (6.2%) that were reported in lower proportions compared to the active comparator. Therefore, gastrointestinal adverse effects are not considered important risks for the product.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety findings (from non-clinical studies)	Relevance to human usage
Tolerability Letermovir, when administered orally to mice for 13 weeks, was well tolerated up to the highest dose tested, 250 mg/kg/day (mean systemic exposure: 357,250 ng.hr/mL; exposure margin ~3.5X). Letermovir was also well tolerated in rats, when administered orally up to 150 mg/kg/day (high dose) for 26 weeks (mean systemic exposure: 657,750 ng.hr/mL; exposure margin ~6.5X), or intravenously up to 100 mg/kg/day for 4 weeks (mean systemic exposure: 682,934 ng.hr/mL; exposure margin ~7X). Dose-limiting toxicity, characterized by emesis, loss of appetite, soft and watery feces, body weight loss/reduced body weight gain at ≥250 mg/kg/day (mean systemic exposure: 609,500 ng.hr/mL; exposure margin ~6X) or intravenous doses ≥150 mg/kg/day (systemic exposure not measured), resulting in morbidity/mortality at oral doses ≥300 mg/kg/day (mean systemic exposure: 1,435,120 ng.hr/mL; exposure margin ~14X) was achieved in monkeys. Oral or IV doses up to 100 mg/kg/day (exposure multiples of <1X for oral and 4X for oral) were well tolerated by monkeys.	
Toxicity target organs The letermovir toxicity target organs, the testes, appear to be species-specific (identified in rats only). The testicular toxicity consisted of vacuolation of the germinal epithelium, germ cell exfoliation, tubular atrophy and damage to Sertoli cells, associated with oligospermia and cell debris in the epididymides, and decreased testes and epididymides weights at doses ≥180 mg/kg/day (mean systemic exposure: 329,865 ng.hr/mL; exposure margin ~3X). In a male fertility study, the testicular toxicity observed after approximately 15 weeks of dosing at 180 mg/kg/day was shown to be associated with decreased Inhibin B plasma concentrations and was shown to not be reversible after a 15-week treatment-free period. There were no male reproductive organ changes at 60 mg/kg/day (mean systemic exposure: 80,628 ng.hr/mL; exposure margin ~1X). Importantly, there were no male reproductive organ changes and no changes in any male sexual hormones, including Inhibin B, in Cynomolgus monkeys administered letermovir up to 250/200 mg/kg/day for 39 weeks (mean systemic exposure: 204,900 ng.hr/mL; exposure margin ~2X), and no male reproductive toxicity in mice administered letermovir up to	Testicular toxicity in rats appears to be species-specific. In the Phase 3 trials in HSCT recipients (P001) and in kidney transplant recipients (P002), there was no evidence of letermovir-related testicular toxicity in male subjects based on analysis of biomarkers used to monitor gonadotoxicity (serum inhibin B, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone). In P001, the shift in values for each of the four hormone levels from baseline was comparable in the letermovir and the placebo groups, both at the end of treatment (EOT) and the Week 24 post-transplant visit. The proportions of subjects with markers indicative of abnormal testicular function (low inhibin B and high FSH) were similar in the letermovir and placebo groups at the Week 24 post-transplant visit. However, these findings were confounded by the impact of induction chemotherapy on testicular function. Further evaluation of biomarkers of testicular toxicity in kidney transplant recipients was conducted in the Phase 3 study (P002). There was no indication of abnormal testicular function (low inhibin B and high FSH), based on the absence of clinically relevant shift from baseline in mean inhibin B and FSH levels in the letermovir group at weeks 28 and 52. Letermovir treatment had no observed impact on sex hormone

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety findings (from non-clinical studies)	Relevance to human usage
250 mg/kg/day (mean systemic exposure: 357,250 ng.hr/mL; exposure margin ~4X) for 13 weeks. There were no male reproductive organ changes noted in a 2-week juvenile toxicity study conducted in rats of 14-day up to 180 mg/kg/day (age at study start: 14-days).	(LH, FSH, testosterone, and inhibin B) levels in male kidney transplant recipients in P002. Therefore, the nonclinical finding of testicular toxicity is not considered an identified or potential risk for human use.
In the intravenous study in rats with letermovir, non-adverse vacuolation noted in the kidneys was attributed to the high dose of 1500 mg/kg/day of cyclodextrin excipient, hydroxypropylbetadex. It is known that cyclodextrins can cause kidney vacuolation in rats when given intravenously at doses > 50 mg/kg/day.	The anticipated clinical exposure to hydroxypropylbetadex with intravenously administered letermovir is expected to be approximately 3600 mg/day (72 mg/kg/day, for a human weight of 50 kg) for a letermovir dose of 480 mg. In patients with moderate to severe renal dysfunction accumulation of cyclodextrin is expected to occur. Hydroxypropylbetadex amounts of approximately 250 mg/kg/day for 21 days were found to be safe in humans older than 2 years [Ref. 5.4: 04KNRJ]. There were no cases of kidney injury in human studies of intravenously administered letermovir with treatment durations of up to 47 days. The numbers of patients with moderate or severe renal impairment (at time of enrollment) in the Phase 3 P001 trial in HSCT recipients were limited. In Phase 3 P002 and P040 clinical trials, exposure to IV formulation was infrequent: 1 participant received IV letermovir for a duration of 2 days in P040, and 3 participants received IV letermovir with the mean duration of 1.7 days in P002. Therefore, the nonclinical finding is not considered an identified or potential risk for human use.
Reproductive and embryo-fetal developmental toxicity: In the fertility and early embryonic development study in the rat, there were no effects of letermovir on female fertility up to the highest dose tested, 240 mg/kg/day (mean systemic exposure: 482,910 ng.hr/mL; exposure margin ~5X). Decreased male fertility was observed in rats at ≥180 mg/kg/day (mean systemic exposure: 355,000 ng.hr/mL; exposure margin ~3X) and were likely secondary to the testicular toxicity. There was no male reproductive organ toxicity observed in repeat dose toxicity studies in monkeys and mice even though these animals had higher systemic exposures to letermovir than those achieved in rat studies of similar duration.	Testicular toxicity in rats appears to be species-specific. In the Phase 3 trials in HSCT recipients (P001) and kidney transplant recipients (P002), there was no evidence of letermovir-related testicular toxicity in male subjects based on analysis of biomarkers used to monitor gonadotoxicity (serum inhibin B, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone). See details above. Therefore, the nonclinical finding is not considered an identified or potential risk for human use.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety findings (from non-clinical studies)	Relevance to human usage
In the embryo-fetal developmental toxicity studies in rats and rabbits, developmental toxicity including common spontaneous malformations (additional lumbar/pelvic shift) and common skeletal variations (additional rib), was observed at doses associated with maternal toxicity (body weight loss, vaginal discharge, and morbidity (in rabbits only)), 250 mg/kg/day in rats (mean systemic exposure: 1,095,279 ng.hr/mL; exposure margin ~11X) and 225 mg/kg/day in rabbits (mean systemic exposure: 170,211ng.hr/mL; exposure margin ~2X). The maternal and developmental NOAEL was 50 mg/kg/day in rats (mean systemic exposure: 258,731 ng.hr/mL; exposure margin ~2.5X) and 75 mg/kg/day in rabbits (mean systemic exposure: 47,355 ng.hr/mL; exposure margin: <1X). Importantly, in the embryo-fetal toxicity developmental studies in rats and rabbits, there were no letermovir-related effects on developing male reproductive organs. Moreover, in the pre- and postnatal development study in rats, there was no developmental toxicity up to the highest dose tested of 180 mg/kg/day (mean systemic exposure: 225,157 ng.hr/mL; exposure margin ~2X).	No adequate human data are available to establish whether or not letermovir poses a risk to pregnancy outcomes. Therefore, letermovir should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.
Genotoxicity: There was no evidence for genotoxicity in *in vitro* or *in vivo* testing, including Ames assay (bacterial reverse mutation assay), Chinese hamster lung cell chromosomal aberration assay and an in vivo assay for micronucleus induction in mouse bone marrow. The top dose was the limit dose or was limited by cytotoxicity in the in vitro genetic toxicity studies and was the maximum tolerated dose in the in vivo genetic toxicity study in mice.	Letermovir does not present a genotoxic risk to humans.
Carcinogenicity: The 6-month oral carcinogenicity study in rasH2 transgenic mice showed no evidence of human-relevant carcinogenic potential.	Letermovir does not represent a risk of carcinogenicity to humans, based on results of the 6-month oral carcinogenicity study in rasH2 transgenic mice which showed no evidence of human-relevant carcinogenic potential, the absence of genotoxicity in *in vitro* or *in vivo* testing, and the absence of a proliferative signal in the chronic toxicity studies.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety findings (from non-clinical studies)	Relevance to human usage
Safety Pharmacology: Letermovir was tested for potential effects on cardiovascular, respiratory and central nervous systems in well characterized safety pharmacology experimental models. There were no changes of concern, specifically no changes in blood pressure, heart rate and ECG parameters in non-clinical studies with letermovir. Therefore, letermovir was devoid of any effects of concern.	The nonclinical data do not indicate a potential for neurological, cardiovascular or respiratory effects in humans. Letermovir specifically targets the CMV-encoded terminase, for which there is no human homologue. There were no preclinical cardiac findings and no findings in the Phase 1 thorough QT trial to indicate that letermovir prolongs the QTc interval to a clinically relevant extent or has a pro-arrhythmic potential.
Intravenous (IV) local tolerance: Local tolerance of the hydroxypropylbetadex clinical letermovir IV formulation (20% hydroxypropylbetadex solution) was evaluated in 28-day rat and monkey IV studies and in a local tolerability IV study in rabbits. In these studies, there was no evidence of major local intolerability of the formulations up to the highest letermovir concentration tested (20 mg/mL), the only local changes consisting of microscopic findings of myopathy / myositis and cellulitis at the injection sites in monkeys administered the formulation containing 20 mg/mL of letermovir. There was evidence of partial reversal of these microscopic changes after the 2-week treatment-free period. .	Animal data did not indicate any concern relative to the local tolerance of the clinical IV formulation of letermovir. Infusion-site AEs were reported in two Phase 1 studies (n=50 subjects; P017 and P018) with the arginine formulation leading to premature discontinuation of the formulation. Phase 1 studies (n=90 subjects) with single doses of IV letermovir (hydroxypropylbetadex formulation) up to 960 mg and multiple doses up to 480 mg once daily were specifically evaluated for venous tolerability. No dose-limiting administration site toxicity was observed over this range of doses up to a maximum of 7 days of IV dosing. In the Phase 3 trial P001, infusion site reactions were unusual, and infusions were generally well tolerated for durations up to 47 days. Only 2 subjects in the letermovir group reported mild drug-related injection site AEs (erythema and inflammation). The infusion site thrombosis AEs observed in 13 (26%) of subjects who received the arginine formulation in Phase 1 was not observed with the hydroxypropylbetadex formulation. In Phase 3 P002 and P040 clinical trials, exposure to IV formulation was infrequent: 1 participant received IV letermovir for a duration of 2 days in P040, and 3 participants received IV letermovir with the mean duration of 1.7 days in P002. No administration site reactions were reported in P040. In P002, one subject had infusion site bruising. Therefore, infusion site reactions are not considered important identified or potential risks for the formulation of intravenous letermovir.

Conclusions on Non-clinical Data

The nonclinical safety profile of letermovir has been well characterized in a series of *in vitro* and *in vivo* studies in multiples species (rodent and non-rodent). The only target organ of toxicity identified at microscopic examination was the male reproductive system, which appears to be species specific (rat only). The lack of findings in the male reproductive system following letermovir dosing in monkeys for 39 weeks and mice for 13 weeks, and the results of the evaluation of biomarkers of testicular toxicity in the Phase 3 studies in HSCT and kidney transplant recipients which showed no evidence of letermovir-related testicular toxicity in humans supports the argument that the findings were species-specific. Therefore, the missing information of "Abnormal findings in rat fertility studies with an unknown significance to male patients" is proposed for removal from the Summary of important safety findings from non-clinical studies.

Embryofetal toxicity was observed in rats and rabbits at maternally toxic systemic exposures (approximately 11- and 2-fold, respectively, the exposure at the recommended human dose (RHD)). No adequate human data are available to establish whether or not letermovir poses a risk to pregnancy outcomes. The potential risk for humans is unknown.

In conclusion, the nonclinical profile supports the safe use of letermovir at the approved clinical dose for the prevention of CMV infection in hematopoietic stem cell and kidney transplant recipients administered via both the oral and the intravenous route.

Table SII.2: Summary of Important Safety Concerns from Non-clinical Data

Important identified risks	None
Important potential risks	None
Missing information	None*
* Note that the Missing information of Abnormal findings in rat fertility studies with an unknown significance to male patients included in prior versions of the RMP in Table SII.2 is proposed for removal based on the review of accumulated clinical data and the guidance in GVP Module V (Rev 2).	

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

A summary of the overall extent of exposure to letermovir, placebo and active control in the clinical development program is presented in Table SIII.1. These data include completed Phase 1 trials in healthy adult subjects and subjects with renal or hepatic impairment and completed Phase 2 and 3 trials in mainly kidney/pancreatic transplant (P019), HSCT (P020, P001, P040) and kidney transplant (P002) recipients. The summary of subject exposure in the following tables includes data from 1675 subjects exposed to letermovir in the clinical development program; of these, 750 were healthy subjects and subjects with hepatic or renal impairment in Phase 1 trials, and 925 were subjects in Phase 2 and 3 trials. In the completed Phase 3 trials (P001, P002, and P040), the protocol-specified dose of letermovir was 480 mg QD with a dose adjustment of 240 mg QD when administered in combination with CsA. For the purposes of presenting exposure by indication, both dose regimens of letermovir (480 mg and 240 mg + CsA) are summarized together in Table SIII.1.

Table SIII.1: Summary of Subject Exposure in Letermovir Phase 1, 2 and 3 Trials

Treatment	Phase 1*	Phase 2†	Phase 3‡	Total Number of Subjects
Letermovir§	750	116	809	1675
Oral	620	116	803	1539
Intravenous	142	0	103	245
Placebo	138	33	605	776
Other‖	331	0	0	331
Active Control	0	9¶	297	306
Total Enrolled	848	158	1711	2717

* Includes 32 Phase 1 trials.
† The Phase 2 trials were P019 and P020.
‡ The Phase 3 trials were P001 , P002 and P040.
§ Letermovir treatment includes the treatment groups of letermovir alone and letermovir + other drugs in Phase 1 trials, and letermovir alone in Phase 2 and 3 trials. In the Phase 1 trials, n=12 subjects received **both** oral tablet and IV arginine formulations of letermovir and are therefore included in both the oral and IV categories. Of those who received IV in the Phase 3 trials, only 6 received IV only. All others received IV and oral.
‖ Other treatment includes comparators for Phase 1 DDI trials.
¶ Subjects in the active control group (observational) of the Phase 2a trial (P019) received local Standard of Care (SOC).

Phase 1

The exposure data from Phase 1 trials includes 32 Clinical Pharmacology trials for letermovir in which 848 subjects (including special populations) were enrolled and received at least 1 dose of study drug (letermovir, other drug or placebo). Data are available from healthy subjects and subjects with hepatic or renal impairment; all are referred to as 'subjects'.

Single dose (SD) administration of letermovir up to 960 mg once daily (QD) and multiple dose (MD) administration up to 720 mg twice daily (BID) were evaluated across the 32 trials. Of the 848 subjects administered at least one dose of trial drug, 750 received at least one dose of letermovir (either alone or in combination with another drug). Of these, 710 received the

dose of 480 mg letermovir and 26 received the dose of 240 mg letermovir coadministered with CsA. This overall exposure to letermovir includes both oral (oral solution and oral tablet) and intravenous (IV; arginine and hydroxypropyl betadex) formulations.

Phase 2/3 Clinical Trial Exposure by Duration of Exposure

The durations of exposure in phase 2 and 3 trials for letermovir are shown in Table SIII.2 through Table SIII.5. Both dosing regimens (480 mg once daily and 240 mg once daily with CsA) were summarized as one letermovir treatment group for the analysis of extent of exposure and safety.

Phase 2

P019 was an open-label, proof-of-concept trial to evaluate the safety, tolerability, and antiviral activity of letermovir compared to active control (oral valganciclovir), when given over a period of 14 days. Subjects were randomly assigned to 1 of 3 treatment groups: 40 mg BID letermovir; 80 mg QD letermovir; or an active control.

P020 was a randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of letermovir versus placebo as prophylaxis in a total of 131 subjects. Subjects were randomized to 1 of 3 different dose groups of letermovir (60, 120, or 240 mg QD) or placebo. Treatment was given orally for 84 days.

Phase 3

P001 was a randomized, double blind, placebo-controlled trial to evaluate the efficacy and safety of letermovir versus placebo for prophylaxis of clinically significant CMV infection in adult, CMV-seropositive allogeneic HSCT recipients (R+). A total of 570 allogeneic HSCT recipients (R+) were randomized in a 2:1 ratio to receive letermovir or placebo at any time from the day of transplant through 28 days post-transplant. The dose of letermovir used in P001 was 480 mg QD with a dose adjustment to 240 mg QD when given concomitantly with CsA. The duration of treatment for an individual participant varied from 10 to 14 weeks post-transplant because a subject could be randomized to treatment at any time over a period of 28 days following transplantation. However, all subjects were to complete treatment at the same time point post-transplant, i.e. Week 14 (~100 days) post-transplant.

P002 was a randomized, double-blind, active comparator-controlled trial to evaluate the efficacy and safety of letermovir versus valganciclovir for the prevention of CMV Disease in Adult [D+/R-] kidney transplant recipients. A total of 601 D+/R- kidney transplant recipients were randomized in a 1:1 ratio to letermovir or VGCV at any time from the day of transplant through 7 days post-transplant. The dose of letermovir used was 480 mg QD with a dose adjustment to 240 mg QD when given concomitantly with CsA. Each individual participant received study medication for 200 days post-transplant.

P040 was a randomized, placebo-controlled, parallel assignment, multicenter, double-blind, efficacy and safety study evaluating extending letermovir prophylaxis to 200 days post-transplant in CMV-seropositive recipients (R+) of an allogeneic HSCT who had received letermovir prophylaxis through Week 14 (~100 days) post-transplant and who were at high

risk for CMV infection and/or disease after completion letermovir prophylaxis through 100 days posttransplant. Eligible participants were randomized in a 2:1 ratio to receive letermovir through Week 28 (LET through 200 days) post-transplant or to receive placebo through Week 28 (LET through 100 days) post-transplant. The dose of letermovir used was 480 mg QD with a dose adjustment to 240 mg QD when given concomitantly with CsA.

Table SIII.2: Clinical Trial Exposure to Letermovir by Duration Phase 2 (019 and 020) and Phase 3 Protocols (001, 002, and 040) IV and/or Oral Route

Duration of Exposure	Subjects	Subject Time (years)
≥ 1 day	925	263.2926
≥ 1 week	888	262.9723
≥ 2 weeks	849	261.9510
≥ 3 weeks	805	260.0947
≥ 4 weeks	790	259.1091
≥ 6 weeks	764	256.7435
≥ 8 weeks	744	254.1480
≥ 10 weeks	719	249.8248
≥ 12 weeks	594	223.1984
≥ 14 weeks	379	170.0854
≥ 16 weeks	260	137.6629
≥ 20 weeks	253	135.2398
≥ 24 weeks	250	133.9640
≥ 28 weeks	137	74.6249
Each subject is counted once on each applicable duration category row.		

Table SIII.3: Clinical Trial Exposure to Letermovir by Duration Phase 2 (019 and 020) and Phase 3 Protocols (001, 002, and 040) Oral Route

Duration of Exposure	Subjects	Subject Time (years)
≥ 1 day	918	259.4513
≥ 1 week	875	259.0762
≥ 2 weeks	836	258.0687
≥ 3 weeks	799	256.5409
≥ 4 weeks	785	255.6264
≥ 6 weeks	759	253.2335
≥ 8 weeks	737	250.3094
≥ 10 weeks	695	242.9964
≥ 12 weeks	551	212.3809
≥ 14 weeks	372	168.1634
≥ 16 weeks	259	137.3426
≥ 20 weeks	253	135.2371
≥ 24 weeks	250	133.9612
≥ 28 weeks	137	74.6249
Each subject is counted once on each applicable duration category row.		

Table SIII.4: Clinical Trial Exposure to Letermovir by Duration Phase 2 (019 and 020) and Phase 3 Protocols (001, 002, and 040) IV Route

Duration of Exposure	Subjects	Subject Time (years)
≥ 1 day	103	3.8413
≥ 1 week	76	3.5675
≥ 2 weeks	46	2.7790
≥ 3 weeks	22	1.6893
≥ 4 weeks	8	0.7885
≥ 6 weeks	3	0.3669
≥ 8 weeks	0	0.0000
≥ 10 weeks	0	0.0000
≥ 12 weeks	0	0.0000
≥ 14 weeks	0	0.0000
≥ 16 weeks	0	0.0000
≥ 20 weeks	0	0.0000
≥ 24 weeks	0	0.0000
≥ 28 weeks	0	0.0000
Each subject is counted once on each applicable duration category row.		

Table SIII.5: Clinical Trial Exposure to Letermovir by Dose Phase 2 (019 and 020) and Phase 3 Protocols (001, 002, and 040) IV and/or Oral Route

Dose of Exposure	Subjects	Mean Duration (days)	Subject Time (years)
Any dose	925	104.0	263.2926
<240 mg	82	49.9	11.2036
240 mg	321	62.4	54.8078
480 mg	609	118.2	197.1580
960 mg	14	3.2	0.1232
Each subject is counted once on each applicable dose category row.			

Clinical Trial Exposure by Age Group and Gender

The following tables (Table SIII.6 through Table SIII.9) summarize clinical trial exposure, by age group, gender, IV or oral formulation, race, ethnicity, and special populations (including pregnancy, renal impairment, and hepatic impairment).

Table SIII.6: Clinical Trial Exposure to Letermovir by Age Category and Gender
Phase 2 (019 and 020) and Phase 3 Protocols (001, 002, and 040)
IV and/or Oral Route

Age Category (years)	Subjects			Mean Duration (days)			Subject Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<20	6	2	8	141.3	7.5	107.9	2.3218	0.0411	2.3628
20 to 29	57	23	80	112.6	117.4	114.0	17.5775	7.3951	24.9726
30 to 39	83	45	128	109.2	87.7	101.6	24.8111	10.8039	35.6149
40 to 49	109	59	168	116.9	90.4	107.6	34.8894	14.6096	49.4990
50 to 59	138	99	237	108.4	96.7	103.5	40.9512	26.2102	67.1613
60 to 64	93	60	153	105.1	86.4	97.8	26.7714	14.1907	40.9621
65 to 74	95	48	143	105.5	96.5	102.5	27.4368	12.6821	40.1188
75 to 84	4	4	8	129.0	108.5	118.8	1.4128	1.1883	2.6010
≥ 85	0	0	0	0.0	0.0	0.0	0.0000	0.0000	0.0000
Total	585	340	925	110.0	93.6	104.0	176.1718	87.1208	263.2926

Table SIII.7: Clinical Trial Exposure to Letermovir by Race
Phase 2 (019 and 020) and Phase 3 Protocols (001, 002, and 040)
IV and/or Oral Route

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian	3	196.3	1.6126
Asian	63	83.8	14.4590
Black Or African	36	127.3	12.5424
Multi-Racial	33	103.9	9.3856
Native Hawaiian	3	89.7	0.7365
White	776	104.3	221.5968
Missing	11	98.3	2.9597
Total	925	104.0	263.2926

Table SIII.8: Clinical Trial Exposure to Letermovir by Ethnicity
Phase 2 (019 and 020) and Phase 3 Protocols (001, 002, and 040) IV and/or Oral Route

Ethnicity	Subjects	Mean Duration (days)	Subject Time (years)
Hispanic or Latino	104	125.8	35.8340
Not Hispanic or Latino	747	102.9	210.3740
Not Reported	35	97.5	9.3418
Unknown	9	75.8	1.8673
Missing	30	71.5	5.8756
Total	925	104.0	263.2926

Clinical Trial Exposure in Special Populations

Table SIII.9: Clinical Trial Exposure to Letermovir by Special Population Phase 2 (019 and 020) and Phase 3 Protocols (001, 002, and 040) IV and/or Oral Route

Population	Subjects	Mean Duration (days)	Subject Time (years)
Pregnant Women	0	0.0	0.0000
No renal impairment	506	72.4	100.2519
Renal impairment	416	142.5	162.2905
Hepatic impairment	16	97.6	4.2739

A subject is counted for each applicable population.
Renal impairment is defined as Creatinine Clearance < 60 mL/min/1.73 m^2 at baseline or a kidney transplant recipient.
Hepatic impairment is defined as ALT or AST ≥ 3x upper limit of normal at baseline.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

There were exclusion criteria in the phase 3 trials (P001, P002, ad P040) that had the aim of facilitating evaluation of efficacy and ensuring that patients were able to complete the study. Most of the exclusion criteria are not relevant to post-approval treatment with letermovir and none of these criteria reflects a safety concern with letermovir.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Previous allogeneic HSCT (P001) Previous allogeneic HSCT or solid organ transplant, or multi organ recipient (P002)	Potential to confound study results	**No**	These patients would receive the same recommended regimen for CMV prophylaxis as first-time or single organ transplant recipients.
Creatinine clearance less than 10 mL/min,. or on dialysis or plasmapheresis	No data were available from clinical studies to support safety in patients with creatinine clearance less than 10 mL/min or on dialysis or plasmapheresis. However, there are PK data available from the Phase 1 renal impairment study in 8 patients with severe renal impairment. (creatinine clearance <30 mL/min). The IV formulation of letermovir contains the excipient hydroxypropylbetadex (hydroxypropyl-β-cyclodextrin), which may accumulate in patients with severe renal impairment. At high doses (> 50 mg/kg/day) accumulation of cyclodextrins can cause kidney vacuolation in animals when given intravenously. It is unknown whether accumulation can result in toxicity in humans. Patients with post-transplant creatinine clearance less than 10 mL/min or on dialysis or plasmapheresis suggests the transplant was compromised the results of which could have confounded study analyses. Additionally, the effect of dialysis on letermovir exposure is not known.	**No**	There are no data to support dosing recommendations for patients with creatinine clearance less than 10 mL/min or on dialysis or plasmapheresis. This limitation has been included in product labeling. No additional studies are planned in this population.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Severe hepatic impairment (Child Pugh Class C)	Based on Phase 1 PK data the increase in letermovir exposures is > 3-fold for subjects with severe hepatic impairment.	**No**	There are no data to support dosing recommendations for patients with severe hepatic impairment. Administration of letermovir to patients with severe hepatic impairment is not recommended in product labeling.
Moderate hepatic impairment AND moderate or severe renal impairment (creatinine clearance of less than 50 mL/min)	No data are available in subjects with moderate hepatic AND moderate to severe renal insufficiency Based on Phase 1 PK data, the suggested increase in letermovir exposure is > 3-fold for subjects with moderate hepatic impairment (Child Pugh-B) combined with moderate or severe renal impairment.	**No**	Administration of letermovir is not recommended in patients with moderate hepatic impairment combined with moderate or severe renal impairment (SmPC Sec. 2.7).
History of CMV end-organ disease or initiation of PET for CMV (P001) history of CMV disease or suspected CMV disease (P002) within 6 months	Pre-existing or recent CMV end organ disease could confound the assessment of clinically significant CMV infection as well as assessment of safety during the placebo-controlled trial	**No**	Patients remain at high risk for clinically significant CMV infection or disease and may benefit from prophylaxis. The safety and efficacy established in completed clinical trials is relevant to this population
HIV or active chronic HBV/HCV co infection (P001/P040)	Pre-existing diseases would confound the assessment of efficacy and safety endpoints during the study.	**No**	Such patients remain at high risk for clinically significant CMV infection or disease and may benefit from prophylaxis. The safety and efficacy of letermovir prophylaxis established in completed clinical trials is relevant to this population
Pediatric patients	The safety and efficacy of letermovir in adolescents and children < 18 years of age have not been established.	**No**	The completed Phase 3 clinical trials were conducted in adult HSCT and kidney transplant recipients only. Letermovir is not indicated in children and adolescents under 18 years of age (SmPC Sec 6.4).
Pregnant women	The safety and efficacy of letermovir in pregnant women have not been established.	**No**	It is unlikely that pregnant women will undergo HSCT or a kidney transplant. It is also unlikely that patients post-HSCT or kidney transplantation would become pregnant within the first year post-transplant due to the use of other concomitant medications and therapies with significant risk to the fetus (SmPC Sec 6.1)

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Breastfeeding Mothers	The safety and efficacy of letermovir in women who are breastfeeding have not been established.	**No**	It is unlikely that women will continue to breastfeed during HSCT or kidney transplantation and the post transplantation phase due to the use of immunosuppressive therapies that carry risk to the infant (SmPC Sec 6.2).

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions or those caused by prolonged exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment	Hepatic Impairment – ALT and/or AST ≥ 3 XULN at baseline: P001: 7 (1.9%), P002: 8 (2.7%), P040: 1 (0.7%) Renal Impairment – Creatine Clearance <60 ml/min at baseline: P001: 32 (8.6%), P002: 292 (100%), P040: 46 (31.9%) Cardiovascular Impairment –Medical History at baseline: P001: 161 (28.5%), P002: 364 (61.8%), P004 53 (24.3%)

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Population with relevant different ethnic origin	The majority of subjects exposed to letermovir in P001, P002, and P040 were white (301 [80.7%], 253 [86.6%], and 113 [78.5%] respectively). The proportion of non-white subjects (number and % of total analysis set) enrolled included: Asian: P001: 40 (10.7%), P002: 4 (1.4%), P040: 16 (11.1%) Black or African American: P001: 8 (2.1%), P002: 21 (7.2%), P040: 3 (2.1 %) Multiple: P001: 22 (5.9%), P002: 9 (3.1%), P040: 2 (1.4%) Native Hawaiian or Pacific Islander: P001: 1 (0.3%), P002: 0 (0.0%), P040: 2 (1.4%) Native American or Alaska Native: P001: 0 (0.0%), P002: 3 (1.0%), P040: 0 (0.0%)
Subpopulations carrying relevant genetic polymorphisms	No relevant genetic polymorphisms affecting letermovir exposure were studied in the phase 3 trials (P001, P002, and P040).

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

A summary of the worldwide distribution of letermovir for the cumulative period from market introduction to 01-NOV-20022[1] is presented in Table SV1.2.1 based on the available data. This estimation was based upon the usual dose of letermovir of 480 mg once daily (or 240 mg once daily for patients who receive cyclosporine) and the usual duration of therapy of up to 100 days post-transplant, depending on the degree of immunosuppression. This estimation was based upon clinical trial experience with prophylaxis in HSCT recipients where patient exposure was comprised of a mean duration of 14.1 days of intravenous administration of letermovir, 66.7 days of oral tablet administration, and a mean duration of 69.4 days of exposure to either formulation for both strengths of letermovir (480 mg once daily, or 240 mg once daily for patients receiving co-administration of cyclosporine, which was approximately 50% of the HSCT patients).

The estimated patient exposure is based upon Patient Years of Treatment (PYT) = Patient Treatment Days /365.25 (1 Patient Treatment Day is one vial or one tablet of either 240 mg or 480 mg strength), therefore the total number of tablets and total number of vials (patient treatment days) was divided by 365.25 to estimate patient treatment years.

Patient exposure estimates were calculated from our Company's internal distribution data from the Worldwide Financial Reporting System (WFRS), and the Financial Sharing Area database(s). Patient exposure estimates were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide. The effects of this update may be apparent when comparing current estimates of patient exposure to those of prior reporting periods.

It is important to note the estimated PYT are not equivalent to the absolute number of patients treated. Overall PYT estimates are likely to underestimate the true number of patients exposed to letermovir due to the fact that PYT estimates are calculated assuming one year of treatment.

SV.1.2 Exposure

The estimated number of doses of letermovir distributed worldwide from market introduction through 01-NOV-2022 is 8,062,246. This corresponds to 22,073 estimated PYT.

[1] The estimate of patient exposure from market introduction is based on the availability of monthly drug distribution figures; hence, this estimate has been calculated from market introduction to 31-OCT-2022, rather than from market introduction to 01-NOV-2022

Table SV.1.2.1: Exposure Table by Post-authorization (non-study) Exposure: Doses Distributed and Patients Treated, Cumulative through 01-Nov-2022

Strength	Number of Doses	Estimated Number of Patients Treated	Patient-Years of Treatment
Oral tablet, 240 mg (tablets)	4,046,815	60,672	11,080
Oral tablet, 480 mg (tablets)	3,697,698	55,438	10,124
240 mg concentrate for solution for infusion (vials)	220,163	15,614	603
480 mg concentrate for solution for infusion (vials)	97,570	6,920	267
Total for all dosage forms	**8,062,246**	**138,644**	**22,073**

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Letermovir is available only through prescribing physicians and other health care providers with prescriptive authority. Neither letermovir nor its components are known to possess addictive properties.

The MAH has not been made aware of any reports for misuse for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

There are no identified or potential risks for letermovir in this RMP.

SVII.3.2 Presentation of the Missing Information

There is no missing information for letermovir in this RMP.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Not applicable.

III.2 Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance studies that are required for letermovir.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or proposed post-authorization efficacy studies (PAES) for letermovir.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimization Measures

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
None	Not applicable

V.2 Additional Risk Minimization Measures

Not applicable.

V.3 Summary of Risk Minimization Measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
None	Not applicable	Not applicable

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for Prevymis® (letermovir)

This is a summary of the risk management plan (RMP) for Prevymis®. The RMP details important risks of Prevymis®, and how more information will be obtained about Prevymis®'s risks and uncertainties (missing information).

Prevymis®'s summary of product characteristics SmPC and its package leaflet give essential information to healthcare professionals and patients on how Prevymis® should be used.

This summary of the RMP for Prevymis® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Prevymis® 's RMP.

I. The Medicine and What it is Used for

Prevymis® is authorised for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT). PREVYMIS is also indicated for prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor [D+/R-] (see SmPC for the full indication).

It contains letermovir as the active substance and it is given by oral tablets (240mg and 480mg) and as concentrate for solution for infusion (20mg/mL, 240mg and 20mg/mL, 480mg).

Further information about the evaluation of Prevymis®'s benefits can be found in Prevymis®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/documents/rmp-summary/prevymis-epar-risk-management-plan-summary_en.pdf.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Prevymis®, together with measures to minimise such risks and the proposed studies for learning more about Prevymis®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of Prevymis® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Prevymis®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

Not Applicable

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Prevymis®.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Prevymis®.

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ANNEXES

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable