9 November 2017
EMA/CHMP/490007/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

PREVYMIS

International non-proprietary name: letermovir

Procedure No. EMEA/H/C/004536/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Background information on the procedure 5
1.1. Submission of the dossier 5
1.2. Steps taken for the assessment of the product 6
2. Scientific discussion 8
2.1. Problem statement 8
2.2. Quality aspects 9
2.2.1. Introduction 9
2.2.2. Active Substance 9
2.2.3. Finished Medicinal Product 12
2.2.4. Discussion on chemical, pharmaceutical and biological aspects 17
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects 17
2.2.6. Recommendation(s) for future quality development 17
2.3. Non-clinical aspects 18
2.3.1. Introduction 18
2.3.2. Pharmacology 18
2.3.3. Pharmacokinetics 20
2.3.4. Toxicology 22
2.3.5. Ecotoxicity/environmental risk assessment 29
2.3.6. Discussion on non-clinical aspects 31
2.3.7. Conclusion on the non-clinical aspects 33
2.4. Clinical aspects 34
2.4.1. Introduction 34
2.4.2. Pharmacokinetics 37
2.4.3. Pharmacodynamics 52
2.4.4. Discussion on clinical pharmacology 57
2.4.5. Conclusions on clinical pharmacology 63
2.5. Clinical efficacy 64
2.5.1. Dose response studies 64
2.5.2. Main study 66
2.5.3. Discussion on clinical efficacy 95
2.5.4. Conclusions on the clinical efficacy 97
2.6. Clinical safety 97
2.6.1. Discussion on clinical safety 114
2.6.2. Conclusions on the clinical safety 115
2.7. Risk Management Plan 115
2.8. Pharmacovigilance 116
2.9. New Active Substance 116
2.10. Product information 117
2.10.1. User consultation 117
2.10.2. Labelling exemptions 117

2.10.3. Additional monitoring 117
3. Benefit-Risk Balance 118
3.1. Therapeutic Context 118
3.1.1. Disease or condition 118
3.1.2. Available therapies and unmet medical need 118
3.1.3. Main clinical studies 118
3.2. Favourable effects 119
3.3. Uncertainties and limitations about favourable effects 119
3.4. Unfavourable effects 120
3.5. Uncertainties and limitations about unfavourable effects 121
3.6. Effects Table 122
3.7. Benefit-risk assessment and discussion 122
3.7.1. Importance of favourable and unfavourable effects 122
3.7.2. Balance of benefits and risks 123
3.8. Conclusions 123
4. Recommendations 123

List of abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
AUCtau	Area under the concentration-time curve to the end of the dosing period
$AUC_{T,ss}$	Area under the concentration-time curve steady state
CMV	Cytomegalovirus
DAO	Data-As-Observed
DILI	Drug-Induced Liver Injury
ECI	Event of clinical interest
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Set
FSH	Follicle-stimulating hormone
GAP	Genotypic Analysis Population
GCCA	Global Clinical Compliance Assurance
GCV	Ganciclovir
GV	Genotypic variant
GVHD	Graft-versus-host disease
HSCT	Hematopoietic stem cell transplant
HSV	Herpes simplex virus
LLoQ	Lower limit of quantification
LOTTR	Last observed time point
MDRD	Modification of diet in renal disease
PET	Pre-emptive therapy
QTcF	Fridericia correction of the QT interval
VGCV	Valganciclovir
VZV	Varicella Zoster Virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme Limited submitted on 31 March 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for PREVYMIS, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 June 2016.

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 applicant applied for the following indication: for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Prevymis as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0155/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001631-PIP01-14 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance letermovir contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 October 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Sinan B. Sarac

- The application was received by the EMA on 31 March 2017.
- Accelerated Assessment procedure was agreed-upon by CHMP on 23 March 2017. The procedure was reverted to standard timetable on 12 October 2017 with the adoption of a List of Outstanding Issues.
- The procedure started on 20 April 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 June 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 21 June 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 26 June 2017.
- During the meeting on 06 July 2017 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 18 July 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 05 September 2017.
- During the PRAC meeting on 01 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 12 September 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 September 2017.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 September 2017
- During the CHMP meeting on 10 October 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 12 October 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- During the meeting on November 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to PREVYMIS on 09 November 2017.

2. Scientific discussion

2.1. Problem statement

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.

Annually, approximately 27,000 allogeneic HSCTs are performed worldwide (Gratwohl 2015): in 2014 around 16,000 such transplants were performed in 47 European countries (Passweg 2014). Globally, the number of allogeneic HSCTs has increased yearly (Gratwohl 2015).

Allogeneic hematopoietic stem cell transplant (HSCT) recipients are immune-compromised, which increases the risk for CMV infection, mostly due to reactivation of latent CMV infection. Hematopoietic stem cell transplant recipients with prior CMV infection (R+) are at highest risk for developing CMV reactivation, especially during the first 100 days post-transplant (Özdemir 2007). Some 20-35% of this population progress to CMV disease in the absence of preventive measures (Ljungman 2011).

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.

All currently available anti-CMV agents, whether used for prophylaxis or pre-emptive therapy (PET), are nucleoside analogues with target related toxicities such as myelotoxicity and nephrotoxicity. The most widely used agents, ganciclovir (GCV) and valganciclovir (VGCV), are associated with myelotoxicity, which is particularly problematic in the HSCT setting. Due to concerns of the toxicities associated with anti-CMV agents, PET is currently the preferred preventive approach in the majority of centres worldwide, especially during the first 100 days post-transplant. However, CMV viremia is associated with an increased risk of overall mortality even after adjustment for PET (Green 2016).

Considering the challenges for PET as well as the toxicities associated with current anti-CMV agents, there is a role for an effective and well-tolerated antiviral agent for the prevention of CMV reactivation and disease in allogeneic HSCT recipients.

About the product

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

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on a conclusion that this medicinal product is likely to address an unmet medical need, and is of major interest from the point of view of public health. Furthermore, it was considered to represent a major therapeutic innovation.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as there were pending issues related to the quality development of the product that could not be solved within the timeframe of accelerated assessment. The applicant was required to prepare a plan to further evaluate and develop a terminal sterilisation process for the product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as:

A. Film-coated tablets containing 240 mg or 480 mg of letermovir as active substance.

Other ingredients are:

Tablet core: Microcrystalline cellulose (E460), Croscarmellose sodium (E468), Povidone (E1201), Colloidal anhydrous silica (E551), Magnesium stearate (E572).

Film-coating: Lactose monohydrate, Hypromellose (E464), Titanium dioxide (E171), Triacetin (E1518), Iron oxide yellow (E172), Iron oxide red (only for 480 mg tablets) (E172), Carnauba wax (E903).

The film-coated tablets are available in Polyamide/Aluminium/PVC – Aluminium blister cards containing 28 tablets, as described in section 6.5 of the SmPC.

and,

B. Concentrate for solution for infusion containing 240 mg or 480 mg of letermovir as active substance.

Other ingredients are: hydroxypropylbetadex, sodium chloride, sodium hydroxide (E524), water for injections.

The concentrate for solution for infusion is available in a pack size of one Type I (30 ml) clear glass vial with a 20 mm fluorocoated chlorobutyl stopper with aluminium flip-off cap containing 12 mL (medium green cap) or 24 mL (dark blue cap) of solution, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of letermovir is (4S)-2-{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid corresponding to the molecular formula $C_{29}H_{28}F_4N_4O_4$ and has a relative molecular mass 572.55 g/mol and has the following structure:

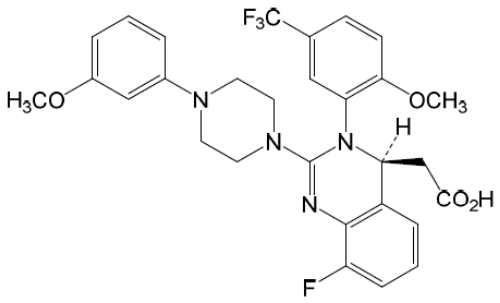


Figure 1: Structure of letermovir

The molecular structure of letermovir has been confirmed by UV, IR, 1H-NMR, 13C-NMR, MS and single crystal x-ray crystallography.

The active substance is a white to off-white powder, slightly hygroscopic, very slightly soluble in water and very soluble in acetonitrile, acetone, dimethylacetamide, ethanol and 2-propanol.

Letermovir exhibits stereoisomerism due to the presence of one chiral centre. Letermovir is the S-form. Polymorphism has not been observed for letermovir. No crystalline forms or solvates have been identified. The active substance obtained using the proposed route of synthesis is an amorphous form.

The applicant provided relevant information on the investigation of structural features of the proposed active substance when compared to known active substances marketed in EU. Based on the presented information, the CHMP considers that letermovir can be qualified as a new active substance.

Manufacture, characterisation and process controls

Letermovir is synthesized in six main steps using well defined starting materials with acceptable specification.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of ICH Q8 and Q11 such as risk assessment and design of experiment (DOE) studies. Attributes and parameters were categorised as either critical or noncritical, based on their impact to product quality. Where a quality attribute was been designated as critical (CQA), associated elements of the control strategy were elaborated. The applicant did not propose any design space for the process.

Critical process parameters (CPPs) were identified through an assessment of the extent to which their variation over established ranges can impact the quality of the active substance (which included considerations of scientific first principles, quality risk management, prior knowledge, appropriate experimentation and in-process controls).

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced during development have been presented in sufficient detail and have been justified.

Detailed comparative physico-chemical investigations, structural elucidation, in-process data, batch analysis data and stability data on active substance from both synthetic routes demonstrated that the changes in the route of synthesis did not have a significant impact on the quality of the product. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in double polyethylene (LDPE) liners with desiccant in an outer containment of a high density polyethylene (HDPE) drum which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: description, assay (HPLC), impurities (HPLC), chiral purity (HPLC), residual solvents (GC), sulfated ash/residue on ignition (Ph. Eur.), water content (KF), identification (IR), bacterial endotoxins (Ph. Eur.) and microbial enumeration test (Ph. Eur.).

The choice of specification parameters and acceptance criteria have been adequately justified in accordance with the relevant EU and ICH guidelines. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (commercial route/scale and development batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial scale batches of active substance from the proposed manufacturerstored in the intended commercial package under long term conditions at 25ºC / 60% RH and under accelerated conditions at 40ºC / 75% RH according to the ICH guidelines were provided.

The following parameters were tested: identification (IR and XRPD), description, assay, water, impurities and chiral purity. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

During the procedure the applicant also provided data up to 3 months under long term conditions at 25ºC / 60% RH, on a further four recent batches manufactured with different routes of synthesis. All tested parameters were within the specifications. The results confirmed that the changes in manufacturing process did not have an impact on the quality of the product.

Photostability testing following the ICH guideline Q1B was performed on one batch. Letermovir has been exposed to acidic, basic, oxidative, thermal and photolytic stress conditions to induce the formation of potential degradation products and demonstrate the stability indicating nature of the analytical procedures.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container at the proposed storage conditions.

2.2.3. Finished Medicinal Product

A. Film-coated Tablets

A. Film-coated Tablets

Description of the product and Pharmaceutical development

Letermovir tablets are formulated as an immediate-release, film-coated tablet for oral administration. The two strengths, 240 mg and 480 mg, are weight multiples of a common granulate. The tablets are packaged in Polyamide/Aluminium/PVC – Aluminium blisters.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Letermovir exhibits pH dependent solubility. Letermovir is classified as a BCS class II compound by the applicant (low solubility, high permeability). The ranges of particle size have been determined to yield product which reproducibly meets all intermediate and finished product specifications, including blend uniformity, tablet content uniformity, and dissolution performance.

Pharmaceutical development of the finished product contains QbD elements. The quality target product profile (QTPP) was defined as an oral immediate release solid dosage form containing 240 mg or 480 mg of letermovir, providing adequate bioavailability to maintain desired plasma levels and consistency in oral absorption (e.g. lack of food effect), all impurities controlled in line with ICH or qualified levels and packaged to provide a shelf life of at least 2 years.

The formulation and manufacturing development for the commercial product / process have been evaluated through the use of risk assessment, prior knowledge and design of experiments to identify the critical product quality attributes (CQAs) and critical process parameters (CPPs). A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The CQAs and CPPs have been adequately identified. The understanding resulting from this development has been used to establish a control strategy consisting of proven acceptable ranges (PARs), design space and in-process controls.

The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is Polyamide/Aluminium/PVC – Aluminium blisters. 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.

Manufacture of the product and process controls

The manufacturing process consists of five main steps:

1. Blending & Lubrication,
2. Roller Compaction and Milling,
3. Lubrication,

4. Compression,
5. Film Coating & Wax Polishing.

The process is considered to be a standard manufacturing process.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space and PARs. The in-process controls for compression and primary packaging are adequate for this type of manufacturing process and pharmaceutical form. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The manufacturing process will be validated at the registered batch size prior to commercialisation. A prospective validation protocol describing these planned studies has been provided.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form; description, identification (HPLC, UV), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (HPLC) and microbial quality (Ph. Eur.)

The choice of specification parameters and acceptance criteria have been adequately justified in accordance with the relevant EU and ICH guidelines. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for full scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 3 full scale batches of each strength of finished product stored under long term conditions for 18 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products, dissolution, microbial testing and water activity. The analytical procedures used are stability indicating. No significant changes were observed in any tested parameters.

One batch of each tablet strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Photo exposure of the samples shows no significant change in assay degradation products, or dissolution compared to the control sample.

Stability of the film coated tablets in bulk containers was also evaluated. Based on the stability results obtained a 12 month hold time period was supported.

Based on available stability data, the proposed shelf-life of 30 months and “Store in original package to protect from moisture” as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of

ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products..

B. Concentrate for solution for infusion

Description of the product and Pharmaceutical development

The finished product Letermovir is supplied as a 20 mg/mL colourless aqueous concentrate for solution for infusion in 30 mL Type I glass vials and is supplied in two presentations, containing either 240 mg/vial or 480 mg/vial. The concentrate for solution for infusion contains 240 mg or 480 mg of letermovir as active substance. Other ingredients are: hydroxypropylbetadex, sodium chloride, sodium hydroxide (E524), water for injections.

The finished product is intended for single-use after dilution. Accompanying dilution solvent is not supplied with the finished product. The solvents to be used for dilution are sodium chloride and dextrose which both are readily available in EU.

Letermovir is an intravenous formulation that has been developed to meet the need for treatment of patients who are not able to swallow the letermovir oral tablet. The development of the finished product has been described, the choice of excipients justified and their functions explained. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Pharmaceutical development of the finished product contains QbD elements, although no design space is claimed. The quality target product profile (QTPP) was defined as a liquid concentrate for intravenous infusion, containing 240 mg or 480 mg of letermovir, for once daily dosing, all impurities controlled in line with ICH or qualified levels, sterility and bacterial endotoxins controlled per compendial requirements and acceptable injection site tolerability.

The formulation and manufacturing development for the commercial product / process have been evaluated through the use of risk assessment, prior knowledge and design of experiments to identify the critical product quality attributes (CQAs) and critical process parameters (CPPs). A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The CQAs and CPPs have been adequately identified.

In line with the Decision trees for the selection of sterilisation methods (CPMP/QWP/054/98), terminal sterilisation is preferred to sterilisation by filtration and/or aseptic treatment because it is lethal to the microorganisms and a reliable sterility assurance level (SAL) is possible to calculate, validate and control, and thus incorporates a safety margin. For sterile filtration followed by aseptic treatment this is not applicable as accidental contamination caused by inadequate technique cannot be reliably eliminated by monitoring, control or validation. Therefore, terminal sterilisation provides the highest assurance of sterility and should be used whenever possible.

The applicant selected sterile filtration in combination with aseptic processing as studies of potential terminal sterilization cycles showed physical and chemical changes to the formulation at some combinations of autoclave time/temperature. The applicant presented a proposal to further evaluate, develop and implement

a terminal sterilisation method as a post-approval commitment. In light of the overall positive benefit/risk balance of the product, the CHMP agreed that the applicant's justification for the use of sterile filtration in combination with aseptic processing instead of terminal sterilisation could be accepted provided that, that in order to optimise the sterility assurance level (SAL) of the manufacturing process, the applicant performs a number of post-authorisation measures to further develop, validate and introduce a terminal sterilisation process for the product. These measures have been clearly outlined by the applicant in a stepwise approach in a Post Approval Change Management Protocol.

The primary packaging is Type I (30 ml) clear glass vial with a 20 mm fluorocoated chlorobutyl stopper with aluminium flip-off cap containing 12 mL (medium green cap) or 24 mL (dark blue cap) of solution. 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.

Information related to the manufacturers of the packaging components well as sterilisation site for the same have been presented. At the time of Opinion, the CHMP, noting the EMA Quality Q&A which states that "*In the absence of GMP certification or confirmation that the component is a CE-marked Class Is medical device, certification that the sterilisation process has been conducted and validated in accordance with the relevant ISO standards should be provided*", recommends that the applicant should submit a report from an external auditor showing compliance of the sterilisation site with the ISO audit criteria for sterilisation of stoppers (ISO-17665-1 and ISO-17665-2) and arrange for the validation of sterilisation of stoppers to be included within the scope of the upcoming EU GMP inspection of the finished product manufacturing site.

Manufacture of the product and process controls

The commercial manufacturing process consists of the following steps:

1. Weighing and dispensing active substance and excipients
2. Formulation of final formulated bulk (FFB) in vessel
3. Sterile filtration
4. Aseptic filling and sealing.

Based on the risk assessments and evaluation of the relationships between the process and Critical Quality Attributes (CQAs) performed throughout development. No design space is claimed. Proven acceptable ranges (PARs) have been defined for a number of finished product manufacturing steps. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. During the procedure the applicant amended the proposed holding times and maximum processing times and introduced additional in-process bioburden tests.

The main steps of the manufacturing process have been investigated in a number of development batches and one production scale batch of each presentation. The proposed manufacturing process would normally be considered non-standard as per Annex II of EU "Guideline on process validation for finished products – information and data to be provided in regulatory submissions" however the applicant considers that the process can be considered to be a standard process based on the extensive manufacturing knowledge and experience of the finished product manufacturing site. Based on the information provided, the applicant's justification to consider it to be a standard process was accepted. It has been demonstrated that the

manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The manufacturing process will be validated at the registered batch size prior to commercialisation. A prospective validation protocol describing these planned studies has been provided.

Product specification

The finished product release and stability specifications include appropriate tests for this kind of dosage form; description, visible particulates (Ph. Eur.), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), pH (Ph. Eur.), sub-visible particles (Ph. Eur.), volume of injection in container (Ph. Eur.), container closure integrity (dye ingress by UV), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The choice of specification parameters and acceptance criteria have been adequately justified in accordance with the relevant EU and ICH guidelines. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 3 full scale batches of each strength of finished product stored under long term conditions for 18 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, visible particles, assay, degradation products, pH, osmolality, sub-visible particles, container closure integrity, sterility and bacterial endotoxins. The analytical procedures used are stability indicating.

An in-use stability study was carried out by simulating in-use practice for patient delivery in IV infusion bag solutions of dextrose and saline. Chemical and physical in-use stability has been demonstrated for 48 hours at 25 °C and for 48 hours at 2 to 8 °C.

One batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results indicated that the light exposed sample shows no significant change in assay, degradation products, osmolality, pH or particulate matter, however the color of the solution was observed to darken slightly upon exposure to light. Therefore the product will be labeled to store in the original carton to protect from light.

Additional studies on leachable compounds, temperature excursion and freeze thaw were also performed. No significant changes were observed in any tested parameters.

Based on available stability data, the proposed shelf-life of 30 months when stored in the original carton to protect from light as stated in the SmPC (section 6.3) are acceptable. The product should be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Adventitious agents

Hydroxypropylbetadex is manufactured from starch using an enzyme of microbiological origin. In the fermentation process to produce this enzyme, a casein-hydrolysate is used. There is no concern about BSE for this product. Confirmation has been given that other excipients used are non-animal and non-human origin, hence no TSE/BSE risk.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished products has been presented in a satisfactory manner. The results of tests carried out indicate 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.

The control applied to the active substance and the finished product, along with the controls over the manufacturing process of the active substance and the finished products, support the view that the products can be routinely manufactured to conform to the current expectations for this type of dosage form. Furthermore, the stability data submitted supports that both the active substance and the finished products will remain of the appropriate quality when stored as recommended storage conditions.

Concerning the concentrate for solution for infusion, while sterile filtration in combination with aseptic processing is considered sufficient to ensure a positive benefit-risk balance, with a low risk of residual contamination, in line with the Decision trees for the selection of sterilisation methods (CPMP/QWP/054/98), terminal sterilization is the state of the art method with respect to ensuring no microbial contamination, and should be used whenever possible. The measures proposed by the applicant to develop, validate and introduce a terminal sterilisation process should be implemented post-approval. Documentation confirming compliance of the rubber stopper sterilisation site with the ISO audit criteria for sterilisation of stoppers will be provided by the applicant as a post-authorisation measure.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of these products are 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.

The CHMP has identified the following measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the concentrate for solution for infusion:

- In order to optimise the sterility assurance level (SAL) of the manufacturing process, the marketing authorisation holder should implement the measures outlined in the Post Approval Change Management Protocol (PACMP), agreed with the CHMP, concerning development, validation and introduction of terminal sterilisation.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should submit a report from an external auditor showing compliance of the chlorobutyl stoppers manufacturer with the ISO audit criteria for sterilisation of stoppers (ISO-17665-1 and ISO-17665-2) and arrange for the validation of sterilisation of stoppers to be included within the scope of the upcoming EU GMP inspection of the finished product manufacturing site.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Mechanism of action

Letermovir has activity (single-digit nanomolar EC_{50} values) against laboratory and clinical CMV isolates in cell-culture models of infection. Characterization of DNA processing, virion maturation, and viral resistance mutations in CMV-infected, letermovir-treated cells implicate CMV DNA terminase as the target of letermovir. The process of cleaving concatameric 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 letermovir is distinct from that of already approved anti-CMV agents that target CMV DNA replication.

Primary pharmacodynamic studies

Please refer to section on clinical pharmacodynamics.

Secondary pharmacodynamic studies

Early in the development of letermovir, preliminary studies in cell culture were performed to assess the potential for cellular cytotoxicity (CC). These experiments were conducted with mouse, rat and human cell lines including epithelial cells derived from liver and kidney, heart muscle cells, fibroblasts derived from embryos and dermis, monocytes, T-lymphocytes, macrophages, and neuroblastoma and hepatoma cells. Values for 50% effect in the cell proliferation assay (CC50) ranged from 27 ± 1.0 µM to > 30 µM, which was the highest concentration of letermovir tested.

Letermovir was analysed in 63 radioligand-binding assays to evaluate potential off-target effects (interaction with mammalian receptors and enzymes). None of the results met the criteria for a significant effect at the concentration tested (10 µM).

Letermovir at a final concentration of 30 µM (0.1% DMSO) did not exhibit significant activity (≥ 50% change) in the following tissue assays:

- 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

Safety pharmacology programme

Safety pharmacology studies were performed in both *in vitro* and *in vivo* test systems to assess the potential cardiovascular, respiratory, and neurobehavioral effects of letermovir. In addition, renal function, lipid metabolism, haematology parameters, blood glucose concentrations, gastrointestinal motility were also investigated following administration of letermovir.

The C_{max} values in the phase 3 study in HSCT patients ranged from 2,549 ng/mL to 21,570 ng/mL. The highest C_{max} value of 21,570 ng/mL was used to provide the most conservative estimate of exposure margins.

Cardiovascular Function

In the functional patch-clamp electrophysiology study, letermovir inhibited hERG current with an IC50 of 67 μM (~38,360 μg/L). Taking into account that the hERG assay is conducted in absence of protein and that letermovir is 98.7% protein bound in humans, the IKr IC50 is ~137X the unbound C_{max} in HSCT patients (approximately 280 ng/mL at an IV dose of 480 mg).

To evaluate the effect of letermovir on QT/QTc interval, a surrogate for assessment of ventricular repolarization, an anesthetized dog telemetry study was conducted. There were no QT/QTc effects and no changes in any ECG parameters in anesthetized dogs up to the highest dose tested (45 mg/kg given intraduodenally). In conscious dogs up to the highest oral dose tested, 10 mg/kg, letermovir was devoid of any effects on cardiovascular function, ECG evaluations, respiratory function, and acid/base-status and plasma electrolytes. There was no pharmacokinetic evaluation in the study performed in conscious animals. In anesthetized dogs, the Cmax at the highest dose tested, 45 mg/kg, was 6886 ng/mL (<1-fold the Cmax in HSCT patients). Additionally, there were no ECG changes in the 13-week repeat-dose oral studies in monkeys at a Cmax of 16,780 ng/mL, which represents ~1-fold the Cmax in HSCT patients. Of note, in a QTc clinical study, IV administration of a supratherapeutic dose of 960 mg (Cmax of 68000 ng/mL) did not result in QTc prolongation in healthy volunteers. Based on these data, it is unlikely that hERG-blockade mediated delayed ventricular repolarization will occur at clinically relevant exposures.

In conclusion, letermovir had no impact on heart rate and blood pressure in anesthetized dogs up to the highest dose tested, 45 mg/kg given intraduodenally and in conscious dogs up to the highest oral dose tested, 10 mg/kg (C_{max} of 6886 ng/mL at 45 mg/kg in dogs; <1-fold the C_{max} in HSCT patients), and in repeat-dose oral toxicity study in monkeys up to the C_{max} of 16,780 ng/mL (~1-fold the C_{max} in HSCT patients).

Respiratory Function

Letermovir had no impact on respiratory function in anesthetized dogs up to the highest dose tested, 45 mg/kg given intraduodenally (C_{max} of 6886 μg/L; <1-fold the C_{max} in HSCT patients). Additionally, there were no clinical signs indicative of respiratory concern in the repeat-dose studies in rats and monkeys up to the highest doses tested (sexes-combined C_{max} in monkeys of 249,687 ng/mL on Week 4 of repeat-dose IV toxicity study in monkeys, ~11-fold the Cmax in HSCT patients; mean C_{max} value in male rats of 272,011 ng/mL, ~12-fold the C_{max} in HSCT patients).

Nervous System Function

Letermovir had no impact of concern on neurobehavioral parameters in a central nervous function study conducted at single doses up to 45 mg/kg in rats. There was no pharmacokinetic evaluation in this study. There was no evidence of effects on the nervous function in repeat-dose studies in rats and monkeys up to the highest doses tested (C_{max} in monkeys of 249,687 ng/mL, ~11-fold the C_{max} in HSCT patients; C_{max} in rats of 272,011 ng/mL, ~12-fold the C_{max} in HSCT patients).

Additional studies

Additionally, letermovir had no impact on blood parameters, lipid metabolism and blood glucose levels up to 45 mg/kg. In another rat study, up to a dose of 45 mg/kg, letermovir had no impact on urine volume and excretion of potassium and chloride, but there was a dose dependent increase in sodium.

Conclusion on safety pharmacology

There were no letermovir-related effects of concern on cardiovascular, nervous system, and respiratory functions observed in well characterized safety pharmacology experimental models. However, due to the low exposure margins to patients in the majority of the preformed dedicated in vivo safety pharmacology studies the actual risk cannot, with confidence, be extracted from the generated data. Consequently, any effect on safety pharmacology parameters at supra-therapeutic exposure cannot be ruled out. However in light of the data from the clinical QTc study, in which IV administration of a supratherapeutic dose of 960 mg (Cmax of 68000 ng/mL) did not result in QTc prolongation in healthy volunteers the risk for delayed ventricular repolarization is considered low. It can also be concluded that, due to the clinical signs of toxicity in the animals, the animals were exposed up to MTD in these studies.

Pharmacodynamic drug interactions

Letermovir was evaluated for antiviral activity in pairwise combinations with the anti-CMV agents GCV, CDV, FOS and acyclovir. Using two mathematically techniques for analysis, the combination of letermovir with each drug was additive, with no evidence of antagonism.

2.3.3. Pharmacokinetics

Methods

Plasma concentrations for the evaluation of the PK/ADME (non-GLP pharmacokinetic experiments) of letermovir were determined by LC/MS/MS using Turbo Ion Spray in positive ion mode, following protein precipitation. For toxicokinetic studies, plasma concentrations of letermovir were determined by LC/MS/MS methods validated in accordance with GLP. Radioactivity was determined by direct liquid scintillation, counting of samples or the HPLC eluent was analysed for ^{14}C-content by accelerator mass spectrometry. Metabolite structures were proposed using mass spectrometry and in the case of the acyl-glucuronide M7, authenticated using a synthetic standard.

Absorption

Following IV administration to Wistar rat and Rhesus monkey, letermovir 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 IV doses tested (0.3 mg/kg in rat and 0.1 mg/kg in monkey), the mean plasma clearance (CLp) was 35.8 mL/(min·kg) and 17.3 mL/(min·kg), the steady state volume of distribution (Vdss) was 3.01 L/kg and 1.30 L/kg, and the elimination half-life (t½) was 3.3 hr and 4.9 hr in rat and monkey, respectively. At the lowest oral dose (1 mg/kg), the bioavailability of letermovir

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%.

Distribution

The tissue distribution of letermovir was assessed in Wistar rats, Long Evans rats and pregnant Sprague Dawley rats by QWBA following a single oral dose of [^{14}C]letermovir. In addition, quantitative whole body autoradiography was performed in male Wistar rats after a single IV dose of [^{14}C]letermovir.

The distribution pattern of letermovir across Wistar, Sprague Dawley and Long Evans rats was similar. Letermovir 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 letermovir 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 letermovir-related radioactivity does not bind to melanin. Elimination of radioactivity was nearly complete from most tissues by 72 hours post-dose.

In pregnant Sprague-Dawley rats, the highest concentration of radioactivity was identified in uterus, clitoris, gastrointestinal tract, bile duct and liver. Letermovir was observed in foetal tissues, suggesting that letermovir can cross the placental barrier.

Letermovir was extensively bound to plasma protein with minimal differences in percent unbound across nonclinical species and human (percent unbound: 2.38% in mouse, 2.19% in rat, 2.12% in rabbit, 0.73% in dog, 1.84% in Rhesus monkey, 4.05% in Cynomolgus monkey, and 1.33% in human. Letermovir does not partition preferentially into the blood cellular compartment in animals (rat, dog, Rhesus monkey) or humans.

Metabolism

The *in vitro* biotransformation of [^{14}C]letermovir was investigated in NADPH-fortified liver microsomes from CD-1 mouse, NMRI mouse, Wistar rat, Himalayan rabbit, Beagle dog, Rhesus monkey, and human as well as in plated hepatocytes from CD-1 mouse, Wistar Hannover rat, Himalayan rabbit, Beagle dog, Cynomolgus monkey and human.

In vitro, [^{14}C]letermovir showed low 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 letermovir was the major route of metabolism in all species, including human, forming M7, M8, and M9. An additional acyl-glucuronide metabolite M10 was observed in incubations with recombinant UGT isoforms. Several minor oxidative metabolites were observed, of which M11, an N-dealkylation metabolite, was observed in all species except rabbit. Additional metabolites observed only in hepatocyte incubations from preclinical species were derived either from oxidation or a combination of oxidation and glucuronidation or methylation. All human metabolites were observed in liver preparations from the safety species.

The *in vivo* metabolism of [^{14}C]letermovir was studied in bile duct-cannulated and intact rats (and in humans). In rats, independent of the route of administration, letermovir represented 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. Oxidative demethylation of the 2-methoxy-5-trifluoromethylphenyl moiety followed by an intramolecular nucleophilic substitution of the 3-methoxyphenyl-piperazinyl moiety is the proposed mechanism for the formation of M5.

In the human ADME study, letermovir was the major circulating constituent in human plasma, accounting for 96.6% of total drug related material. The remaining radioactivity of 3.4% belonged to three structurally uncharacterized metabolites. The oxidative metabolite M5, found to circulate in rats, was not observed in human plasma.

Excretion

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.

In rats, a combination of biliary excretion and metabolism via glucuronidation and oxidation were the major routes of elimination for letermovir. In Rhesus monkeys, the majority of radioactivity was recovered in faeces (86.9%) with a minimal amount recovered in urine (4.06%).

In the human ADME study, letermovir-related radioactivity was primarily eliminated via the biliary/faecal route and was recovered in the faeces as parent drug (~70% of dose), an acyl-glucuronide (~6% of dose, M7) and four metabolites (~4% each) of unknown chemical transformation.

Following oral administration of letermovir to lactating Sprague Dawley rats, letermovir was shown to be secreted into milk at Day 10 postpartum.

2.3.4. Toxicology

The pivotal toxicity studies were performed in rat and monkey, in which the animals were dosed either orally or intravenously for up to 39 weeks.

Rat and Cynomolgus monkey were selected as the main non-clinical species based on the *in vitro* and *in vivo* metabolic profiles and based on the demonstration of satisfactory pharmacokinetics in these species. The Applicant´s justification is considered acceptable by CHMP and consequently the data generated in these species is regarded as relevant.

Single dose toxicity

Single-dose toxicity studies have been performed, however in light of the data generated in the repeat-dose toxicity studies, the relevance of the data collected in these studies has some limitations. In short, mortality was observed after a 2000 mg/kg oral dose in rats and a 200 mg/kg IV dose in rats and mice.

Repeat dose toxicity

Morbidity and mortality

In the 14-day monkey study, one female and one male from the high-dose group (500 mg/kg) were euthanized on day 14 and 12, respectively. The kidneys of the male and female had moderate, multifocal degeneration/regeneration of tubules in the cortex and medulla. Tubules were lined by acidophilic, sloughing cells or plump basophilic regenerating cells. Many affected tubules contained granular casts of epithelial cells and/or neutrophils. In addition, the transitional cell epithelium lining the pelvis had many vacuolated or sloughed cells. It is unclear to what extent letermovir was the actual cause of death in these two animals. One female in the high-dose group (300/250 mg/kg) in the 13 week study was terminated on day 21 after

cessation of dosing on day 18, since the health status did not improve. There were no macroscopic or microscopic findings in this animal and no cause of death was established.

Clinical observations

Clinical observations made in exposed animals included transient post dose mouth rubbing in high-dose (250 mg/kg) mice, increased water consumption in high-dose (180 mg/kg) rats, salivation, mouth rubbing and limb paddling immediately after dosing in rats dosed ≥50 mg/kg. Additional clinical observations in rat i.v. dosed included decreased activity, laboured breathing, mouth rubbing, and swollen tails at 100 mg/kg.

In monkeys orally administered 100 mg/kg the animals displayed abnormal faeces (soft or liquid) and salivation. Salivation was also observed after i.v. administration of 100 mg/kg.

Body weight and food consumption

Decreased body weight gain and decreased food consumption was observed in all tested species. In mouse, males exposed to 100 mg/kg had a decreased body weight gain of 23% at the end of the 13 week study. Also in male rats dosed 180 mg/kg had a 13% decrease in body weight gain after 13 weeks. In the prolonged 26 weeks study in rat body weight gain was decreased in females at all doses (-7.4%, -5.7% and -5.3% at 17, 50, and 150 mg/kg/day, respectively). In the same study the male body weight gain was decreased at all dose levels (-6% and -11% at 50 mg/kg/day and 150 mg/kg/day, respectively). These findings were resolved in the 4 week treatment-free period. No changes in these parameters were observed in rat after i.v. administration.

In monkey there was a progressive loss of body weight in both males and females dosed 500 mg/kg for 14 days. This signal was also detected in the prolonged studies in this species and in the 39-week study body weight gain was slightly less than that of the controls (males gained 7.8 or 16% less weight and females gained 20 or 9.0% less weight, respectively). No changes in these parameters were observed in monkey after i.v. administration.

Haematology

Several haematological parameters were affected in all species after letermovir exposure. The most extensive data on this aspect were generated in the 13-week rat study. In this high-dose (180 mg/kg) study, decreased haematocrit and mean corpuscular volume (MCV) were observed in both sexes (up to -7% and -6%, respectively) and decreases in haemoglobin and mean corpuscular haemoglobin (MCH) were observed in females only (-5% and -4%, respectively). These findings showed partial reversibility at the end of the 4 week treatment-free period. In the same dose-group there was an increase in CD45 low cells, B cells (Pan B) and antigen presenting cells (I-a) in both sexes as well as in T-helper cells (CD4 total from CD4/CD8 double labelling), CD45total cells and splenic cell counts in females. Also at the lower dose (60 mg/kg) letermovir increased leukocyte and monocyte counts, CD45low cells, T-helper cells (CD4total) and T-helper cells (CD4total from CD4/CD8 double labelling) in females.

In monkeys exposed to 300/250 mg/kg a decrease in erythrocytes, haemoglobin, and haematocrit were observed in males (7%) and females (8, 6, and 6%, respectively). These findings were reversible after recovery. After i.v. administration to monkey at all doses (≥10 mg/kg) an increase in absolute reticulocyte counts in females (up to 2-fold at 100 mg/kg) and an increase white blood cell counts in males (1.2-fold) were observed. In the same study there was an increase reticulocyte counts in females (up to 2.4-fold) at ≥30 mg/kg. At 100 mg/kg an increase in reticulocyte counts in males (up to 2.8-fold), red cell and platelet distribution (minimally increased) in females (up to 1.2-fold), and lymphocytes (1.3 fold, males only) was detected.

Clinical chemistry

In both mouse and rat, letermovir induced changes in several clinical chemistry parameters. These changes were observed in mid- and high-dosed animal groups. In mouse these changed were observed for ALT (+50% at 100 mg/kg), AST (+87% at 250 mg/kg), globulin (+18% at 250 mg/kg), bilirubin (+43% in 250 mg/kg), albumin (-9% at 250 mg/kg), albumin/globulin ratio (-19% at 250 mg/kg), potassium (-20% at 250 mg/kg) in females, creatinine (-25% at 250 mg/kg), cholesterol (-56% at 250 mg/kg) in males.

In the rat 4-week study there was a decrease in creatinine excretion, triglycerides, cholesterol, albumin and an increase in alkaline phosphatase and bilirubin in animals dosed 180 mg/kg. In the extended 13-week, animals dosed ≥60 mg/kg were recorded to have a decrease in in ALT (up to -27%) and glutamine dehydrogenase (up to -58%) in males, decreases in cholesterol (up to -44%), triglycerides (up to -60%), proteins (up to -7%) and in albumin (up to -5%). At the same time the animals showed an increase in ALP (+41%) in females, total bilirubin (up to 3.6-fold), T4 (with no increases in T3 or thyroid stimulating hormone) in females dosed at 180 mg/kg/day.

In monkey an increase in ALT was also detected in both sexes dosed 300/250 mg/kg for 13 weeks. This signal showed reversibility after 4-weeks of recovery. Also in the 39-week monkey study at 250/200 mg/kg there was in decrease in cholesterol in treated females (up to 11% compared to pre-test). This was reversible after recovery. In monkeys administered ≥10 mg/kg letermovir i.v. there was a slight decrease in gamma glutamyl transferase across all male groups (0.93 to 0.61-fold) and in all female groups (0.87 to 0.67-fold) and in total bilirubin (males only). In the ≥30 mg/kg there was a decrease in total bilirubin (females only) up to 0.6-fold.

Macroscopic observations

In the mid-dose (60 mg/kg) rat dosed for 13-weeks there was an increased liver weights in females at and in both sexes at 180 mg/kg/day. In addition, the male from the high-dose group (180mg/kg) a decreased testes and epididymitis weigh was observed which was still present after 4 weeks of recovery. Also in rats administered letermovir i.v. soft and/or small appearance of the testes and small epididymis was noted.

In monkey, there was an increase in testes/epididymides weights, adjusted to overall body weight, in males at 10, 30 and 100 mg/kg/day by 2.5, 1.5 and 2.0-fold, respectively, when compared to controls. The above change was not dose-related in degree and was without any histopathological correlates.

Microscopic observations

Liver

Mouse

In mice dosed 250 mg/kg for 13-weeks hepatocyte vacuolation characterized by enlarged, usually centrilobular, hepatocytes containing microvacuoles sometimes coalescing to macrovacuoles was detected. Also at lower doses (≥ 40 mg/kg) centrilobular hypertrophy associated with increased liver weights was recorded.

Rat

In rat dosed 180 mg/kg for 13-weeks minimal liver cell hypertrophy, changes in the pattern of lobular fat deposition in males was seen at the end of dosing. However, this was not observed after recovery.

Kidney

As indicated above, euthanized monkeys displayed changes to the kidneys.

Testis

A general finding in rat includes testicular toxicity. Already in animals dosed 180 mg/kg for 4 weeks a minimal to slight spermatic exfoliation in the seminiferous tubules, minimal spermatic retention and increased vacuolation of the tubular epithelium were seen in testes and a minimal to slight spermatic debris and minimal oligospermia were seen in the epididymides. In the longer studies testicular toxicity was also observed. These data show testicular degeneration and changes of the epididymal sperm content (oligospermia, increased spermatic debris) in animals dosed 180 mg/kg for 13 weeks and after 4 weeks of recovery residuals of degeneration (vacuoles) were still present in the testes while the epididymides appeared normal after the recovery time.

Rats administered letermovir intravenously (100 mg/kg) showed minimal or slight germ cell degeneration, spermatid retention and an increased incidence and severity of tubular cell vacuolation in the testes, accompanied by oligospermia and cell debris in the epididymis, which correlated with the decrease in testes/epididymis weights that were noted at necropsy. This signal was not recovered after 2 weeks, since germ cell degeneration and slight increased levels of tubular cell vacuolation were still present in the testes of previously treated males. In addition, tubular atrophy of testis and oligospermia/cellular debris in the epididymis was observed.

This testicular toxicity has influenced the reproductive toxicity program for letermovir and has also resulted in specific SmPC labelling (see reproduction toxicity below).

Genotoxicity

Letermovir was found to be non-mutagenic and non-genotoxic in a battery of in vitro or in vivo studies carried out according to ICH guidances that included a microbial mutagenesis assay, a chromosomal aberration assay, and an in vivo assay for micronucleus induction in mouse bone marrow. The top dose was the limit dose which was limited by cytotoxicity in the in vitro genetic toxicity studies, or was the maximum tolerated dose in the in vivo genetic toxicity study in mice. Systemic exposure to letermovir has been determined in mice after oral dosing. The IP route was used in the in vivo bone marrow micronucleus assay in mice with letermovir. The exposure following IP administration is expected to be similar or higher than following oral administration. The highest dose in the mouse in vivo micronucleus study was 48 mg/kg/day, given for 2 days to male mice. At 40 mg/kg/day in the repeat dose oral study in mice, the exposure (AUC0-24hr) on Day 1 study was 295,100 ng.hr/ml in males, which exceeds the highest human exposure of 99,960 ng.hr/ml at the 480 mg IV dose (exposure margin ~3X).

Carcinogenicity

There were no carcinogenicity studies presented. The lack of carcinogenicity studies is deemed acceptable by CHMP, considering the limited clinical use (100 days). However, should the clinical use be extended beyond 6 months the applicant should consider performing carcinogenicity studies according to the relevant guidelines.

Reproduction and Developmental Toxicity

Fertility and early embryonic development

Fertility and early embryonic development was assessed in rats. As discussed above, repeat dosing with letermovir induced alterations in the rat testis such as vacuolation of the germinal epithelium, germ cell exfoliation, tubular atrophy and damage to Sertoli-cells at doses ≥180 mg/kg/day. In the male fertility study in rats (TT#16-7150), effects on male fertility were observed at 180 mg/kg/day (~2.3-fold the exposure in HSCT recipients), were associated with toxicity on male reproductive organs including impaired sperm quality, and were likely secondary to this toxicity. There was no male reproductive organ toxicity and there were no changes in male fertility at ≤60 mg/kg/day (~1-fold the exposure in HSCT recipients). Overall, the fertility and early embryonic development studies did not indicate any effects of letermovir on female fertility up to the highest dose tested, 240 mg/kg/day (~5-fold the exposure in HSCT recipients).

In addition, in a study investigating thoroughly the male reproductive organs and the potential effects on male fertility (which included electron microscopy examination of the testes, evaluation of Inhibin B plasma concentrations and potential reversibility of male reproductive changes) it was shown that the testicular toxicity:

- was characterized by degenerating germ cells and degenerating Sertoli cells in seminiferous tubules with impaired spermatogenesis but also in tubules with normal spermatogenesis which correlated with a marked decrease in Inhibin B plasma concentrations;
- was not reversible after a 15-week treatment-free period in rats previously dosed with letermovir for 15 weeks.

To thoroughly investigate any potential effects of letermovir on male reproductive organs in monkeys, a 13-week oral male fertility study in Cynomolgus monkeys with an 8-week recovery phase was conducted (TT # 11-7863). A set of investigations of male reproductive organs and male hormones was completed on the main study as well as in recovery animals. Oral dosing of sexually mature non-human primates (60 to 240 mg/kg/day for 13 weeks) did not induce any alterations of the male reproductive system. Therefore, the NOAEL for effects on male reproductive tissues was ≥240 mg/kg/day in Cynomolgus monkeys, which corresponds to a systemic exposure of 211,000 ng·h/mL (~2-fold the exposure in HSCT recipients).

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 (approximately 2-fold the exposure in HSCT recipients), and no male reproductive toxicity in mice administered letermovir up to 250 mg/kg/day (~3.5-fold the exposure in HSCT recipients) for 13 weeks. There were no male reproductive organ changes noted in the embryo-foetal developmental studies in rats (high dose: 250 mg/kg/day) and rabbits (high dose: 225 mg/kg/day), in the pre- and postnatal developmental study in rats (high dose: 180 mg/kg/day) and in a 2-week juvenile toxicity study conducted in rats of 14-day age at study start (high dose: 250 mg/kg/day). Based on these nonclinical results, biomarkers of testicular toxicity including luteinizing hormone, follicle-stimulating hormone, testosterone and Inhibin B were evaluated in HSCT patients dosed with letermovir at 480 mg or 240 mg (in patients on CsA) in the phase 3 clinical study. There was no evidence of letermovir-induced changes in these biomarkers in this clinical study. The applicant concluded that the lack of findings in the male reproductive system following letermovir dosing in monkeys and mice and the lack of changes in biomarkers of testicular toxicity in Phase 3 clinical study is suggestive that testicular findings in rats are specific for this species and letermovir may not modulate spermatogenesis in humans.

The CHMP agrees with the applicant that the testicular toxicity may be rat specific, and with no risk for toxicity in humans. However, no mechanistic explanation is available, showing why this toxicity is only seen in rats and not in other species (humans included). Further, the patient population in the present phase 3

study cannot be considered the best suitable to rule out this toxicity for several reasons (prior treatment, baseline values etc.). Therefore the issue of testicular toxicity should be closely monitored. Also, since no rat-specific mechanism has been presented, the SmPC and labelling of Prevymis on this issue reflect actual data and is non-speculative, i.e. any reference to a possible rat-specific mechanism was removed from the SmPC. However, in relation to the indication (HSCT) the issue of potential irreversible testis toxicity is of somewhat less importance when considering the pre-conditioning regiment (cytostatic drugs and radiation) applied before transplantation which virtually makes every patient sterile. Nevertheless, it is not unlikely that letermovir may be tested in other indications, for instance solid organ transplantation, where patients are not co- or pre-treated with medicines which impact the fertility. In such cases the relevance of the data generated in rat is of high importance to male patients. Consequently, this issue will be re-scrutinized in any upcoming extension of indication applications holding patients which are not pre- or co-treated with medicines known to decrease fertility. The above reasoning can also be applied to the issue of a SmPC-recommendation for semen conservation (which is more or less standard for males undergoing stem cell transplantation).

Embryo-foetal development

The embryo-foetal developmental study in rats was conducted at 0, 10, 50, and 250 mg/kg/day. In rats, foetal developmental effects were identified at dose levels exhibiting maternal toxicity. The NOAEL for both maternal and developmental toxicity was 50 mg/kg (~2.5-fold the exposure in HSCT recipients). Maternal findings at 250 mg/kg/day included decreased food consumption together with decreased water intake and reduced amount of faeces, as well as moderate body weight loss and impaired body weight gain, reddish vaginal discharge (with no associated post-implantation loss) and possible reduction in placental weight. Reddish vaginal discharge occurred at 50 mg/kg/day, but this was not considered to be adverse as it was not associated with post-implantation loss. At 250 mg/kg/day, decreased foetal weights together with retarded ossification, increased incidence of shortened umbilical cord and slightly oedematous foetuses and increased incidence of generally common spontaneous malformations (additional lumbar/pelvic shift) and common skeletal variations (additional 14th rib and altered shape of sacral vertebral arches) were observed.

The embryo-foetal developmental study in rabbits was conducted at 0, 25, 75, and 225 mg/kg/day. Similarly to rats, in rabbits developmental toxicity was observed, but only in the presence of maternal toxicity at high dose levels. One female at the high-dose of 225 mg/kg/day had to be sacrificed due to moribund condition and three other females in this dose group aborted after they each had shown signs of severe maternal toxicity. Decreases in food consumption and marginal body weight loss during treatment period and histomorphological findings in the intestine and liver were also noted in dams at 225 mg/kg/day. A treatment related effect cannot be ruled out for two foetuses with one supernumerary presacral vertebra with 13th ribs (malformation) and an increased incidence of 13th ribs (floating and comma shaped or fully present, deviations) at 225 mg/kg/day. The NOAEL for both maternal and developmental toxicity in this study was 75 mg/kg/day (~0.5-fold the exposure in HSCT recipients).

It is acknowledged that “supernumerary 14th ribs” is a common finding. Findings of lumbosacral malformations and variations, including pelvic shift, supernumerary lumbar vertebrae, altered shape of sacral vertebrae arches, and the supernumerary 14th ribs in the high dose, which was maternally toxic, are considered treatment related and are discussed in the SmPC.

Pre- and postnatal development

The potential effects of letermovir on development, growth, behaviour, reproductive performance, and fertility of F_1 generation in rats following oral administration of 0, 10, 45 or 180 mg/kg to F_0 females from Gestation Day 6 through Day 22 postpartum were evaluated (TT #11-7860). The NOAEL for F_0 generation was 45 mg/kg/day (1-fold, based on toxicokinetic data on Study Day 1, the exposure in HSCT recipients). In F_1 generation, the changes limited to 180 mg/kg/day, including slight transient reduction in body weight gain as well as slight delayed vaginal opening in the F_1 generation were considered to be non-adverse and the NOAEL was ≥180 mg/kg/day (~2-fold the exposure in HSCT recipients). Of note, there were no changes in male reproductive organs and no decreased fertility in the F_1 generation.

Toxicokinetic data

It is clear that Letermovir is toxic and that consequently the exposure margins between patients and toxic exposure in animals are generally low (0.7 times in mouse, 7.8 times in female rats and 4.3 in monkeys).

Local Tolerance

When letermovir was dissolved in 20% 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 in a rabbit study; this cyclodextrin formulation produced only test item-related histopathological changes (focal necrosis of muscle cells) after intramuscular injection (which is not the clinical route of administration). There were no injection site changes observed in a local tolerance study in rats conducted with Polysorbate 80-containing and arginine-containing IV formulations. However, based on local tolerance results obtained in rabbits, it cannot be totally excluded that letermovir when applied as the clinical form for IV administration (an arginine-phosphate buffer lyophilisate reconstituted in water for injection) at a concentration of 5 mg/mL or higher may exert slight local intolerabilities in humans.

Other toxicity studies

Juvenile toxicity studies

The potential toxicity of letermovir was assessed in juvenile male rats following daily oral administration for 2 weeks starting at 14 days of age. In addition, the potential for letermovir to interfere with the establishment of the blood-testis barrier was assessed. There were no findings in the study except for a slight decrease in body weight gain at 180 mg/kg/day. Oral administration of 60 or 180 mg/kg/day of letermovir to juvenile male rats (postnatal Day 14 through 27) did not interfere with Sertoli cell proliferation or the germinal epithelium. Therefore the NOAEL in this study was ≥180 mg/kg/day.

In relation to the juvenile toxicity data it can be concluded that they are of less importance to this application since the intended indication is confined to adults. CHMP noted that this study should have been prolonged until PD 40 to ensure exposure over the period of testicular development.

Antigenicity

There were no observations or changes in the routine repeat-dose toxicity studies that were considered to be due to potential antigenicity induced by letermovir. Therefore, no antigenicity evaluations were conducted.

Immunotoxicity

Specific immunotoxicity endpoints were evaluated in the 4 and 13-week repeat-dose toxicity studies in rats. The changes noted in the study report as adverse were observed only at 180 mg/kg and were limited to increased CD4 T cells, B cells, antigen presenting cells, and $CD45^{total}$ and $CD45^{low}$ cells and decreased $CD45^{high}$ cells. Upon consideration of the totality of these nonclinical data for letermovir, these findings are not considered adverse or indicative of immunotoxicity.

Metabolites

No circulating metabolites were detectable in human plasma at exposures greater than 10% of total drug-related exposure. Therefore, the ICH M3(R2) guidance requirements relative to metabolite safety assessment have been met with letermovir and no studies were conducted with any individual metabolites.

Impurities

No nonclinical studies were conducted with any individual impurities. The levels of all impurities were below the qualification threshold as defined in the ICH guideline on Impurities in New Drug Substances [ICH Q3A(R2)].

Phototoxicity

The molar extinction coefficient of letermovir at 290 nm is 10173 $L.mol^{-1}cm^{-1}$, which is above the threshold of 1000 $L.mol^{-1}cm^{-1}$ for phototoxicity assessment as per ICH S10 Guidance. Hence, to evaluate the potential phototoxic effects of letermovir, Long-Evans pigmented female rats were administered oral (gavage) doses of letermovir (0, 100 and 500 mg/kg/day) for three consecutive days followed by exposure to radiation from a xenon lamp to simulate sunlight. There were no letermovir-related cutaneous or ocular findings indicative of phototoxicity.

2.3.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) is based on the parent compound letermovir, which has a molecular weight of 572.56 g/mol and has a water solubility of 573 mg/mL (pH 7) and a log KOW = 2.29 (pH 7). All ERA studies are performed in compliance with GLP. The ERA Phase I surface water predicted environmental concentration (PECSW) was calculated to 2.4 µg/L using the default Fpen (0.01) and the maximum dose of 480 mg/day. Based on the OECD TG308 test, the persistence against aerobic degradation in whole fresh water-sediment systems is between DT50 22–34d (20°C), and 47-62d (12°C) with a tendency to sediment accumulation (AR >10% after 14d). There was some primary degradation with several transformation products (two products M1 and M7 at AR>10% with DT50 (20°C) for M7 being 65d) but only very minor ultimate biodegradation. The organic content solid adsorption coefficients for letermovir were below 10000 L/kg for sludge and soil (log Koc 2.49 to 3.46 L/kg) – making it unlikely that there is a terrestrial environmental risk due to agricultural use of sludge. The lowest NOEC for aquatic toxicity was 1 mg/kg (the maximum concentration in the FELS test using P. promelas) while the most sensitive NOEC for sediment-dwellers (C. riparius; NOEC 25mg/kg, OC10% normalized to 100mg/kg dry weight) was for midge development.

Summary of main study results

Substance (INN/Invented Name): Letermovir			
CAS-number (if available): 917389-32-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.51 (pH 5) 2.29 (pH 7) 1.01 (pH 9)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.29	not B
	BCF	NA	B/not B
Persistence	DT_{50}	No conclusion drawn, see LoQ.	P/not P
Toxicity	CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default	2.4	µg/L	>0.01 threshold (Y)
Other concerns (e.g. chemical class)			(Y/N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = $Soil_{DU}$ = 1550 L/kg $Soil_{RMN}$ = 2908 L/kg $Soil_{MSL}$ = 1063 L/kg $Soil_{CA\ Clay}$ = 2685 L/kg $Sludge_{Wareham}$ = 701 L/kg $Sludge_{New\ Bedford}$ = 312 L/kg	K_{oc} < 10000 L/kg, no terrestrial testing required
Biodegradation in Activated Sludge	OECD 314B	Biodegradation half-life = 6.7 days The elimination rate constant, ke = 0.1028 $days^{-1}$	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Tauton River $DT_{50,\ water,\ 20°C}$ = 8.3 days $DT_{50,\ sediment,\ 20°C}$ = 47 days $DT_{50,\ whole\ system,\ 20°C}$ = 22 days $DT_{50,\ water,\ 12°C}$ = 18 days $DT_{50,\ sediment,\ 12°C}$ = 101 days $DT_{50,\ whole\ system,\ 12°C}$ = 47 days Weweantic River	Shifting to sediment triggers sediment testing

		$DT_{50,\ water,\ 20°C}$ = 11 days $DT_{50,\ sediment,\ 20°C}$ = 21 days $DT_{50,\ whole\ system,\ 20°C}$ = 29 days $DT_{50,\ water,\ 12°C}$ = 24 days $DT_{50,\ sediment,\ 12°C}$ = 45 days $DT_{50,\ whole\ system,\ 12°C}$ = 62 days >10% shifting to sediment		
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	8.8	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	1.2	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	1	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{10} (NOEC) EC_{50}	29.6 >972	mg/L	
Phase IIb Studies					
Chronic Toxicity to Sediment Dwelling Organisms	OECD 218	$NOEC_{development}$ $NOEC_{OC10,\ development}$ $NOEC_{emergence}$ $NOEC_{OC10,emergence}$	25 100 100 400	mg/kg	*Chironomus riparius*

Ecological risk: Letermovir is not classified as a PBT or vPvB candidate. Based on the Phase I PEC_{SW}, the applicant has provided a set risk quotients/ratios (RQs) that are below 0.1 for sludge microorganisms and below 1 for other compartments (the highest RQ being 0.5 for sediment-dwellers based on a sediment PEC of 0.5mg/kg).

2.3.6. Discussion on non-clinical aspects

Letermovir has activity (single-digit nanomolar EC50 values) against laboratory and clinical CMV isolates in cell-culture models of infection. Characterization implicates CMV DNA terminase is the target of letermovir. The applicant has conducted several in vitro studies to address the primary pharmacodynamics of letermovir. However, since data generated by these studies are an intricate part of the clinical efficacy data, they are presented and assessed in conjunction with the clinical data.

A mouse xenograft model of human CMV infection the data illustrates that letermovir was at least as effective as VGCV at inhibiting CMV replication outside of typical cell culture conditions.

There were no letermovir-related effects of concern on cardiovascular, nervous system, and respiratory functions observed in well characterized safety pharmacology experimental models. However, due to the low exposure margins to patients in the majority of the dedicated in vivo safety pharmacology studies, the actual risk cannot be extracted with confidence from the generated data. CHMP agreed that these limitations were acceptable, in light of the whole generated data package. Data from the clinical supratherapeutic QTc study did not result in QTc prolongation.

The absorption of letermovir was adequately characterised in rats and monkeys following IV and oral administration. In rat distribution studies, letermovir was rapidly and widely distributed in tissues with the highest levels of radioactivity observed in the gastrointestinal tract, bile duct and liver. Elimination of radioactivity was nearly complete at 3 days post-dose. Extensive plasma protein binding was observed across all non-clinical species.

The in vitro biotransformation of [14C]letermovir was investigated in all relevant non-clinical species studied and all human metabolites were observed in liver preparations from the safety species. The *in vivo* metabolism of [14C]letermovir was studied in bile duct-cannulated and intact rats and in humans. In rats, letermovir represented the majority of drug-related radioactivity circulating in rat plasma accounting for ~60% 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. In the human ADME study, letermovir was the major circulating constituent in human plasma, accounting for 96.6% of total drug related material. No *in vivo* metabolism data was generated in Cynomolgus monkeys. The absence of in vivo data may question its relevance as a toxicology species. However, as letermovir is the major circulating constituent in human plasma and based on the comparable in vitro metabolism and in vivo elimination data between species, further metabolism data in Cynomolgus monkeys is not requested by CHMP.

The pivotal toxicity studies were performed in rat and monkey in which the animals were dosed either orally or intravenously for up to 39 weeks. Rat and Cynomolgus monkey were selected as the main non-clinical species based on the in vitro and in vivo metabolic profiles and the demonstration of satisfactory pharmacokinetics in these species. The Applicant´s justification is considered acceptable by CHMP and data generated in these species is regarded as relevant.

In mice, oral administration of letermovir up to the highest dose tested, 250 mg/kg/day (~3.5-fold the exposure in HSCT recipients) for 13 weeks was well tolerated. The main antemortem change was decreased body weight gain in males (up to -23% compared to controls) with no impact on the general health status of the animals. The NOAEL was 100 mg/kg/day (~2- to 4-fold the exposure in HSCT recipients), based on hepatocyte vacuolation with slight increases in AST, ALT and bilirubin at 250 mg/kg/day. However, the dose of 250 mg/kg/day was considered minimally toxic in the absence of evidence of liver inflammation, degeneration or necrosis at microscopic examination.

In rats, oral administration up to the highest dose tested, 150 mg/kg/day (~6- to 7.5-fold the exposure in HSCT recipients) for 26 weeks was well tolerated. The high dose of 150 mg/kg/day was selected based on evidence of effects of letermovir on body weight and identification of target organ toxicity (testes) at the high dose of 180 mg/kg/day in the 13-week repeat dose toxicity study. The main antemortem changes were decreased food consumption (up to -6% compared to controls) and body weight gain in males (up to -11% compared to controls) with no impact on the general health status of the animals. The NOAEL was ≥150 mg/kg/day in females (approximately 7.8-fold the exposure in HSCT recipients) and 60 mg/kg/day in males (~1-fold the exposure in HSCT recipients) based on male reproductive organ toxicity observed in most toxicity studies in rats, including fertility studies at doses above 60 mg/kg/day. The male reproductive organ toxicity consisted of vacuolation of the germinal epithelium, germ cell exfoliation, tubular atrophy and damage to Sertoli cells, and oligospermia and cell debris in the epididymides, with decreased testes and epididymides weights. This signal was irreversible after recovery and further exploited in dedicated rat reprotoxicity studies. In these studies a decrease in male fertility was observed. It is considered that this is a rat specific effect, as it was not observed in mice or monkeys. A risk for human testicular toxicity can still not be excluded; a mechanistic reason why such severe toxicity was seen in rats and not in other species has not been presented, and the lack of findings in biomarkers in the present phase 3 study is not considered

sensitive enough to rule out a toxicity, having baseline findings in these patients in mind. This issue should be closely monitored in PSURs. In addition, the unknown relevance for human is reflected in sections 4.6 and 5.3 of the SmPC. For the present indication, where measures such as semen collection are standard due to other treatments, no specific recommendation is necessary in the SmPC (outside an adequate wording in SmPC section 5.3).

The toxicity profile of letermovir in IV rat studies was consistent with the oral studies. IV administration up to the highest dose tested, 100 mg/kg/day (~7.5-fold the exposure in HSCT recipients) for 4 weeks was well tolerated. The NOAEL was ≥100 mg/kg/day in females (~7-fold the exposure in HSCT recipients) and 30 mg/kg/day in males (~1-fold the exposure in HSCT recipients) based on male reproductive organ toxicity observed at 100 mg/kg/day.

In monkeys, oral administration up 100 mg/kg/day (<1-fold the exposure in HSCT recipients) for 39 weeks was well tolerated. The high-dose of the 39-week study, 250 mg/kg/day (~5- to 7-fold, males and females, respectively, the exposure in HSCT recipients) was not tolerated, as evidenced by body weight loss and signs of poor general health status, which resulted in the lowering of this dose to 200 mg/kg/day (1- to 2-fold the exposure in HSCT recipients). The 200 mg/kg/day dose was generally better tolerated, with the main antemortem change being a decreased body weight gain in females (-55% relative to controls). Doses higher than 250/200 mg/kg/day, 300 and 500 mg/kg/day (>11-fold the exposure in HSCT recipients) were evaluated in shorter-term monkey studies and were shown to be associated with signs of gastrointestinal toxicity including emesis and abnormal faeces, and morbidity. Based on the antemortem changes observed at ≥250/200 mg/kg/day, the NOAEL in monkeys was 100 mg/kg/day (<1-fold the exposure in HSCT recipients). There were no adverse histomorphologic changes identified in monkeys. Of note, in a controlled Phase 3 study in HSCT patients, treatment related gastrointestinal adverse events in the letermovir group were reported at similar rates to the placebo group.

The toxicity profile of letermovir in IV monkey studies was consistent with the oral studies. IV administration up to the highest dose tested, 100 mg/kg/day (~4-fold the exposure in HSCT recipients) for 4 weeks was well tolerated. Letermovir is not classified as a PBT or vPvB candidate. Based on the Phase I PEC_{SW}, the applicant has provided a set risk quotients/ratios (RQs) that are below 0.1 for sludge microorganisms and below 1 for other compartments (the highest RQ being 0.5 for sediment-dwellers based on a sediment PEC of 0.5mg/kg).

2.3.7. Conclusion on the non-clinical aspects

CHMP agreed that there are no objections to an approval of letermovir from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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

Summary of Phase 1 studies

Trial Type	Merck Trial No. (AiCuris No., as Applicable*)	Trial Short Title/Design	Primary Objective	Number of Subjects who Received Letermovir
Phase 1				
Healthy Subject PK and Initial Tolerability Trial Reports	MK-8228 P007 (AIC001-1-001)	**First-In-Human, Single Rising Oral PEG Solution and Tablet Doses**	Safety and tolerability of oral letermovir	40
	MK-8228 P011 (AIC001-1-005)	**Single Rising Oral Doses**	Safety and tolerability of oral letermovir	36
	MK-8228 P021 (AIC246-01-I-08)	**Single Oral Dose, Multiple Rising Oral Doses and ADME**	Part 1: Safety and tolerability of oral letermovir, PK Part 2: Safety and tolerability of oral letermovir, PK Part 3: Evaluate mass balance, identify metabolites and identify routes of elimination	Part 1: 6 Part 2: 36 Part 3: 8
	MK-8228 P009 (AIC001-1-003)	**Multiple Rising Oral Doses and Drug Interaction with Midazolam**	Safety and tolerability of oral letermovir	23
	MK-8228 P018 (AIC246-01-I-13)	**Single and Multiple Rising Oral and IV Doses and Drug Interaction with Digoxin**	Part 1: Safety and tolerability, letermovir exposure at steady state, effect of high doses on QT/QTc interval Part 2: Letermovir PK Part 3: Effect of letermovir on digoxin PK	Part 1: 28 Part 2: 16‡ Part 3: 12
	MK-8228 P026	**Multiple Oral and IV High Dose**	Part 1: Safety and tolerability of oral letermovir Part 2: IV letermovir PK	Part 1: 18 Part 2: 9
	MK-8228 P005 (AIC246-01-I-14)	**Single Rising IV Dose and Multiple IV Dose**	Safety and tolerability of single rising IV doses and multiple IV doses of letermovir	Part 1: 30 Part 2: 8

Trial Type	Merck Trial No. (AiCuris No., as Applicable*)	Trial Short Title/Design	Primary Objective	Number of Subjects who Received Letermovir
Bioavailability (BA) Trial Reports	MK-8228 P008 (AIC001-1-002)	**Bioavailability of Letermovir PEG Solution and Oral Tablet FFP2 Formulation, and Food Effect**	Relative bioavailability of 5 mg and 20 mg letermovir tablets (single doses) compared to 20 mg oral solution; evaluation of food intake (high fat, high calorie) on bioavailability of the 20 mg tablet	11
	MK-8228 P017 (AIC246-01-I-12)	**Bioavailability of Letermovir IV and PMF1 Tablet Formulations**	Cohort 1: Assess relative exposures of 30 mg IV versus 30 mg oral letermovir Cohorts 2-5: Safety and tolerability of IV letermovir	34[ll]
	MK-8228 P029	**Food Effect on Letermovir Pharmacokinetics**	Comparative bioavailability of 480 mg letermovir under fed and fasted conditions	14
Comparative BA and Bioequivalence (BE) Trial Reports	MK-8228 P014 (AIC246-01-I-09)	**Comparative Bioavailability of Letermovir Tablet FFP2 and PMF1 Formulations**	Relative bioavailability of a new tablet formulation (4 different dose strengths)	15
	MK-8228 P028	**Comparative Bioavailability of Letermovir Tablet FMF Formulations**	Compare primary PK parameters of letermovir after single dose administration of 1 x 480 mg tablet (test) versus 2 x 240 mg tablets (reference)	14
Intrinsic Factor PK Trial Reports	MK-8228 P015 (AIC246-01-I-10)	**Pharmacokinetics in Patients with Hepatic Impairment**	Evalute the effect of hepatic impairment on letermovir PK	33
	MK-8228 P006 (AIC246-01-I-16)	**Pharmacokinetics in Patients with Renal Impairment**	Evalute the effect of renal impairment on letermovir PK	24
	MK-8228 P027	**Single Rising Oral and IV Doses in Healthy Japanese Subjects**	Safety and tolerability of single rising oral and IV doses of letermovir	Part 1: 8 Part 2: 8
	MK-8228 P032	**Multiple Rising Oral Doses and Drug Interaction with Cyclosporine in Healthy Japanese Subjects**	PK of letermovir in Japanese and compare to historical PK from non-Japanese; effect of CsA on letermovir PK	14
Extrinsic Factor PK Trial Reports	MK-8228 P016 (AIC246-01-I-11)	**Drug Interaction with Midazolam**	Effect of letermovir on IV and oral midazolam PK	16
	MK-8228 P010 (AIC001-1-004)	**Drug Interaction with Cyclosporine**	Effect of letermovir on CsA PK; effect of 2 different doses of CsA on letermovir PK	Part 1: 8 Part 2: 12
	MK-8228 P003	**Drug Interaction with Cyclosporine and Tacrolimus**	Part 1: Effect of letermovir on CsA PK Part 2: Effect of letermovir on tacrolimus PK	Part 1: 14 Part 2: 14
	MK-8228 P013 (AIC001-1-007)	**Drug Interaction with Tacrolimus**	Effect of letermovir on tacrolimus PK	16
	MK-8228 P036	**Drug Interaction with Sirolimus**	Effect of letermovir on sirolimus PK	14
	MK-8228 P022	**Drug Interaction with Mycophenolate Mofetil**	Effect of letermovir on mycophenolic acid PK	14
	MK-8228 P034	**Drug Interaction with Acyclovir**	Effect of letermovir on acyclovir PK	16
	MK-8228 P025	**Drug Interaction with Voriconazole**	Effect of letermovir on voriconazole PK	14

Trial Type	Merck Trial No. (AiCuris No., as Applicable*)	Trial Short Title/Design	Primary Objective	Number of Subjects who Received Letermovir
	MK-8228 P033	**Drug Interaction with Posaconazole**	Effect of letermovir on posaconazole PK	13
	MK-8228 P023	**Drug Interaction with Atorvastatin**	Effect of letermovir on atorvastatin PK	13
	MK-8228 P035	**Drug Interaction with Ethinyl Estradiol and Levonorgestrel**	Effect of letermovir on ethinyl estradiol and levonorgestrel PK	22
Healthy Subject PD and PK-PD Trial Reports	MK-8228 P004	**Letermovir Thorough QT/QTc**	Effect of supra-therapeutic and therapeutic doses of letermovir on QTc interval	37

* AiCuris protocol numbers are provided for Phase 1 and 2 trials sponsored by AiCuris.
‡ MK-8228-018 Part 2: All 16 subjects received only the IV arginine formulation of letermovir.
ǁ MK-8228-017: Of the 34 subjects exposed to letermovir, 22 subjects received only the IV arginine formulation of letermovir. The remaining 12 subjects received both the oral tablet and IV arginine formulations of letermovir.
QD= once daily; BID=twice daily

Summary of Phase 2 and Phase 3 studies

Trial Type	Merck Trial No. (AiCuris No., as Applicable*)	Trial Short Title/Design	Primary Objective	Number of Subjects who Received Letermovir
Phase 2				
	MK-8228-019 (AIC001-2-001)	Phase 2a, randomized, active controlled, multi-center, open-label dose ranging trial in a majority of kidney and kidney/pancreas transplant recipients (and 1 HSCT recipient) with CMV viremia	To determine the decline in human cytomegalovirus (CMV) DNA load after a 14-day treatment for each letermovir dosing regimen and to compare this to an observational control group	18
	MK-8228-020 (AIC246-01-II-2)	Phase 2b, multi-center, randomized, double-blind, placebo-controlled, dose-ranging trial to investigate safety and efficacy of 3 different oral doses of letermovir in comparison with matching placebo over 12 weeks in CMV-seropositive, allogeneic HSCT recipients	To compare the safety and efficacy of 3 different doses of letermovir with matching placebo as prophylaxis in the prevention of CMV infection	98
Phase 3				
	MK-8228-001	Phase 3 randomized, placebo-controlled trial to evaluate the safety and efficacy of letermovir in adult, CMV-seropositive allogeneic HSCT recipients	To evaluate the efficacy of letermovir as prophylaxis in the prevention of clinically significant CMV infection through Week 24 (~6 months) post-transplant following adminstration of letermovir or placebo.	373

* AiCuris protocol numbers are provided for Phase 1 and 2 trials sponsored by AiCuris.
‡ MK-8228-018 Part 2: All 16 subjects received only the IV arginine formulation of letermovir.
ǁ MK-8228-017: Of the 34 subjects exposed to letermovir, 22 subjects received only the IV arginine formulation of letermovir. The remaining 12 subjects received both the oral tablet and IV arginine formulations of letermovir.
QD= once daily; BID=twice daily

2.4.2. Pharmacokinetics

Absorption

Bioavailability

The bioavailability of letermovir from the phase III formulation was estimated to 94% in healthy volunteers by population PK analysis. However, there are indications from inter-study comparisons of multiple dose studies that the bioavailability is ca 50% during 480 mg qd dosing to healthy volunteers. According to the popPK analysis in HSCT patients, the bioavailability of Letermovir was much lower (35%) (but increased to 85% when 240 mg qd was administered with CsA). It is noted that when making an inter-study comparison of the multiple dose PK data, the exposure after iv administration appears double the exposure at oral administration. The bioavailability during multiple-dose conditions in healthy volunteers may then be ca. 55% at the 480 mg qd dose. Thus, the bioavailability may be reduced under multiple-dose conditions also in healthy volunteers. There may be a time-dependent decrease in absorption due to auto induction of intestinal Pgp/BCRP. Auto induction affecting letermovir exposure is observed under multiple-dose conditions. Moderate induction in vivo has been observed on CYP2C19 and some intestinal induction has also been observed on digoxin, which is not that sensitive for changes in intestinal Pgp activity (see below).

Formulation comparisons

The bridging BE studies confirms extrapolation of data obtained with different formulations within healthy volunteers. PMF3 and FMI formulations were used in the pivotal Phase 3 trial (P001).

Food-effect

There is a small effect of concomitant food intake on Cmax (30% increase) but not on AUC under single-dose conditions in healthy volunteers. As the bioavailability appears different during multiple dose conditions/ in patients, the magnitude of the food effect may be different during clinical use. However, the effect is not likely to be clinically relevant and lletermovir was administered regardless of food intake in the phase III studies The present SmPC recommendation is supported by data from the phase III studies.

Solubility/pH dependency

Solubility for letermovir is low between pH ~4 and ~7, (0.3-0.4 mg/mL). It increases below pH 4, and from pH ~7.

Permeability

The permeability cannot be classified as neither high nor low, as the study was not optimally designed for making this classification.

Intestinal transport

Letermovir is efflux transported by P-gp and BCRP. Available data suggest that the transporters limit letermovir absorption during multiple-dose conditions. It is unknown whether an intestinal uptake transporter aids the absorption.

Distribution

Volume of distribution

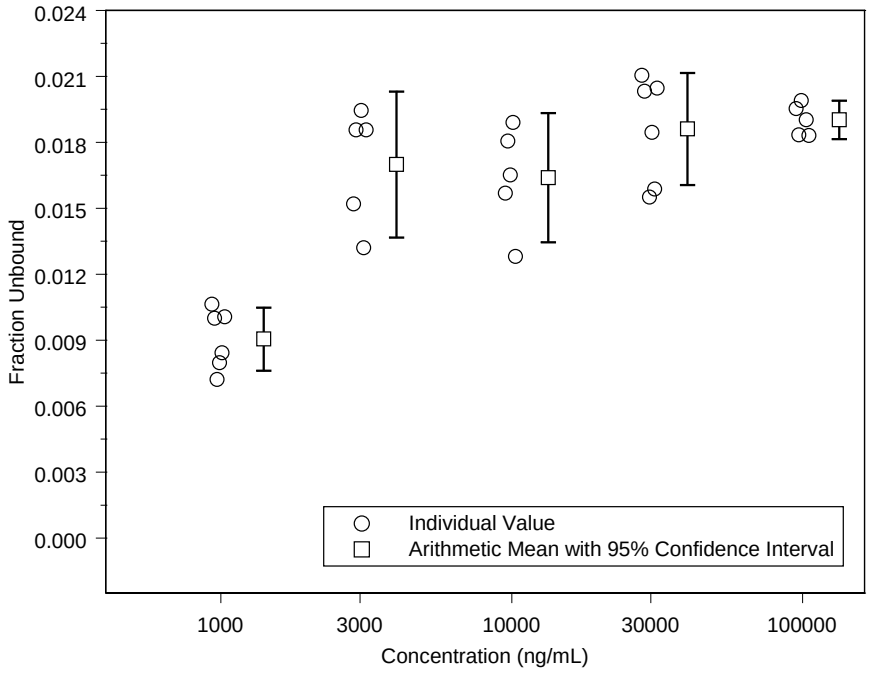
The volume of distribution is reduced with increasing doses of letermovir. This is likely a consequence of a reduced distribution to OATP1B1/3 expressing tissues such as the liver. The volume of distribution was 87 L

after an iv infusion of 480 mg and 50 L during 240 mg qd. The population PK analysis estimates a population mean V (sum of central and peripheral compartments volume) to be 46 L in HSCT recipients.

Protein binding

Letermovir is extensively bound to human plasma protein in vitro. Letermovir bound both to serum albumin and AAG. In an initial study, using radiolabelled drug and ultrafiltration, the protein binding appeared to be concentration dependent (fraction unbound ranging from 1.0 to 2.1%) within the range of 000 to 93000 ng/mL. However, in a more recent study using equilibrium dialysis and LC-MS, the fraction unbound was 1.8% at concentrations ≥3000 ng/ml and maintained so to the maximum studied 100000 ng/ml. The free fraction of letermovir was ca 0.9% at 1000 ng/ml and ca. 1.8 at higher concentrations. The protein binding of letermovir thus appears linear at concentrations corresponding to marked increases in drug exposure. However, to ensure the right conclusion is drawn and the results of the extrinsic factor studies in healthy volunteers can be trusted, the binding will be studied in a DDI study recommended as PAM (the rifampicin DDI study). It is possible that the binding in patients has the plateau at higher concentrations if the AAG concentrations are higher in the patients. However, this has no impact on the assessment of the interpretation of the results of the studies performed in healthy volunteers. It may have an impact on PK in patients. Red blood cell partitioning of letermovir was 0.56 and independent of the concentration range (0.1 to 10 mg/L).

Figure 2 The protein binding of letermovir vs concentration (new study)



Organ distribution

The distribution of letermovir may be influenced by the expression of OATPs as well as P-gp and BCRP as it is a substrate to these transporters. In albino rats, highest distribution was to the GI tract, bile ducts and liver. No penetration was observed to the CNS. However in another study in pregnant albino rats, the results indicated passage over the blood-brain barrier. The volume of distribution is dose-dependent likely due to the auto inhibition of OATP1B1/3 reducing distribution to organs expressing these transporters such as the liver.

Elimination

The mass-balance investigation was performed at multiple-dose (80 mg bid) conditions using [^{14}C]letermovir the dose before sampling. The mean recovery of total radioactivity from excreta was 95%. The major recovery of total radioactivity was in faeces and accounted for 93% with negligible amounts (<2%) recovered in urine. The radioactivity in faeces consisted of letermovir (70% of dose) as the major component and the acyl-glucuronide M7 (6%, unstable in faeces) as a minor component. The remaining 17% of radioactivity in faeces corresponded to a total of four structurally uncharacterized metabolites each representing similar amounts. The two pathways are both counted as main elimination pathways. OATP1B1/3 is responsible for the uptake of letermovir into the hepatocyte. BCRP and Pgp mediate the efflux from the hepatocyte into the bile. Glucuronidation to the acyl glucuronide observed in vivo was catalysed by UGT isoforms 1A1 and 1A3. There is little in vivo DDI support of the elimination pathways of letermovir. There is no study investigating the effect of a strong OATP inhibitor or a strong Pgp/BCRP inhibitor.

Interconversion
Letermovir contains one chiral centre with an absolute configuration of S. Ex vivo data indicate that there is no conversion to the R-enantiomer in vivo.

Metabolites in circulation
Seventy-six % of total radiolabelled material in plasma was parent drug and the remainder was related to other metabolites. The extraction efficiency of the AUC plasma pool (0-24 hours) was 84% (60-88%) with 16% of radiolabelled material not being extractable. This unextractable material may have been, in part, the 1-O-acyl-β-D-glucuronide (M7).

Pharmacogenetics

Polymorphism in SLCO1B1 (coding for OATP1B1) was expected to influence the AUC of letermovir in healthy volunteers. Pooled analysis was performed on data from phase 1 studies. Homozygous carriers of SLOC1B1 rs4149056 had a mean 42% increase in drug exposure. The *1b/*5 and *5/*5 haplotypes were statistically significantly associated with increased letermovir AUC (by 25 and 58%, respectively). Subjects carrying the UGT1A1*6 rs4148323 minor allele (A) have a 36% increase in a pooled analysis. As there is no study with stratified inclusion and the numbers reside from pooled analysis, there is some uncertainty regarding the exposure change estimates. However, the effects of the studied polymorphisms are unlikely clinically relevant.

Dose proportionality and time dependencies

Single-dose conditions
Letermovir shows clear dose dependent pharmacokinetics due to saturation of drug elimination. CL decreased from 16.6 to 5.7 L/h after giving iv single doses from 30 to 480mg, respectively. In another study, CL decreased from 9.4 to 4.0 L/h after single-dose administration of 120 and 960 mg iv, respectively. The nonlinearity was not that pronounced between iv 240 and 480 mg. After iv administration of 720 mg, there was a plateau in the dose normalised AUC indicating either that the saturable pathway was completely saturated. The data on oral administration is partly aligned with iv data. One study investigating oral single doses up to 120 mg showed nonlinear elimination kinetics. In another study when increasing the dose from 240 to 280 and 320 mg, the exposure was not increased further. These results are difficult to explain by full saturation of the elimination pathway alone. In yet another study investigating oral single doses, linear PK

was observed,. The applicant has performed a PBPK analysis to investigate the cause of the saturated elimination. The platform has not been qualified for this purpose and simulations are particularly difficult regarding transporters due to lack of scientific data. However, the conclusion that OATP1B1 inhibition is responsible for the saturated elimination is agreed upon, without relying on the simulations.

Multiple-dose conditions

Clearance in multiple-dose conditions at the therapeutic dose (the true clearance varies with concentration) during 480 mg qd, CL and t1/2 were ca. 4.66 L/h and 12 hours, respectively. There was little accumulation during multiple-dose conditions and the exposure was nonlinear. The lack of accumulation is somewhat surprising based on the half-life and saturable elimination. This may again be a result of auto induction. There was no study investigating many different dose levels aiming to understand the dynamics of the nonlinearity observed at single-dose conditions. The exposure was quite dose-proportional comparing 120 and 240 mg qd iv. No other good comparative iv datasets are available. After oral administration, one study show saturable pharmacokinetics between 240 and 360 mg bid and one between 40 mg qd and 40 mg bid, but not between 40 mg bid and 80 mg bid.

At oral high doses (720 mg qd and 480 mg qd), auto induction is observed. During iv administration of 480 mg qd for 7 days, trough concentrations were increasing and there was no clear auto induction. This suggests that the majority of the auto induction resides in the intestine, possibly through induction of Pgp and/or BCRP. An autoinduction component was also needed in the population PK model to obtain satisfactory predictions.

These exposure parameters are concluded from the data in healthy volunteers:

- 480 mg qd iv infusion for 7 days mean Cmax 27000 ng/ml and AUC 129000 ngh/ml
- 480 mg qd po for 9 days Cmax 13018 ng/ml and AUC 71484 ng*h/ml

It is noted that when making an inter-study comparison of the data above, the exposure after iv administration is double the exposure at oral administration. The bioavailability may then be ca. 55% at this dose level, maybe due to absorption limitations and/or auto induction of intestinal Pgp/BCRP. This is in line with the low (35%) bioavailability observed in patients indicated by the population PK analyses.

Table 16 Letermovir AUC (ng•hr/mL) values in HSCT Recipients

480 mg Oral, no cyclosporine	34,400 (16,900, 73,700)
480 mg IV, no cyclosporine	100,000 (65,300, 148,000)

The time needed to reach steady state appears to be dependent on mode of administration. Looking at the IV 480 mg qd data, steady state may be obtained after ca. 5 days, while after oral administration, steady state may be reached later, after ca. 10 days. The population PK analysis indicate a time needed to obtain steady state of 9-10 days.

Intra- and inter-individual variability

According to the population PK analysis in 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%.

Pharmacokinetics in target population

Based on population PK analysis of phase 1 data, healthy volunteers have a higher bioavailability (approximately 94%) as compared to patients (approximately 35% without concomitant cyclosporin A treatment). Further, co-treatment with cyclosporin A results in increased bioavailability in patients (approximately 85% with concomitant cyclosporin A treatment). Clearance in patients was decreased from 4.8 L/h to 3.4 L/h in patients that received cyclosporin A.

Special populations

Renal impairment

The pharmacokinetics of letermovir has been investigated at multiple dose condition (120 mg qd) for 8 days in patients with moderate and severe renal impairment. Patients with ESRD have not been studied. The unbound exposure of letermovir was doubled in both moderate and severe renal function impairment. One of the eight subjects with severe RI had an 8-fold increased unbound exposure.

Hepatic impairment

The pharmacokinetics of letermovir has been investigated at multiple dose condition 60 and 30 mg qd for 8 days in patients with moderate and severe hepatic impairment, respectively, and compared to healthy controls matched for each group and having the same dose. The exposure of unbound letermovir was increased 4-fold in severe hepatic impairment and 81% increased in moderate impairment. Use in severe impairment is not recommended but in moderate impairment, the SmPC states that no dose adjustment is required. The exposure of letermovir in patients with moderate hepatic impairment treated with CsA combined with letermovir is estimated to be within the target exposure range.

Japanese

The pharmacokinetics of letermovir has been studied in Japanese subjects after single doses of 240, 480, and 720 mg orally and 240, 480, and 960 mg iv. Furthermore, multiple doses of 480 mg qd for 7 days have been studied and also of 240 mg qd but with a 200 mg CsA dose on the sampling day (day 8). The exposure was doubled in Japanese as compared to Non-Japanese as historical controls. This increase is considered not clinically relevant. The dose dependency (saturable elimination) was more pronounced in the Japanese.

Blacks

There was no significant difference in the exposure of letermovir estimated in Blacks.

Gender

Based on population PK analyses, gender did not have a clinically relevant effect on letermovir exposures.

Body Weight

Letermovir exposure decreased with an increase in body weight. The population PK analyses showed that letermovir exposures changed slightly with changes in body weight; within the White subgroup, letermovir exposures were 18.7% lower for subjects with high weight (80- 100 kg) compared to the average weight of 67.1 kg observed in the population PK analysis dataset.

Age

The median age in the population PK analysis data set was 51 years. No patients older than 75 years were included in the population pharmacokinetic analysis of patient data.

Pharmacokinetic interaction studies

Drug Interactions

In vitro studies

The application contains many *in vitro* studies on drug interaction potential of letermovir as perpetrator of DDIs as well as on the enzyme and transporter involvement in the disposition. The results of the in vitro studies of Letermovir as perpetrator and their in vivo relevance (0 or 1) are presented below.

Input parameters: P.O*

Cmax (µM)	Protein binding (%)	Dose (mg)
22,7	98,5	480

*setting F to 90% as worst case
Cut-off I.V: 35 uM (50xCmax u)

Cut-off´s P.O *

50*Cmax(u) (µM)	25*Inlet Cmax(u) (µM)	0.1*ose/250 ml (µM)
17,1	8,5	335,3

In vitro inhibition

Table 17 Summary of the *in vitro* DDI findings regarding Letermovir as an inhibitor of enzymes and transporters, and the potential *in vivo* relevance assessment of the findings.

		Possible in vivo relevance(1=yes, 0=no)		
Protein	IC_{50}/2, Ki or K_I [#]	Oral	Oral	IV
Enzymes	(µM)	Systemic	Intestine	IV systemic
CYP1A2	>68	0	na	0
CYP2B6	26	0	na	1
CYP2C8	0.15	1	na	1
CYP2C9	>68	0	na	0
CYP2C19	>68	0	na	0
CYP2D6	>68	0	na	0
CYP3A	K_I 24 µM, k_{inact} 0.0473 min-1	1	1	1
UGT1A1	11	1	1	1
UGT1A6	>68	0	nd	0
UGT1A7	>68	0	nd	0
UGT2B7	>68	0	nd	0
Transporters				
P-gp	6.8	1	1	1
BCRP	14.5	1	1	1

MRP-2	23.6	0	na	1
OATP1B1	1.45	1	0	1
OATP1B3	0.55	1	0	1
OATP2B1	15	1	1	1
OAT1	>100	0	0	0
OAT3	1.25	1	na	1
OCT2	50	0	na	0
OCT1	32.5	0	0	0
MATE1	nd	nd	nd	nd
MATE2-K	nd	nd	nd	nd
BSEP	15.2	1	0	1

[#] $IC_{50}/2$, Ki and K_I values for drug metabolising enzymes were normalised for nonspecific binding
na=not applicable, nd=not determined

Summary of the interpretation of the in vivo relevance of the in vitro inhibition results: Letermovir was found to inhibit CYP2B6 in the liver, CYP3A4 in intestine and liver (TDI), CYP2C8 in intestine and liver, UGT1A1 in intestine and liver, Pgp at intestine and liver/kidney, BCRP in intestine and liver, hepatic MRP-2 after iv administration only, OATP1B1 and 3 in liver, OATP2B1 in intestine and liver, OAT1 in liver, OAT3 in kidney and, finally BSEP in liver. The intestinal inhibition is of course only relevant for orally administered letermovir.

In vitro induction

Induction of CYP3A4 and CYP2B6 (model enzymes for PXR and CAR mediated induction, respectively) was observed at relevant concentrations. For CYP2B6, the induction signal was more pronounced at an activity level. No induction of CYP1A2 (Ah-receptor mediated induction) was observed. The calculated EC50 values obtained in two lots were 0.83 ± 0.60 µM and 0.70 ± 0.38 µM with Emax values reaching 5.4 and 5.3 fold increase over solvent control, respectively.

In vivo DDI studies

MECHANISTIC STUDIES

A) Letermovir as perpetrator of DDIs

Midazolam (CYP3A4)

Letermovir is a moderate, time-dependent, inhibitor of CYP3A4. The AUC of midazolam after oral administration increased by 125% on the 6th day of treatment with letermovir 240 mg qd p.o. (half the therapeutic dose.) The effect on the AUC of iv administered midazolam on the 4th day of treatment was 47%. The effect of oral and iv letermovir is likely larger after 480 mg qd. This is also supported by sirolimus DDI data (see below).

Digoxin

On the 6th day of 240 mg letermovir BID digoxin was administered. Digoxin AUC0-last and Cmax were reduced by 12 and 25%, respectively, likely due to Pgp induction mainly in the intestine. The effect may not

be present for iv administered Letermovir. The effect may be larger on drugs for which intestinal Pgp is more important such as dabigatran and sofosbuvir.

Statins

Atorvastatin is a substrate of OATP1B1/3, BCRP and CYP3A. The OATP1B1 involvement appears higher than for pravastatin and rosuvastatin. When atorvastatin was administered as a 20 mg single-dose on the 8th day of letermovir 480 mg qd, atorvastatin exposure was increased by 230%. Tmax of atorvastatin was prolonged. The half-life of atorvastatin was unaffected. The exposure of orthohydroxyatorvastatin and parahydroxyatorvastatin was unchanged while the observed median Tmax for both metabolites were markedly prolonged. Most statins may be markedly affected by letermovir with or without cyclosporine.

B) Letermovir as victim of DDIs

The applicant did not perform any mechanistic study providing in vivo support to the elimination pathways of Letermovir. The studies with cyclosporine single-dose (see below) provide some support to the OATP involvement. However, it may not be used to quantify the involvement as CsA also inhibits Pgp and BCRP. The effect of potently inhibiting Pgp/BCRP alone is not known. Cyclosporine is used by half the patients. The effect of adding a Pgp/BCRP or an OATP1B1/3 inhibitor to the Letermovir-CsA combination is also not known. There are no DDI studies with inducers. PAMs have been requested to provide some of the missing information.

Between pH ~4 and ~7, letermovir exhibits low intrinsic solubility. Solubility increases below pH 4, above pH ~7, solubility increases again. The solubility appears high enough for the pH dependency not to reflect in DDIs with PPIs (see table). In addition, exploratory population PK analysis did not indicate any relevant effect by PPIs.

STUDIES WITH COMMON CONCOMITANT MEDICATION

The patient population has many concomitant medications (see below).

Table 18 Subjects With Specific Concomitant Medications (Incidence ≥10% in One or More Treatment Groups) (P001, ASaT Population; Treatment Phase and letermovir arm only

	Letermovir	
	n	(%)
Subjects in population	373	
With one or more concomitant medications	373	(100.0)
With no concomitant medications	0	(0.0)
alimentary tract and metabolism		
antidiarrheals, intestinal antiinflammatory/antiinfective agents	**121**	**(32.4)**
loperamide	63	(16.9)
antiemetics and antinauseants	**188**	**(50.4)**
ondansetron	102	(27.3)
ondansetron hydrochloride	78	(20.9)
bile and liver therapy	**237**	**(63.5)**
ursodiol	237	(63.5)
drugs for acid related disorders	**357**	**(95.7)**
famotidine	57	(15.3)
magnesium oxide	87	(23.3)
omeprazole	101	(27.1)
pantoprazole	90	(24.1)
pantoprazole sodium	90	(24.1)
drugs for constipation	**112**	**(30.0)**
docusate sodium	36	(9.7)
lactulose	29	(7.8)
drugs for functional gastrointestinal disorders	**187**	**(50.1)**
metoclopramide	40	(10.7)
metoclopramide hydrochloride	68	(18.2)
drugs used in diabetes	**74**	**(19.8)**
mineral supplements	**297**	**(79.6)**
magnesium (unspecified)	42	(11.3)
magnesium sulfate	180	(48.3)
potassium chloride	159	(42.6)
stomatological preparations	**89**	**(23.9)**
vitamins	**177**	**(47.5)**
cholecalciferol	42	(11.3)
vitamins (unspecified)	71	(19.0)
antiinfectives for systemic use		
antibacterials for systemic use	**360**	**(96.5)**
cefepime	54	(14.5)
ciprofloxacin	76	(20.4)
levofloxacin	137	(36.7)
meropenem	119	(31.9)
metronidazole	72	(19.3)

	Letermovir	
	n	(%)
antiinfectives for systemic use		
antibacterials for systemic use	**360**	**(96.5)**
piperacillin sodium (+) tazobactam sodium	107	(28.7)
sulfamethoxazole (+) trimethoprim	238	(63.8)
vancomycin	89	(23.9)
antimycotics for systemic use	**321**	**(86.1)**
amphotericin B	40	(10.7)
caspofungin acetate	42	(11.3)
fluconazole	170	(45.6)
posaconazole	73	(19.6)
voriconazole	106	(28.4)
antivirals for systemic use	**364**	**(97.6)**
acyclovir	287	(76.9)
foscarnet sodium	20	(5.4)
ganciclovir	13	(3.5)
valacyclovir hydrochloride	125	(33.5)
valganciclovir hydrochloride	16	(4.3)
immune sera and immunoglobulins	**67**	**(18.0)**
globulin, immune	65	(17.4)
antineoplastic and immunomodulating agents		
antineoplastic agents	**138**	**(37.0)**
methotrexate	87	(23.3)
immunostimulants	**151**	**(40.5)**
filgrastim	125	(33.5)
immunosuppressants	**366**	**(98.1)**
cyclosporine	193	(51.7)
mycophenolate mofetil	123	(33.0)
sirolimus	36	(9.7)
tacrolimus	174	(46.6)
antiparasitic products, insecticides, and repellents		
antiprotozoals	**103**	**(27.6)**
atovaquone	47	(12.6)
pentamidine isethionate	56	(15.0)
blood and blood forming organs		
antianemic preparations	**153**	**(41.0)**
folic acid	137	(36.7)
antihemorrhagics	**92**	**(24.7)**
phytonadione	76	(20.4)
antithrombotic agents	**153**	**(41.0)**
enoxaparin sodium	58	(15.5)

	Letermovir	
	n	(%)
blood and blood forming organs		
antithrombotic agents	**153**	**(41.0)**
heparin	55	(14.7)
blood substitutes and perfusion solutions	**245**	**(65.7)**
blood cells, red	147	(39.4)
platelet concentrate	131	(35.1)
sodium chloride	100	(26.8)
cardiovascular system		
agents acting on the renin-angiotensin system	**71**	**(19.0)**
beta blocking agents	**91**	**(24.4)**
calcium channel blockers	**138**	**(37.0)**
amlodipine	76	(20.4)
cardiac therapy	**45**	**(12.1)**
diuretics	**170**	**(45.6)**
furosemide	123	(33.0)
furosemide sodium	34	(9.1)
lipid modifying agents	**55**	**(14.7)**
vasoprotectives	**39**	**(10.5)**
dermatologicals		
antifungals for dermatological use	**163**	**(43.7)**
nystatin	127	(34.0)
antiseptics and disinfectants	**101**	**(27.1)**
chlorhexidine gluconate	66	(17.7)
corticosteroids, dermatological preparations	**100**	**(26.8)**
emollients and protectives	**68**	**(18.2)**
genitourinary system and sex hormones		
urologicals	**44**	**(11.8)**
musculoskeletal system		
antigout preparations	**38**	**(10.2)**
antiinflammatory and antirheumatic products	**52**	**(13.9)**
nervous system		
analgesics	**288**	**(77.2)**
acetaminophen	188	(50.4)
fentanyl	38	(10.2)
hydromorphone	46	(12.3)

nervous system		
analgesics	**288**	**(77.2)**
morphine	64	(17.2)
oxycodone	63	(16.9)
tramadol hydrochloride	69	(18.5)
anesthetics	**110**	**(29.5)**
lidocaine hydrochloride	49	(13.1)
antiepileptics	**63**	**(16.9)**
psychoanaleptics	**76**	**(20.4)**
psycholeptics	**270**	**(72.4)**
lorazepam	136	(36.5)
prochlorperazine	58	(15.5)
zolpidem tartrate	36	(9.7)
respiratory system		
antihistamines for systemic use	**182**	**(48.8)**
diphenhydramine	61	(16.4)
cough and cold preparations	**53**	**(14.2)**
drugs for obstructive airway diseases	**103**	**(27.6)**
budesonide	42	(11.3)
nasal preparations	**49**	**(13.1)**
sensory organs		
ophthalmologicals	**75**	**(20.1)**
systemic hormonal preparations, excl. sex hormones and insulins		
corticosteroids for systemic use	**246**	**(66.0)**
hydrocortisone	45	(12.1)
hydrocortisone sodium succinate	50	(13.4)
prednisolone	38	(10.2)
prednisone	80	(21.4)
various		
all other therapeutic products	**141**	**(37.8)**
leucovorin calcium	61	(16.4)
various		
general nutrients	**54**	**(14.5)**

Table 19 Summary of Concomitant Immunosuppressive Regimen Use (ASaT Population; Treatment phase and letermovir arm only)

	Letermovir	
	n	(%)
Subjects in population	373	
Calcineurin Inhibitors	**353**	**(94.6)**
Cyclosporin A	193	(51.7)
Tacrolimus	174	(46.6)
Selected Immunosuppressants	**161**	**(43.2)**
Everolimus	7	(1.9)
Leflunomide	1	(0.3)
Mycophenolate[†]	139	(37.3)
Sirolimus	36	(9.7)
Systemic Corticosteroid	**246**	**(66.0)**

IMMUNOSUPPRESSANTS

Cyclosporine

A high fraction of the patients were co-treated with cyclosporine. A 50% reduction of the dose (to 240 mg qd) was used when letermovir was administered with cyclosporine in phase III studies. Cyclosporine is a CYP3A substrate and an inhibitor of OATP1B1, Pgp and BCRP.

In transplantation, the recommended dose of CsA is approximate, but 2-6 mg/kg is proposed divided on two administrations. For a person weighing 70kg, the dose translates to 70-210mg bid.

There are two conventional DDI studies with cyclosporine but they included only a CsA single dose and a quite low such dose. On the seventh day of letermovir 80 mg bid p.o, the AUC of CsA administered as a 50 mg single-dose was 80% increased. Letermovir AUC was 90% increased by the CsA 50mg single-dose. During letermovir 40 mg bid treatment, single doses of CsA were administered; 50 mg on day 7, 200 mg on day 14. There was an increase by 130% in letermovir AUC after coadministration of 50 mg CsA and an increase by 240%, after coadministration of 200 mg CsA.

In another study, a single oral CsA 50 mg dose was administered on the 8th day of letermovir 240 mg qd. CsA exposures were 50-70% increased and C12 and C24 doubled. Very unfortunately, the study did not include an arm with letermovir alone. Thus, direct comparisons investigating the effect on letermovir are not possible. The CsA dose was subtherapeutic.

The recommendation in the SmPC section 4.5 regarding co-treatment with CsA is to reduce the letermovir dose by 50% (from 480 to 240 mg qd) and to TDM for CsA. This recommendation was used in phase III studies.

-The above Phase 1 DDI studies with CsA informed the dose selection for the Phase 3 trial. A more pronounced effect by CsA was observed in the population PK analysis where the exposure was doubled after 240 mg qd with CsA as compared to 480 mg qd without CsA (see below). The interaction was not as pronounced after iv administration and thus the 240 mg taken with CsA did not reach the exposure obtained with 480 mg qd iv (see below). The difference between iv and po administration may be the Pgp mediated

efflux in the intestine after the oral but not iv administration. The net result is that the exposure obtained with oral letermovir without CsA is markedly lower than the exposure obtained with the other treatments.

Table 20 Letermovir AUC (ng x hr/mL) values in HSCT recipients

Treatment Regimen	Median (90% Prediction Interval)*
480 mg Oral, no cyclosporine	34,400 (16,900, 73,700)
480 mg IV, no cyclosporine	100,000 (65,300, 148,000)
240 mg Oral, with cyclosporine	60,800 (28,700, 122,000)
240 mg IV, with cyclosporine	70,300 (46,200, 106,000)
* Population post-hoc predictions from the population PK analysis using Phase 3 data	

There is another DDI study where a CsA 50 mg single dose was administered with and without letermovir 240 mg qd. No effect of CsA on letermovir was determined in this study but numerically the AUCs observed when taken with the CsA single dose was very similar to the result of the population PK analysis in the 240 mg qd oral + CsA arm.

A different interaction effect is expected with therapeutic doses of letermovir and CsA and after oral and iv letermovir. This depends on differences in systemic exposure, in intestinal exposure and additional transporter inhibition brought by CsA.

Tacrolimus

Tacrolimus is metabolised by CYP3A4 and 5, and is transported by Pgp, but in contrast to CsA, it is not a known transporter inhibitor. Letermovir 480 mg qd p.o. doubled the exposure of tacrolimus (5 mg single-dose) on the 8th day of of treatment, absorption and half-life were prolonged. In another study letermovir 80 mg bid po increased tacrolimus AUC by 60% after a tacrolimus 5mg single dose. The DDI may be caused by CYP3A4 inhibition but the prolonged absorption also indicates Pgp induction or intestinal uptake transporter inhibition. TDM for tacrolimus is recommended in the SmPC.

Sirolimus

Sirolimus is metabolised by CYP3A and is also transported by Pgp. Sirolimus exposures (AUCs) were approximately 3-fold higher following coadministration with letermovir 480 mg qd p.o. (day 8 of treatment) and a 2 mg sirolimus single-dose. The absorption was delayed by 1.5 hours again indicating intestinal Pgp induction. In the SmPC, frequent monitoring is advised.

Mycophenolic acid (MPA)

MPA is the active metabolite of mycophenolate mofetil. The PI approved at national level indicated that glucuronidation catalysed by UGT1A9 followed by hydrolysis and enterohepatic recirculation is the main elimination pathway of mycophenolic acid. Coadministration of 480 mg qd letermovir at steady state with a single dose of 1 g mycophenolate mofetil (MMF) has no meaningful effect on the PK of mycophenolic acid (MPA).

ANTIVIRALS

Acyclovir

Acyclovir is a very commonly used drug in the target population. The drug is mainly eliminated through renal excretion with a large contribution of active secretion to a significant extent mediated by OCT2, OAT 1 and/or 3 (shown as DDIs with cimetidine and probenecid, respectively). Letermovir inhibits OAT3 in vitro at in vivo relevant concentrations.. Five days of treatment with 480 mg letermovir qd did not influence the pharmacokinetics of acyclovir (400 mg acyclovir single-dose).

ANTIFUNGALS

Antifungals were used in almost all patients. Concomitant treatment is expected with the following: fluconazole, isavuconazole, voriconazole, posaconazole, amphotericin B and echinocandins (caspofungin, anidulafungin and micafungin). Voriconazole and in particular fluconazole were common in the target patient population.

Voriconazole

When letermovir 480 mg qd was administered together with voriconazole multiple dose regimen (as per the product SmPC) for 4 days, the exposure of voriconazole was reduced by 44% due to CYP2C19 induction. The effect on voriconazole was evaluated the 8th day of letermovir treatment. The effect on voriconazole may be somewhat more pronounced at steady state. The effect on letermovir exposure was not studied. The effect by letermovir 240 mg qd (with CsA) is likely lower but it is not known how much the DDI is reduced. TDM is advised to maintain therapeutic concentrations of voriconazole. CYP2C19 PMs will likely have increased exposures.

Posaconazole

Letermovir 480 mg qd for 14 days did not affect the pharmacokinetics of posaconazole (300 mg single-dose). Available in vitro data does not indicate an effect by posaconazole on letermovir.

Fluconazole and other not studied antifungals

The interaction with other antifungals fluconazole, isavuconazole, amphotericin B and capsofungin, anidulafungin and micafungin has not been studied. Based on the available information no DDI is predicted with fluconazole, caspofungin or anidulafungin. Letermovir likely increases isavuconazole exposure through CYP3A inhibition. Available data indicate a clinically not relevant increase in exposure but it is unknown whether isavuconazole also is transported by OATP1B1/3, which could make the DDI more marked. The enzymes and transporters involved in main elimination pathways of micafungin and amphotericin B does not appear to be well characterised. As the data is so sparse, is thus not known whether letermovir will give rise to reduced exposures of amphotericin B or micafungin.

ANTIBACTERIALS

There are no interaction studies with penicillins, cephalosporines, carbapenems or vancomycin. The risk of interactions has been discussed based on the available scientific information. The elimination of piperacillin has partial contribution of metabolism and biliary secretion that may be inducible and thus affected by letermovir. Such contribution in the elimination of tazobactam is smaller. Available information does not indicate an interaction risk for meropenem, imipenem/cilastatin, cefepime, vancomycin and ceftazidime.

Ethinylestradiol and levonorgestrel

The HSCT patients treated on this indication are highly unlikely to be fertile. Letermovir 480 mg qd for 12 days gave rise to a 43% increase in EE AUC, and a 36% increased AUC of levonorgestrel administered as a single-dose. As letermovir is an inducer, a decrease in exposure of the contraceptives is expected unless the effect is counteracted by inhibition of proteins such as CYP3A, BCRP or UGT1A1. The net effect thus depends on the elimination pathways or the specific steroid. Thus, the lack of DDI may not be translated to other systemically acting contraceptive steroids.

Target exposure range

The target range, or here – range of the fold change where it is considered that satisfactory efficacy and safety has been shown – varies by letermovir regimen as the observed exposure in patients treated with the separate regimens is quite different (See table 1). The range for oral letermovir without CsA is 1 to 9-fold. For the other regimens, the range is 0.5 to 4-fold. The differences results in different treatment recommendations for the separate regimens in situations where the exposure of letermovir is affected by other drugs.

2.4.3. Pharmacodynamics

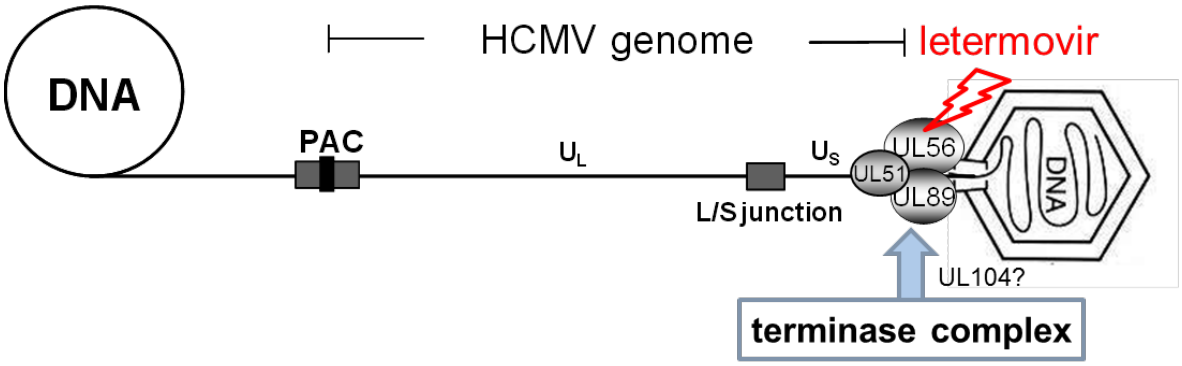
Introduction

Letermovir (also referred to as MK-8228, AIC001, AIC090027, AIC246, BAY 73-6327, EX-30, EX000030, BR-4359) is a novel inhibitor of the human cytomegalovirus (CMV). Virological characterization and sequence analysis of resistant viruses indicate that the viral terminase complex is the target of this compound. Unlike currently marketed anti-CMV drugs, which act via inhibition of the viral DNA polymerase, terminase inhibitors interfere with viral DNA maturation and packaging of monomeric genome units. Consequently, cross-resistance is not expected between letermovir and currently approved medicines for the treatment of CMV infection. There is no known mammalian counterpart of the viral terminase complex. Therefore, this novel mechanism could provide an efficacious and well- tolerated therapy for CMV reactivation and disease.

Mechanism of action

Selection and genotyping of a panel of mutant viruses that escaped letermovir inhibition indicated that the viral terminase complex, which plays a key role in cleavage and packaging of viral progeny DNA, is the target. The terminase complex minimally consists of a large and a small subunit that are encoded by two viral genes (UL56 and UL89). The terminase complex is thought to interact with premature viral capsids by binding to the viral portal protein pUL104. Recently, another viral protein (pUL51) has also been found in complex with pUL56 and pUL89, although its functional role within the viral terminase machinery remains to be elucidated. Consistent with letermovir resistance mutations that map to UL56, biochemical experiments and electron microscopy demonstrated that letermovir affects the formation of proper unit length genomes from viral DNA concatamers and interferes with virion maturation.

Figure. 3 Mechanism of Action: Letermovir Interferes with CMV Genome Cleavage and Encapsidation of Monomeric CMV Progeny DNA



Mutant CMV isolates resistant to letermovir were generated in vitro. DNA sequencing identified mutations in the CMV UL56 terminase gene, and marker transfer analyses confirmed that these mutations were necessary and sufficient to confer letermovir resistance. No resistance-associated mutations were found in the UL51, UL89, or UL104 genes.

While letermovir treatment leads to an immediate cessation of the production of infectious viral particles, it allows DNA synthesis to occur, thus providing DNA copies that are measured by the CMV DNA assay. Valganciclovir, in contrast, is a DNA polymerase inhibitor and thus has an immediate effect on the production of DNA copies.

In the P001 study, CMV DNAemia has been used as a trigger for initiating pre-emptive therapy with GCV/VGCV. However, given that the postulated mechanism of action of letermovir is down-stream of DNA synthesis, CMV DNA might not be the optimal biomarker for the efficacy of letermovir prophylaxis. It may be that CMV DNA levels rise, but without the output of infectious virions that characterizes virologic failure. However, as there are no validated alternative biomarkers or PET initiation thresholds, the use of CMV DNA for monitoring and standard-of-care PET criteria is endorsed although this could be too conservative and result in unnecessary termination of letermovir prophylaxis.

Primary and Secondary pharmacology

Primary pharmacology

The mechanism of action is described above.

Antiviral potency

In cell culture models of infection, letermovir inhibited laboratory and clinical CMV isolates, including several strains resistant to other anti-CMV agents, with low nanomolar EC50 (50% effective concentration) values.

Antiviral Drug Resistance

In order to identify CMV mutations linked to letermovir drug resistance, cell-culture selection procedures were used to isolate mutant viruses that escaped letermovir inhibition. Characterization of these CMV

mutants established that: i) all mutants were resistant to letermovir, with EC_{50} values that were 13- to 5,870-fold higher than those for the wild-type parental virus; and ii) each isolate had a mutation in UL56, the viral gene encoding the large subunit of the CMV DNA terminase complex. The deduced amino acid substitutions in UL56 were clustered in a conserved region between amino acids 231 and 369. Marker transfer experiments and recombinant phenotyping confirmed that each UL56 mutation was necessary and sufficient for resistance to letermovir, and shifts in drug susceptibility for each recombinant mutant virus and its corresponding original mutant isolate were equivalent. No resistance-associated mutations were found in other regions of UL56, or in the UL51, UL89 or UL104 genes. None of the mutations affected virus growth in cell culture, although the fitness of these variants in vivo remains to be determined. The selected UL56 mutations conferred reduced susceptibility to letermovir but had no effect on susceptibility to CMV DNA polymerase inhibitors including ganciclovir, cidofovir, and foscarnet.

Table. 21 Generation and Characterization of Mutant CMV Strains that Escape Letermovir Inhibition

HCMV strain	EC_{50} [µM] [a]		RI [b]	AA substitution [c]			
	Letermovir	GCV		UL56 [d]	UL89 [d]	UL104 [d]	UL51 [d]
AD169	0.0046 ± 0.0019	3.6 ± 1.4	1	n.a. [e]	n.a.	n.a.	n.a.
selected mutants [f]							
rAIC246-1 [g]	1.23 ± 0.32	1.2 ± 0.2	268	L241P	– [h]	–	–
rAIC246-2 [g]	0.37 ± 0.07	4.0 ± 0.9	81	R369S	A345S [i]	–	–
rAIC246-3	27 ± 3.27	3.0 ± 2.4	5870	C325Y	–	–	–
rAIC246-4	0.13 ± 0.01	4.2 ± 1.3	28	V231L	–	–	–
rAIC246-5	0.11 ± 0.01	5.0 ± 0.4	23	R369M	–	–	–
rAIC246-6	0.08 ± 0.02	2.9 ± 0.9	17	R369M	–	–	–
rAIC246-7	0.92 ± 0.12	2.2 ± 0.6	200	L241P	–	–	–
rAIC246-8	25 ± 5.53	2.2 ± 1.2	5413	C325Y	–	–	–
rAIC246-9	0.06 ± 0.04	1.7 ± 0.2	13	R369G	–	–	–
rAIC246-10	0.09 ± 0.02	1.4 ± 0.4	19	V236M	A345S [i]	–	–

a EC_{50}s were determined by a CPE reduction assay. Data are means from at least three independent experiments and are expressed with standard deviation.

b The resistance index (RI) is the letermovir EC_{50} for mutant virus divided by the letermovir EC_{50} for wild-type virus.

c Amino acid substitution identified by HCMV genotyping.

d HCMV genes involved in cleavage/packaging of viral progeny DNA.

e not applicable

f HCMV strain AD169 virus mutants obtained in vitro under selective pressure with letermovir.

g previously published

h —: no AA substitution.

i Interstrain variation not associated with letermovir resistance (Table 3 in PD018, [Sec. 2.6.3.1]).

Common UL56 and UL89 polymorphisms

In addition to the UL56 genotypes whose impact on letermovir susceptibility has been measured, CMV DNA sequences in a public database have been used to identify additional genotypic variants in both UL56 and UL89. One hundred eighty-seven unique whole CMV genome sequences were identified among entries in the NCBI DNA sequence database. The deduced amino acid (AA) sequences for the UL56 and UL89 proteins

generated from these DNA sequence entries were aligned to UL56 and UL89 amino acid sequences from the letermovir-susceptible CMV Merlin strain (NCBI accession number NC_006273.2). Differences from the reference include both rare and common polymorphisms. In UL56, 44 of 850 AAs had one or more variants detected. At 37 of these 44 AAs there was one variant compared to the Merlin reference UL56 AA sequence; at 5 of the 44 AAs there were two variants; and at 2 of 44 AAs there were 3 variants. The total number of variants was 53; included among these 53 variants were 17 whose impact on susceptibility to letermovir had been previously determined. In UL89, 18 of 674 AAs had one variant detected. None of these variants have been characterized for their impact on susceptibility to letermovir. Finally, none of the previously-characterized UL56 letermovir-resistant genotypic variants were found amongst the entries in the NCBI database.

Letermovir resistant strains can be selected with unaffected replicative capacity *in vitro* but the viral fitness *in vivo*, resistance barrier and clinical impact remains to be elucidated. From the entries in the NCBI DNA sequence database it seems that the letermovir resistance mutations selected in vitro are not common naturally existing polymorphisms.

Phenotypic resistance data from clinical isolates drawn from subjects failing letermovir prophylaxis will be submitted post-approval to address CHMP recommendation.

Secondary pharmacology

The marketing authorization application states states that the antiviral spectrum of letermovir is specific for human CMV. With the exception of murine CMV, which had an EC50 value of 4.51 ± 2.01 µM, letermovir was defined as inactive (EC50 > 10 µM) against other herpes viruses (VZV, HSV-1, HSV-2, EBV, HHV-6, and rat CMV) and non-herpes viruses (HIV, influenza A, hepatitis C, hepatitis B, and adenovirus).

For EBV (in a GFP-based replication assay), there is a seemingly dose-dependent response although at micromolar rather than nanomolar concentrations. However, the Cmax values in the Phase 3 study in HSCT patients ranged from 2,549 ng/mL to 21,570 ng/mL (approx. 38 µM).

For HHV-6 (in a PCR assay), the lowest concentration of letermovir that was evaluated (0.12 µM) resulted in an approximately 50% reduction of DNA expression with no further reduction at higher concentrations. Given that the mechanism of action does not primarily reduce DNA expression, antiviral effects cannot be excluded from this assay.

However, an UL56 homology search shows very limited homology between the CMV UL56 and orthologs among other human herpesviruses, supporting the claim that the letermovir mechanism of action is CMV specific. In the P001 study, similar rates of reactivation of other herpesviruses were seen in the P001 letermovir and placebo groups, although the patients were not systematically monitored for these viruses. However, the overall rates reported in the P001 study are very low in comparison to previously published data (eg. Burns et al 2016, Aoki et al 2015) but differences are likely driven by the systematic, hence more frequent, sampling in these studies.

Pharmacodynamic interactions with other medicinal products or substances

Interactions with Approved CMV Antivirals in Inhibition of CMV Replication

The inhibition of CMV by letermovir in combination with several currently approved CMV antivirals that target CMV DNA replication was evaluated in cell culture checkerboard assays. Using two separate mathematical

techniques (Loewe Additivity and Bliss Independence) for analysis, additive effects for the combination of letermovir with either GCV, CDV, FOS or acyclovir were observed. The lack of antagonism between letermovir and these compounds suggests that inhibition of CMV DNA polymerase does not antagonize concurrent inhibition of CMV DNA terminase in a cell-culture model of infection.

Effect of Letermovir on the In Vitro Activity of Selected anti-HIV Drugs

Two-drug combinations of letermovir with anti-HIV agents were evaluated in a cell-culture model of HIV infection. In these checkerboard assays, human MT-4 cells were infected with the HIV-1LAI virus at an MOI of 0.01 in the presence of compounds, and the cytopathic effect was measured using an alamar Blue cell viability assay following 5 days incubation. The anti-HIV compounds included HIV protease inhibitors (ATV, DRV, LPV, and RTV), nucleoside reverse transcriptase inhibitors (FTC, TDF), non- nucleoside reverse transcriptase inhibitors (EFV, ETR, and NVP), and an HIV integrase inhibitor (RAL). The drug-drug interactions were classified according to the method of Prichard and Shipman. All combinations of letermovir with HIV drugs in this study were defined as additive, with the exception of letermovir plus TDF, which was classified as minor antagonism. Given that any HIV- and/or HBV-infected patient that undergo allo-HSCT is most likely fully virologically suppressed, the possibility of a minor PD antagonism during the letermovir treatment is not considered to be of clinical importance.

Additive, but not synergetic effects, were observed between letermovir and currently available DNA polymerase inhibitors.

Genetic differences in PD response

CMV is divided into four genotypes according to the polymorphisms in UL55 gene that encodes for envelope glycoprotein B. The activity of letermovir was not significantly affected by the gB genotype of CMV, and isolates with mutations in the CMV UL54 and/or UL97 genes that confer resistance to GCV and other CMV DNA polymerase inhibitors maintained susceptibility to letermovir.

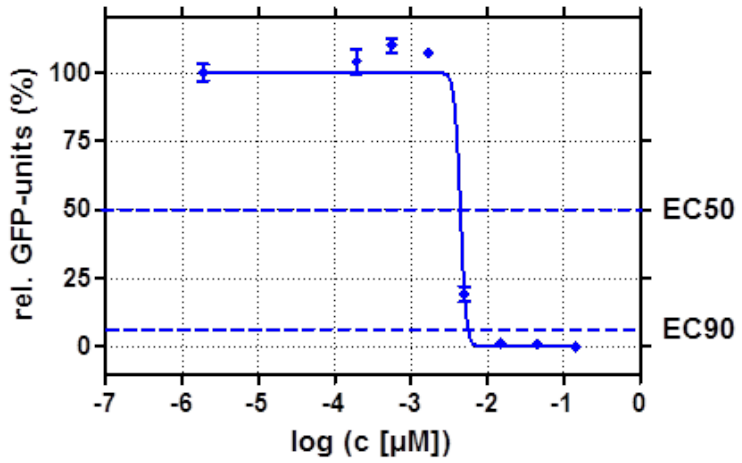
As the pharmacological target is of viral origin, host-related genetic differences are not expected to directly influence the pharmacodynamic response.

Relationship between plasma concentration and effect

In Vitro Dose Response of Letermovir

The EC50 values for letermovir against a collection of 74 CMV isolates (including 50 low–passage clinical strains) ranged from 0.14 to 6.1 nM.

Figure 4 In vitro Dose-response curve of Letermovir Using a Green Fluorescent Protein Based Antiviral Assay



c=drug concentration; rel.=relative

In a separate study, EC50 values for letermovir in the presence of 0/5/10/20/40% human serum were 2.5, 3.5, 4.7, 5.6, and 10.7 nM, respectively. This illustrates that the potency of letermovir in cell culture is shifted ca. 4.3-fold when the serum concentration is increased from 0 to 40% - the predicted EC50 values in 100% serum is 22.4 nM.

Antiviral Activity on Various Cell Types

For some antiviral drugs, large differences in EC50 values have been reported based on either cell culture conditions or the origin of the cells used for the in vitro infection model. EC50 values were determined for the fibroblast-specific AD169 strain using various fibroblast cell lines. The antiviral activity of letermovir was equivalent in all cell lines tested. In contrast, GCV EC50 values varied by as much as 7-fold depending on which fibroblasts were used.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Target range

The target range, or here – range of the fold change where it is considered that satisfactory efficacy and safety has been shown – varies by letermovir regimen as the observed exposure in patients is quite different. The range for oral letermovir without CyA is 1 to 9-fold. For the other regimens, the range is 0.5 to 4-fold. This should be kept in mind when proposing treatment recommendations and the difference in margins depending on regimen composes a communication challenge.

Methods

Non-linear PK was seen in healthy volunteers in the phase 1 population PK analysis. For instance, clearance in healthy volunteers was seen to be concentration as well as time dependent. This non-linear PK of letermovir was not included in the second population PK analysis due to the limited dose range, sparse data

collected in the phase 3 trial and lack of information to support the more complex disposition model built on phase 1 data. Therefore, the two models describe different parts of the letermovir PK data and cannot be used interchangeably.

The current phase 1 model does not provide a proper description of the complex disposition (distribution and elimination) of letermovir, which probably involves non-linear behaviour in hepatic uptake as well as enterohepatic recirculation. Extrapolation to unstudied scenarios using the phase 1 model is discouraged. However, it is agreed that the model can be used to describe the exposure in healthy volunteers following single and repeated dosing of letermovir at the 240 mg and 480 mg dose levels.

The phase 3 population PK analysis included four Phase 1/2 trials and a Phase 3 trial.

Saturable protein binding

Letermovir is extensively bound to human plasma protein in vitro. Letermovir bound both to serum albumin and AAG. The binding is concentration dependent at low concentrations but reached a plateau at concentrations ⩾3000 ng/ml and maintained so to the maximum studied 100000 ng/ml. The free fraction of letermovir was ca 0.9% at 1000 ng/ml and ca. 1.8 at higher concentrations. Letermovir thus appears linear at concentrations corresponding to marked increases in drug exposure. However, to ensure the right conclusion is drawn and the results of the extrinsic factor studies in healthy volunteers can be trusted, the binding will be studied in a DDI study recommended as PAM (the rifampicin DDI study). It is possible that the binding in patients has the plateau at higher concentrations if the AAG concentrations are higher in the patients. However, this is not relevant for this assessment.

Bioavailability

The bioavailability of letermovir may be lower in HSCT patients than in healthy volunteers. The data is not clear. The bioavailability was estimated to approximately 35% in patients by population-PK. The bioavailability of the phase III formulation was estimated to 94% in healthy volunteers by population PK analysis. However, there was very little supportive data at 480 mg qd as basis for the popPK analysis in healthy volunteers. It is noted that when making an inter-study comparison of the multiple dose PK data, the exposure after iv administration is double the exposure at oral administration. Thus these data indicate that bioavailability may then be approximately 55% at the 480 mg qd dose level, maybe due to absorption limitations and/or auto induction of intestinal Pgp/BCRP. The involvement of Pgp/BCRP is also indicated by the markedly larger effect by CsA on oral as compared to iv letermovir. The pop PK analysis indicates that the majority of the effect of CsA is exerted through impact on the bioavailability. The applicant suggests mucositis as explanation for the low bioavailability. However, this is not in line with CsA drug interaction results and this condition is usually not present at the time point when the letermovir treatment is changed from iv to oral administration.

Letermovir elimination

The mass-balance data does not allow a conclusion regarding the relative contribution of biliary excretion and glucuronidation but it can be concluded that these are the two major elimination pathways. OATP1B1/3 is involved in the uptake to the hepatocyte making drug available for metabolism and excretion. There is no DDI study with a potent selective OATP inhibitor. Pgp and BCRP are involved in the efflux to the bile and in the intestine, the transporters appears to limit the bioavailability. There is no in vivo DDI study with a potent selective Pgp/BCRP inhibitor allowing a quantification of the contribution of these proteins. Finally, there is also no in vivo study with an inhibitor of UGT1A1 and 3, which catalyses the glucuronidation. There is some pharmacogenetic support for the in vivo contribution of UGT1A1.

It takes approximately 9 days to reach steady state of letermovir. There is minimal accumulation but there is autoinduction and dose-dependent elimination. The DDI studies have not been performed with letermovir treatments of optimal length. Thus, the steady state effects are in most cases expected to be somewhat more pronounced than indicated by the DDI study results.

Renal impairment

The unbound exposure of letermovir was doubled in both moderate and severe renal impairment. One of the eight subjects with severe RI had an 8-fold increased unbound exposure. The reason for the high exposure in the patient is unknown. The exposure changes in the renal impairment groups is assessed as not clinically relevant as it is within target range. No dose recommendation can be made in ESRD as there are no supportive data and as literature information on effects on biliary secretion and UGTs in ESRD does not provide a consistent view

Hepatic impairment

The dose investigated in the hepatic impairment study was too low and as the elimination is nonlinear, this is of major importance. OATP1B1/3 has been observed to be down-regulated in liver disease. The applicant has used PBPK to answer the question. However, use of PBPK for simulating effect of transporter and/or hepatic impairment has low confidence in the EU at present and thus cannot be used to answer regulatory questions. It is reasonable to believe that the observed effects are worst case scenarios as OATP contribution is lower at higher doses. Thus, the effects of mild and moderate hepatic impairment are within target range. This will likely also be the case for oral letermovir with CsA with the recommended dose adjustment. Overall, the handling of patients who experienced severe hepatic impairment during the Phase 3 study has been described sufficiently and use of letermovir in severe hepatic impairment is not recommended.

Japanese and Blacks

The exposure was doubled and dose dependency more pronounced in the Japanese. The higher exposure likely lacks clinical relevance. There was no significant difference in exposure of letermovir in black patients.

Drug-drug interactions

Mechanistic studies with letermovir as a victim of DDIs

The DDI scenario is complex as the effects of other drugs on letermovir may be influenced by the mode of administration of letermovir and whether CsA is concomitantly used. Furthermore, the clinical relevance of an obtained effect on the letermovir exposure also depends on these factors as the exposure changes considered to be effective and safe differs for the scenarios. Oral letermovir administered without CsA has a lower exposure and is thus more sensitive to decreases in exposure but less sensitive to increases.

The applicant did not perform any mechanistic study providing in vivo support to the elimination pathways of letermovir. The studies with cyclosporine single-dose (see below) provide some support to the OATP involvement but also include the effect of inhibition of Pgp and BCRP. Due to the low exposure, the safety margins for oral letermovir without CsA are very high and it is unlikely that a DDI though Pgp/BCRP inhibition or through OATP inhibition will result in exposures outside this range.

However, for the other letermovir regimens, the margins are not as high, and when combining letermovir with CsA, the multiple transporter inhibition can give rise to unexpected increases in exposure. Current knowledge is not extensive yet for transporter DDIs and the magnitudes of multiple inhibitions is difficult to predict.

The applicant will perform a multiple-dose study with a strong, preferably clinically relevant, Pgp/BCRP inhibitor as a post-authorisation measure. The inhibitor exposure should be as little as possible affected by induction for relevant plasma levels to be obtained. As the safety margin is large for oral letermovir without CsA, the scenario of most concern is the effect of Pgp/BCRP inhibitors on oral letermovir combined with CsA, a regimen where the effects could be outside target range due to multiple transporter inhibition. The applicant will however study the scenario with oral letermovir without CyA. Letermovir 480 mg qd should be administered with and without the Pgp/BCRP inhibitor until steady state. If a significant effect is observed in this study, it will be difficult to estimate the effect on letermovir when combined with CyA. This may have consequences for the SmPC.

There are no DDI studies with inducers. As a PAM, the applicant will perform a DDI study with rifampicin designed to separate induction and OATP inhibition. The proposed design is rifampicin and letermovir multiple dose treatment for at least 10 days, letermovir steady state sampling on the last rifampicin treatment day and on the day after ending rifampicin. The study should start with a single dose of letermovir together with rifampicin followed by sampling for estimating AUCinf before starting letermovir/rifampicin multiple dose treatment. The single dose part of the study should also contain some protein binding determinations to support the assumption of linearity in the protein binding. These two PAMs should include an initial step where the study design is submitted and discussed.

If OATP1B1/3, BCRP or Pgp inhibition should be found to give rise to significant increases in letermovir exposure and it may not be excluded that the DDI will be relevant when letermovir is administered alone of with CsA, the applicant should perform in vitro studies to provide missing data for the azole antifungals regarding inhibition of the particular transporter(s). This is also included in the PAM.

Letermovir as perpetrator of DDIs

The DDI situation for letermovir as perpetrator is also complex and also here it is dependent on mode of letermovir administration and whether CsA is concomitantly used. If the dose of a drug is monitored and titrated, this needs to be performed when changing mode of administration and if adding CsA. In addition, CsA has strong interaction effects of its own, some which are shared also by letermovir leading to additional DDI effects. Letermovir induces enzymes and transporters and also inhibits a number of proteins at in vivo relevant concentrations.

Induction of CYP3A4 and CYP2B6 was observed at relevant concentrations indicating PXR and CAR mediated induction. Many enzymes and transporters are induced by these pathways. Moderate induction was confirmed in vivo for CYP2C19 (voriconazole) and intestinal Pgp induction was indicated by the results of the interaction study with digoxin although being a not so sensitive intestinal Pgp probe. Autoinduction is observed for letermovir. Besides the studied proteins, inducible enzymes and transporters include CYP1A2, CYP2C9, CYP2B6, CYP2C8, the UGTs, probably SULTs, BCRP, other transporters. It is difficult to foresee interactions with enzymes and transporters indicated to both inhibited and induced. This is the case for CYP2C8, CYP2B6, BCRP, UGT1A1 and OATP2B1. The net effect on OAT3 may be inhibition as a rifampicin-tenofovir (a OAT3 substrate) DDI study showed lack of rifampicin (potent inducer) effect on tenofovir.

Mechanistic studies with letermovir as a perpetrator of DDIs

Letermovir is a moderate, time-dependent, inhibitor of CYP3A4. 240 mg qd appears to give moderate inhibition. The effect of iv treatment was small after a short letermovir treatment. It is possible that the steady state effect is even smaller. The size of the effect of 480 mg qd is unknown but based on the tacrolimus and sirolimus DDI studies with 480 mg of letermovir, the effect of 480 mg qd would be consistent with that of moderate CYP3A inhibition.Letermovir 240 mg BID gave rise to a somewhat reduced exposure of

digoxin and a slower absorption. The effect may be larger on drugs for which intestinal Pgp is more important such as dabigatran and sofosbuvir. The effect may not be present for iv administered Letermovir. The effect of 480 mg qd may be likely similar to that of 240 mg bid. This is presently unknown.

Letermovir is an OATP, BCRP and CYP3A inhibitor. As such it affects many statins. Letermovir 480 mg qd increased atorvastatin exposure by 230%. The maximum dose is therefore reduced. A marked effect is expected on simvastatin, pitavastatin and rosuvastatin. Concomitant used of these are "not recommended" in the SmPC. Statins treatment can generally be interrupted during the Letermovir treatment (100 days). Monitoring is advised for pravastatin and during concomitant letermovir treatment. For fluvastatin it is also stated that a dose adjustment may be needed. Less marked effects are expected on these two statins. Further restrictions are made when letermovir is combined with CsA. For the CsA combination, atorvastatin, simvastatin pitavastatin and rosuvastatin are contraindicated.

DDI potential with common medications in the target population

Half the patients in phase III were co-treated with cyclosporine. In phase III, the dose was reduced by 50% when patients were co-treated with CsA. The resulting exposure based on the population PK analysis is somewhat surprising and in particular patients on oral treatment with letermovir and not receiving CsA have a predicted exposure that is 2-3-fold lower than other patients.

The patients are treated with many co-medications. The applicant has discussed likely DDIs between letermovir and common concomitant medication in the target population. The applicant has defined common as >20% use in phase III. The following drugs were selected: acyclovir (77%), valacyclovir (33.5%), sulphamethoxazole + trimethoprim (64%); methylprednisolone (~ 33%), prednisone (21%), pantoprazole (~48%) and omeprazole (~27%). The antifungals (86% of the patients received antifungal medications, including fluconazole (46%), voriconazole (28%), posaconazole (20%), isavuconazonium (prodrug of isavuconazole) (0.8%, n=3) and the echinocandins (anidulafungin, caspofungin), were addressed separately.

The applicant was not able to find information regarding OATP inhibitory potential for aciclovir and valacyclovir, methylprednisolone, sulphamethoxazole, prednisolone, pantoprazole and the PPIs. Thus, the potential for an effect on letermovir by these drugs may not be completely evaluated. However, in many cases, safety of letermovir in combination with the drugs could be considered covered by the clinical data based on the frequent concomitant use. The exposures of markedly CYP2C19 metabolised PPIs are likely reduced and an increase of the dose may be needed based on clinical response.

There is a risk of transient reduced exposure of ganciclovir and cidofovir (used in PET) due to transporter involvement in their elimination. However, maintained efficacy is supported by the clinical data.

Antifungals were used in almost all patients. Voriconazole and in particular fluconazole were commonly used in the target patient population. Oral letermovir 480 qd gave rise to an almost 50% reduction in voriconazole exposure and TDM is advised. The use of TDM will also likely lead to normalised exposures in PMs. CYP2C19 PMs will not have a reduction in exposure, but a likely increase due to the CYP3A inhibition. Due to the higher exposure obtained with letermovir po with CsA, letermovir iv with and without CsA, the induction may be even more pronounced than with letermovir without CsA. Thus, the TDM needs to be performed when changing regimen. Voriconazole is a Pgp inhibitor in vitro. There is no information on OATP1B1/3 or BCRP inhibitory potential of voriconazole. Thus, voriconazole could increase letermovir exposure.

Letermovir did not affect the pharmacokinetics of posaconazole, but will lead to an increased exposure of isavuconazole. No DDI is predicted with fluconazole, caspofungin or anidulafungin. Letermovir likely increases isavuconazole exposure through CYP3A inhibition. Available data indicate a clinically not relevant increase in exposure but it is unknown whether isavuconazole also is transported by OATP1B1/3, which could make the

DDI more marked. It is not known whether letermovir will give rise to reduced exposures of amphotericin B or micafungin. In vitro transporter inhibition data are missing for many of the antifungals. If inhibition of OATP1B1 or Pgp/BCRP is found to affect letermovir exposure to a clinically relevant extent, missing in vitro data should be provided for the DDI evaluation.

There is an uncertainty whether the exposure of piperacillin and imipenem/cilastatin related to potential inducing effects on potential biliary secretion and metabolism of the drugs. Available information does not indicate an interaction risk with meropenem, imipenem/cilastatin, cefepime, vancomycin and ceftazidime.

There was no effect of letermovir on acyclovir in a 5-day study. Acyclovir is transported by OAT3 but the effect of probenecid does not indicate that it is a sensitive marker for the transporter. However, it can probably be concluded that letermovir is not a strong inhibitor of OAT3.

Letermovir 480 mg qd gave rise to an increase in ethinylestradiol and levonorgestrel exposure. The results may not be translated to other contraceptive steroids, as letermovir is an inducer and the net result of enzyme and transporter inhibition and induction will depend on the particular contribution of these proteins in the elimination of each steroid.

Pharmacodynamics

The CMV DNA terminase has been identified as the target of letermovir, based on characterization of DNA processing, virion maturation and viral resistance mutations in CMV-infected, letermovir-treated cells. As the postulated mechanism of action of letermovir is down-stream of DNA synthesis, CMV DNA might not be the optimal biomarker for monitoring the efficacy of letermovir prophylaxis. It may be that CMV DNA levels rise, but without the output of infectious virions that characterizes virologic failure. However, as there are no validated alternative biomarkers or PET initiation thresholds, the use of CMV DNA for monitoring and standard-of-care PET criteria is endorsed although this could hypothetically be too conservative and result in unnecessary termination of letermovir prophylaxis.

Letermovir has nanomolar EC50 values against laboratory and clinical CMV isolates in cell-culture models of infection, with a steep dose-response curve. An UL56 homology search shows very limited homology between the CMV UL56 and orthologs among other human herpesviruses, supporting the claim that the letermovir mechanism of action is CMV specific. Also, in the P001 study similar rates of reactivation of other herpesviruses were seen in the P001 letermovir and placebo groups.

Letermovir resistant strains can be selected with unaffected replicative capacity in vitro, but the viral fitness in vivo, resistance barrier and clinical impact remains to be elucidated. From the entries in the NCBI DNA sequence database it seems that the mutants selected *in vitro* are not common wild-type variants *in vivo*.

Because the mode of action of letermovir is distinct from that of approved anti-CMV agents that target CMV DNA replication (CDV, GCV, and FOS), cross-resistance is unlikely. Studies with letermovir-resistant mutants (with mutations in the CMV UL56 gene) and GCV-resistant mutants (with mutations in the CMV UL54 and/or UL97) have confirmed this assumption.

PD interaction studies were performed with anti HIV compounds targeting either the HIV protease, the HIV (non-) nucleoside reverse transcriptase or the HIV integrase. These targets are all viral proteins. The applicant regards these viral proteins, albeit not terminase proteins, more alike to the CMV terminase, (the target of letermovir) than bacterial, fungal or human proteins which are the targets of antibiotics, antifungals and immune suppressants. Since no or only minor PD interactions between letermovir and anti HIV drugs

were observed, the applicant sees no reason to conduct PD interaction studies with drugs that target bacterial, fungal or human proteins that are much more different to the letermovir target then viral proteins might be. This was considered acceptable by CHMP.

2.4.5. Conclusions on clinical pharmacology

Letermovir inhibits the viral terminase complex, which plays a key role in cleavage and packaging of viral progeny DNA, through a mechanism that is CMV specific among human herpesviruses and where no mammalian counterpart is known. Letermovir resistant strains can be selected with unaffected replicative capacity *in vitro* but the viral fitness *in vivo*, resistance barrier and clinical impact remains to be elucidated and the submission of phenotypic resistance data will be included in a post-authorization commitment.

Letermovir has complex pharmacokinetic behaviour that includes nonlinear kinetics, autoinduction and a multitude of DDI effects such as enzyme and transporter induction, time dependent inhibition of CYP3A4 and inhibition of a large number of enzymes and transporters *in vitro* that has not been followed up *in vivo*.

The exposure in non-CsA treated patients on oral letermovir is 2-3-fold lower that estimated for the other letermovir regimens (oral and iv letermovir with CsA, iv letermovir without CsA). This has implications for the drug interaction potential for letermovir as perpetrator and also for clinical relevance consequences of changes in letermovir exposure. The safety margins are much higher for oral letermovir taken without CsA but the efficacy margins are less generous.

Studies investigating letermovir as victim of DDIs are limited. Only one mechanistic such study (with CsA) has been performed. A DDI study with an inducer is missing as well as a study with a Pgp/BCRP inhibitor. A DDI study with rifampicin will be performed as PAM. The study will be designed to measure effects of OATP inhibition separately from induction. A DDI study with a Pgp/BCRP inhibitor will be performed as a PAM aiming to provide information primarily related to the risk of DDI with Pgp/BCRP inhibitors and letermovir combined with CsA. It will also add mechanistic information on letermovir disposition. Multiple transporter inhibition may give rise to unpredictable DI effects. Hence, translation of the study results to letermovir combined with CyA may be challenging.

Letermovir inhibits quite many enzymes and transporters. It inhibits CYP3A in vivo and is also a moderate general inducer *in vivo*. The patient population has a substantial polypharmacy. DDI studies with common comedication are missing in some respects. Induction affects both enzymes and transporters broadly and thus letermovir could give rise to reduced exposures potentially reducing clinical efficacy of other drugs.

The effects of letermovir on other drugs may differ between letermovir modes of administration and depends also on whether CsA is coadministered. Combining letermovir with CsA will also add to the DDI effects through the OATP, BCRP and Pgp inhibition of CsA. This composes a complex DDI scenario to communicate in the SmPC.

2.5. Clinical efficacy

The clinical development program included two Phase 2 trials (P019 and P020) and one pivotal Phase 3 trial (P001).

Trial Type	Merck Trial No. (AiCuris No., as Applicable*)	Trial Short Title/Design	Primary Objective	Number of Subjects who Received Letermovir
Phase 2				
	MK-8228-019 (AIC001-2-001)	Phase 2a, randomized, active controlled, multi-center, open-label dose ranging trial in a majority of kidney and kidney/pancreas transplant recipients (and 1 HSCT recipient) with CMV viremia	To determine the decline in human cytomegalovirus (CMV) DNA load after a 14-day treatment for each letermovir dosing regimen and to compare this to an observational control group	18
	MK-8228-020 (AIC246-01-II-2)	Phase 2b, multi-center, randomized, double-blind, placebo-controlled, dose-ranging trial to investigate safety and efficacy of 3 different oral doses of letermovir in comparison with matching placebo over 12 weeks in CMV-seropositive, allogeneic HSCT recipients	To compare the safety and efficacy of 3 different doses of letermovir with matching placebo as prophylaxis in the prevention of CMV infection	98
Phase 3				
	MK-8228-001	Phase 3 randomized, placebo-controlled trial to evaluate the safety and efficacy of letermovir in adult, CMV-seropositive allogeneic HSCT recipients	To evaluate the efficacy of letermovir as prophylaxis in the prevention of clinically significant CMV infection through Week 24 (~6 months) post-transplant following adminstration of letermovir or placebo.	373

* AiCuris protocol numbers are provided for Phase 1 and 2 trials sponsored by AiCuris.
‡ MK-8228-018 Part 2: All 16 subjects received only the IV arginine formulation of letermovir.
ǂ MK-8228-017: Of the 34 subjects exposed to letermovir, 22 subjects received only the IV arginine formulation of letermovir. The remaining 12 subjects received both the oral tablet and IV arginine formulations of letermovir.
QD= once daily; BID=twice daily

2.5.1. Dose response studies

P019 (AIC001-2-001) was a Phase 2a open-label, proof-of-concept trial to evaluate the safety, tolerability, and antiviral activity of two doses of letermovir, 40 mg twice daily and 80 mg QD, compared to an active control standard-of care (valganciclovir) given over a period of 14 days in 27 subjects; 26 were kidney or kidney/pancreas transplant recipients and 1 was a HSCT recipient. Of the 27 subjects enrolled, 9 each were in the 40 mg BID, 80 mg QD, and active control (valganciclovir) groups, respectively. The trial assessed the reduction in CMV DNA in subjects with pre-existing CMV viremia and eligible for PET at trial entry.

This exploratory study of oral administration of letermovir to a limited number of patients was considered to have provided proof-of-concept. Of the 17 patients treated with letermovir for 14 days, 13 patients had a measurable CMV viral load in the plasma CMV PCR evaluation on Day 1, and 10 of these 13 patients showed a reduction in plasma CMV PCR on Day 15; the maximum reduction in plasma CMV PCR on Day 15 was 2.6 log10. Furthermore, letermovir was used to successfully treat a patient harbouring a CMV strain multi-resistant to the marketed anti-CMV drugs ganciclovir, cidofovir, and foscarnet. No patients treated during the study developed CMV disease.

For all the treatment groups, a statistically significant decrease in CMV PCR plasma viral load was seen between Days 1 and 15 and no statistically significant difference was observed between the observational control group and the letermovir treatment groups at Day 15. It is therefore concluded that the efficacy of letermovir in this open design trial was not significantly different from the observational control group.

The P019 study provides some insight in viral kinetics when letermovir treatment is initiated in subjects with ongoing CMV viremia, but the dose range was significantly lower than what was selected for phase 3.

P020 (AIC246-01-II-02) was a Phase 2b randomized, double-blind, placebo-controlled trial to evaluate the safety and antiviral activity of letermovir compared to placebo in 133 allogeneic HSCT transplant recipients who were seropositive for CMV immunoglobulin G (IgG) antibodies before transplantation, and had no detectable CMV DNA within 5 days before starting study medication. Subjects were randomized to 1 of 3 different doses of letermovir (60, 120, or 240 mg QD) or placebo, and treatment was given orally for 84 days. In this trial, 131 of the 133 subjects randomized into the trial received study medication, with 31 and 34 subjects in the 120 mg and 240 mg groups, respectively, and 33 subjects each in the 60 mg QD letermovir and placebo groups, respectively. This trial assessed prophylaxis with letermovir (compared to placebo) in the prevention of CMV reactivation.

Following an 84-day treatment period, the incidence of CMV prophylaxis failure (defined as all patients who developed systemic detectable CMV replication and/or CMV end-organ disease, or discontinued treatment prior to Day 84 due to other reasons [AE, death, protocol non-compliance, withdrew consent, or other]) appeared to decrease across increasing letermovir dose groups (48.5%, 32.3%, and 29.4% of patients in the 60, 120, and 240 mg/day groups, respectively) and was highest in the placebo group (63.6% of patients), table and figure below. The mean letermovir AUCs, based on the final covariate model presented in the CSR, are presented in the following table.

In the comparison of active treatment groups vs. placebo, a statistically significant reduction in the incidence of CMV prophylaxis failure was observed in the 120 mg/day letermovir (p=0.014) and 240 mg/day letermovir (p=0.007) groups.

Table 22 P020: Analysis of Incidence of CMV Prophylaxis Failure During the 84 days (12 weeks) of Study Drug Administration (NC=F Approach, FAS Population)

	Letermovir 60 mg/day N=33	Letermovir 120 mg/day N=31	Letermovir 240 mg/day N=34	Placebo N=33
Failure, n (%)				
Yes[a]	16 (48.5)	10 (32.3)	10 (29.4)	21 (63.6)
CMV prophylaxis failure	7 (21.2)	6 (19.4)	2 (5.9)	12 (36.4)
Other discontinuation	9 (27.3)	4 (12.9)	8 (23.5)	9 (27.3)
No	17 (51.5)	21 (67.7)	24 (70.6)	12 (36.4)
Odds ratio (95% CI)[b]	0.538 (0.179, 1.603)	0.272 (0.085, 0.857)	0.238 (0.075, 0.739)	
p-value[c]	0.321	0.014	0.007	
Letermovir AUC(0-tau), ng.h/mL (SD)	10619.01 (7153.11)	24678.97 (13568.42)	42618.37 (22915.32)	-

Abbreviations: CMV = human cytomegalovirus; CI = confidence interval, NC=F = non-completer as failure.

[a] Failed was defined as all subjects who developed systemic detectable CMV replication, developed CMV end-organ disease or discontinued treatment prior to Day 84 due to other reasons (AE, death, protocol non-compliance, withdrew consent or other).

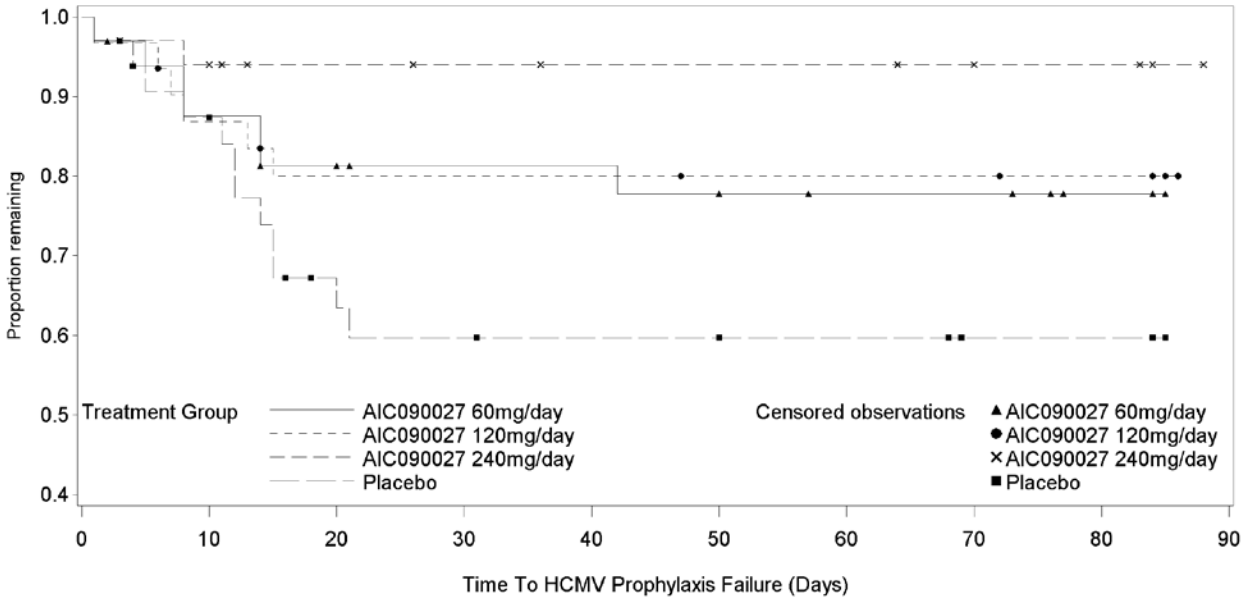
[b] Active dose vs. placebo.

[c] Fisher's exact test of active dose vs. placebo.

Note: For the analysis, subjects who discontinued early without the event were counted in the "yes" category.

One subject in the 240 mg/day group has reason for discontinuation from study medication of Adverse Event (GI-GVHD); however, this subject met the criteria for systemic detectable CMV Replication prior to discontinuation and was therefore counted as a true failure. One subject in the 240 mg/day group and one subject in the placebo group discontinued from study medication due to initiation of alternative anti-CMV medication; however they did not met the criteria for systemic detectable CMV Replication and were therefore counted as other discontinuations.

Table 23 P020: Kaplan-Meier Plot of Time to Onset of CMV Prophylaxis Failure During the 84 days (12 weeks) of Study Drug Administration (FAS Population)



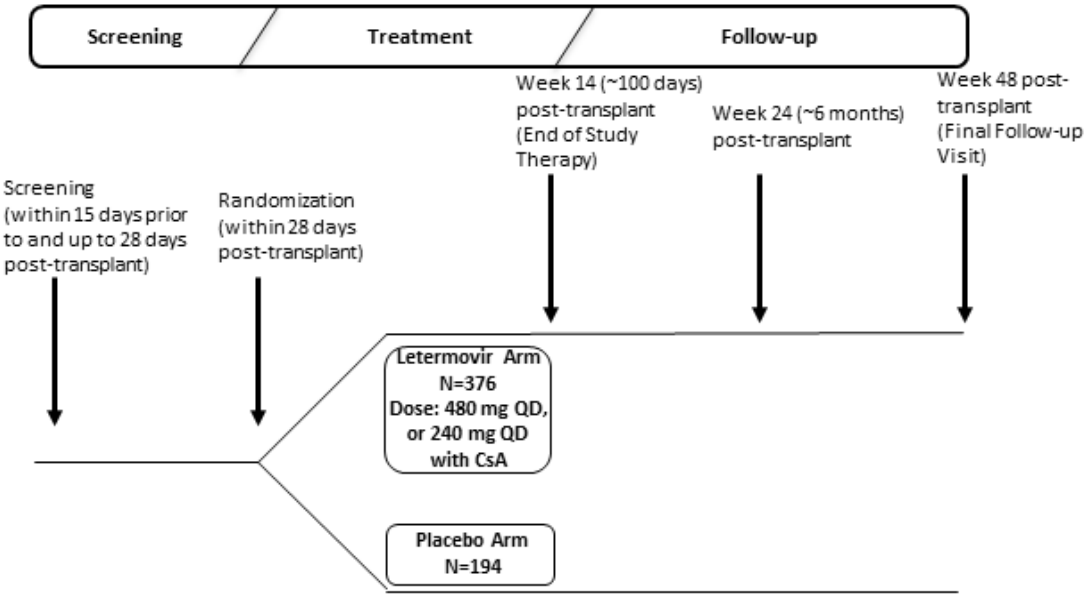
Sensitivity analysis in the per-protocol dataset showed a statistically significant reduction in the incidence of CMV prophylaxis failure in the 240 mg/day letermovir group (p = 0.019). Similar results were observed when non-completers due to reasons other than prophylaxis failure were removed from the analysis (p=0.046 and p=0.001 in the 120 and 240 mg/day letermovir groups, respectively), and when controlling for centre and country effects.

No plateau in treatment response was reached before 240 mg. Only patients in the 240 mg group with CsA co-administration (n=18) are expected to have had a letermovir exposure similar to what was selected for the phase 3 study.

2.5.2. Main study

P001 is a pivotal, randomized, double-blind, placebo-controlled Phase 3 trial designed to evaluate the safety and efficacy of letermovir at a dose of 480 mg QD, adjusted to 240 mg QD when co-administered with CsA, versus placebo in adult, CMV-seropositive allogeneic HSCT recipients (R+). Treatment was administered through Week 14 (~100 days) post-transplant. Overall, 570 subjects were randomized, with 376 in the letermovir group and 194 in the placebo group. This trial assessed prophylaxis with letermovir (compared to placebo) in the prevention of CMV reactivation (i.e., prevention of clinically significant CMV infection or disease).

Figure 5 Study overview



Subjects were monitored for CMV viremia was monitored at weekly intervals during the first 14 weeks post-transplant. CMV viremia was monitored less frequently thereafter at biweekly intervals through Week 24, as the risk for CMV infection and/or disease is considerably reduced during this interval when compared to the first 14 weeks post-transplant.

Patients were randomized in a 2:1 ratio to receive letermovir or placebo at any time from the day of transplant until 28 days post-transplant. The treatment phase was terminated after 10-14 weeks of prophylaxis (until post-transplant week 14) or when the primary endpoint (clinically significant CMV infection, most often DNAemia with PET-initiation) was reached. As the primary endpoint was met more often in the placebo group, the average number of weeks (and hence, exposure) in the treatment phase differs approximately 25% between study groups.

Study Participants

A total of 570 subjects from 67 trial centres in 20 countries were randomized in P001, evaluating letermovir in subjects in a population of CMV-seropositive allogeneic HSCT recipients (R+). Most subjects were enrolled in Europe (50.1%) and North America (41.0%).

Important inclusion criteria included:

1. being ≥18 years of age on the day of signing informed consent.
2. had documented seropositivity for CMV (recipient CMV IgG seropositivity [R+]) within 1 year before HSCT.
3. received a first allogeneic HSCT (bone marrow, peripheral blood stem cell, or cord blood transplant).
4. had undetectable CMV DNA (as confirmed by the central laboratory) from a plasma sample collected within 5 days prior to randomization.

5. been within 28 days post-HSCT at the time of randomization.

Important exclusion criteria included:

The subject was excluded from participating in the trial if the subject:

1. had a history of CMV end-organ disease within 6 months prior to randomization.
2. had evidence of CMV viremia (if tested) at any time from either signing of the informed consent form (ICF) or the HSCT procedure, whichever was earlier, until the time of randomization. (Note: Evidence of CMV viremia as reported by the central laboratory included reporting of test results as “detectable, not quantifiable” or “detected” with a numeric value provided.)
3. received within 7 days prior to screening or planned to receive during the study any of the following:
    - ganciclovir
    - valganciclovir
    - foscarnet
    - acyclovir (at doses >3200 mg PO per day or >25 mg/kg IV per day)
    - valacyclovir (at doses >3000 mg PO per day)
    - famciclovir (at doses >1500 mg PO per day)
4. had severe hepatic impairment (defined as Child-Pugh Class C; see Appendix 12.5 of the protocol) within 5 days prior to randomization.
5. had serum aspartate transaminase (AST) or alanine transaminase (ALT) >5 x the upper limit of normal (ULN) or serum total bilirubin >2.5 x ULN within 5 days prior to randomization.
6. had end-stage renal impairment with a creatinine clearance less than 10 mL/min, as calculated by the Cockcroft-Gault equation using serum creatinine within 5 days prior to randomization.
7. had an uncontrolled infection on the day of randomization.
8. required mechanical ventilation or was hemodynamically unstable at the time of randomization.
9. had a documented positive result for a human immunodeficiency virus antibody (HIVAb) test at any time prior to randomization, or for hepatitis C virus antibody (HCV-Ab) with detectable HCV ribonucleic acid (RNA), or hepatitis B surface antigen (HBsAg) within 90 days prior to randomization.

Of note is that patients with pre-existing CMV viremia (n=84 of 738 screened, 530 included) were not included in the study.

Treatments

In this study, both oral and IV formulations of letermovir were administered. Note that for this study the IV formulation refers to the cyclodextrin-containing IV formulation and the oral formulation refers to the tablets administered orally. As conditioning-induced mucositis is expected in this patient group, the iv formulation is expected to be of particular value in the first weeks post-transplant.

Subjects were to initiate study medication as early as the day of transplant, but no later than 28 days post-transplant. Study medication was administered with or without food and was taken or administered at

approximately the same time each day. Interruptions from the protocol-specified treatment plan for ≥7 consecutive days required consultation between the investigator and the Sponsor.

Objectives

Primary Objective and Hypothesis

Objective: To evaluate the efficacy of letermovir in the prevention of clinically significant CMV infection through Week 24 (~6 months) post-transplant following administration of letermovir or placebo.

Hypothesis: Letermovir is superior to placebo in the prevention of clinically significant CMV infection, as assessed by the proportion of subjects with CMV end-organ disease or initiation of anti-CMV PET based on documented CMV viremia and the subject's clinical condition through Week 24 (~6 months) post-transplant.

Outcomes/endpoints

Primary endpoint

The primary efficacy endpoint for P001 was the proportion of subjects with clinically significant CMV infection through Week 24 (~6 months) post-transplant. Clinically significant CMV infection was defined as the occurrence of either one or the following outcomes:

- onset of CMV end-organ disease

OR

- initiation of anti-CMV PET based on documented CMV viremia (as measured by the central laboratory) and the clinical condition of the subject. Initiation of PET in the trial referred to the practice of initiating therapy with the following anti-CMV agents when active CMV viral replication was documented: GCV, VGCV, foscarnet, and/or cidofovir.

The secondary efficacy endpoints included:

1. Proportion of subjects with clinically significant CMV infection through Week 14 (~100 days) post-transplant: For this endpoint, case counting used the same definition as in the primary efficacy endpoint.

Exploratory Endpoints included

1. Proportion of subjects with CMV disease through Week 48 post-transplant
2. Proportion of subjects with all-causes mortality through Week 14 post-transplant, Week 24 post-transplant, and Week 48 post-transplant
3. Proportion of subjects with opportunistic infection other than CMV infection (i.e., systemic bacterial and invasive fungal infection) through Week 14 post-transplant, Week 24 post-transplant, and Week 48 post-transplant
4. Proportion of subjects with acute and/or chronic GVHD after randomization through Week 14 post-transplant, Week 24 post-transplant, and Week 48 post-transplant
5. Antiviral resistance to letermovir in prophylaxis failures

The study definition of clinically significant CMV infection is considered to be rather liberal. In the vast majority of cases this criterion is fulfilled by patients initiating pre-emptive ganciclovir therapy based on low-level viremia, making the primary and secondary endpoints largely measures of the ganciclovir-saving potential of letermovir. This could be of clinical importance due to the safety profile of ganciclovir, but this is already to some extent mitigated by the pre-emptive protocol where a majority of patients will have left the most critical period post-transplant (before and during engraftment, where myelotoxicity is a particular concern) before initiating pre-emptive therapy.

Of note, all endpoints related to mortality are exploratory.

Sample size, Randomisation and Blinding (masking)

A total of 570 HSCT recipients were randomized in a 2:1 ratio to receive letermovir or placebo at any time from the day of transplant until 28 days post-transplant.

Randomised subjects were stratified by 1) trial centre and 2) risk for CMV reactivation in order to balance any effects of these variables on letermovir safety and efficacy across treatment groups. Clinical practice with regards to HSCT (conditioning regimen used, source of stem cell and immunosuppressant regimen used for prevention and/or treatment of GVHD) varies widely across centres and regions worldwide. Among HSCT recipients, there is considerable variability in the risk for CMV reactivation. Two categories of risk groups were identified for stratification based on available literature and input from external experts on the Scientific Advisory Committee (SAC) as follows:

1. High risk: Subjects meeting one or more of the following criteria at the time of randomization:
    - Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or –DR,
    - Haploidentical donor,
    - Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1,
    - Use of umbilical cord blood as stem cell source,
    - Use of ex vivo T-cell-depleted grafts (including ex vivo use of alemtuzumab),
    - Grade 2 or greater GVHD, requiring the use of systemic corticosteroids (defined as the use of ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid).
2. Low risk: All subjects not meeting the definition of high risk.

The study was double blind.

Statistical methods

Study P001 had a primary follow-up period through Week 24 post-transplant with the primary analysis to be performed when this period had completed; all available data after week 24 pertaining to mortality and CMV disease was to be provided. Analyses were performed according to protocol and supplementary statistical analysis plan.

The primary hypothesis was evaluated by comparing letermovir to placebo in the proportion of subjects with clinically significant CMV infection through Week 24 post-transplant in the FAS population. Other efficacy analyses were considered supportive and/or explanatory.

The FAS consisted of all randomised subjects who received at least one dose of study medication and had no detectable CMV viral DNA (measured by the central laboratory) on Day 1 when study therapy was initiated. A sensitivity analysis including those subjects who had detectable CMV viral DNA on Day 1 was to be provided.

The primary missing data approach was the Non-Completer=Failure approach. Non-completers referred to subjects who prematurely discontinued from the study. A subject who discontinued study medication but remained in the study follow-up was not to be considered as a non-completer. A secondary missing data approach was the Data-As-Observed (DAO); any subject with missing value for a particular endpoint was excluded from the analysis. For the time-to-event analyses, subjects were to be censored at last assessment.

All-cause mortality was defined as an exploratory endpoint and the proportion of all-cause deaths at different time-points was only to be displayed by treatment group using summary statistics and 95% confidence interval. Kaplan-Meier plots was (according to the SAP) to be provided but only for the two exploratory endpoints that initially had been defined as time-to-event endpoints (i.e. time to documented viremia and the time to onset of engraftment through Week 24 post-transplant). The analyses presented (see under “Results”) are hence not according to what was initially planned with comparisons between the treatment arms seemingly post-hoc. The additional analyses of mortality not only all-cause, but also non-relapse and CMV-related mortality, including treatment group comparisons and performed when all subjects had either completed or discontinued from the trial (described in a separate document) was seemingly data driven as justified by the results from the primary analysis of study P001 indicating “the potential for letermovir prophylaxis to provide a significant mortality benefit over placebo at week 48 post-transplant”. Although supported that provided, these analyses can formally only be considered exploratory and hence not serve as firm evidence for any claims.

Results

Participant flow

A total of 738 subjects provided informed consent and were screened for eligibility for randomization. Of these, 570 subjects were randomised.

Figure 6 Participant flow.

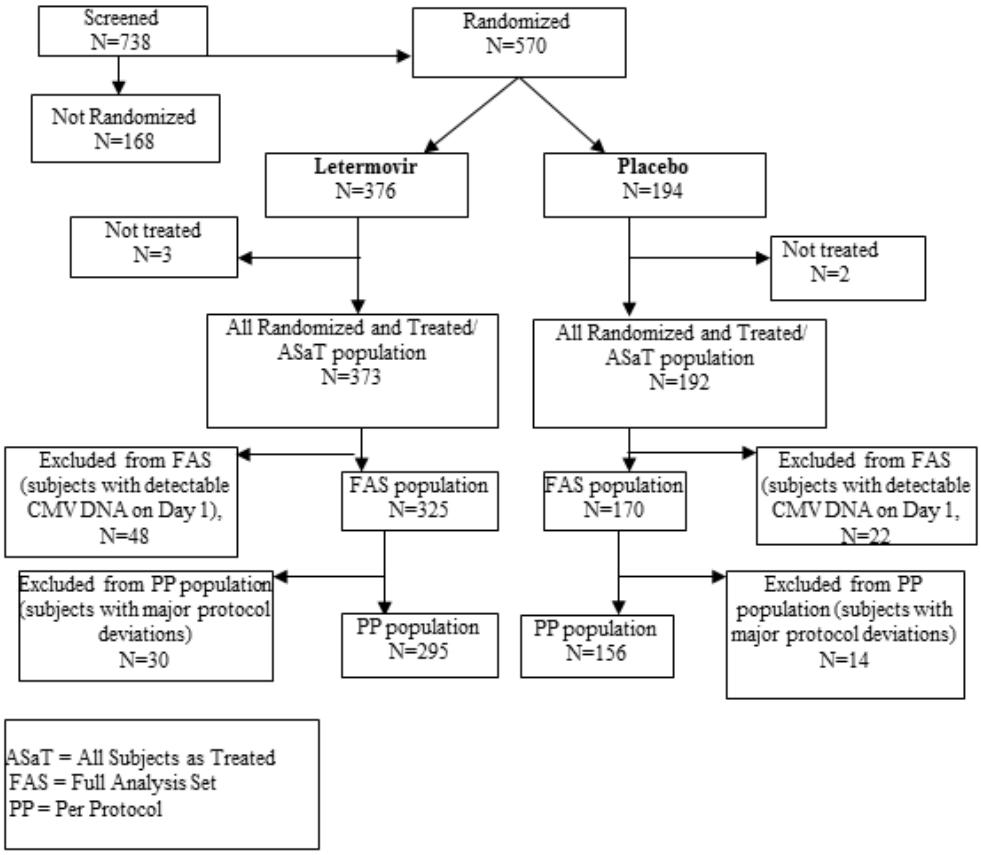


Table 24 Disposition of Subjects With Respect To Trial Status (All Randomized Subjects)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	376		194		570	
Status for Trial Segment Through 24 Weeks Post-transplant						
Randomized but not treated	3	(0.8)	2	(1.0)	5	(0.9)
Completed Week 24 Post-transplant	295	(78.5)	136	(70.1)	431	(75.6)
Discontinued Through Week 24 Post-transplant	78	(20.7)	56	(28.9)	134	(23.5)
Adverse Event	6	(1.6)	3	(1.5)	9	(1.6)
Death	37	(9.8)	28	(14.4)	65	(11.4)
Lost To Follow-Up	2	(0.5)	4	(2.1)	6	(1.1)
Non-Compliance With Study Drug	1	(0.3)	0	(0.0)	1	(0.2)
Physician Decision	9	(2.4)	5	(2.6)	14	(2.5)
Withdrawal By Subject	23	(6.1)	16	(8.2)	39	(6.8)
Status for Next Trial Segment Beyond 24 Weeks Post-transplant						
Entered 24 weeks post-transplant follow-up	295	(78.5)	136	(70.1)	431	(75.6)
Continuing in Study	44	(11.7)	20	(10.3)	64	(11.2)
Discontinued between Weeks 24 and 48 Post-transplant	49	(13.0)	16	(8.2)	65	(11.4)
Completed 48 weeks Post-transplant	202	(53.7)	100	(51.5)	302	(53.0)

Note: Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.
Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with cyclosporin A.
n (%) = Number (percent) of subjects in each sub-category.

Baseline data

Study groups are comparable in all baseline characteristics and overall representative of an allogenic HSCT population.

Table 25 Subject characteristics

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	N	(%)
Subjects in population	373		192		565	
Male gender	211	(56.6)	116	(60.4)	327	(57.9)
Race						
Asian	40	(10.7)	18	(9.4)	58	(10.3)
Black or African	8	(2.1)	4	(2.1)	12	(2.1)
Multi-Racial	22	(5.9)	9	(4.7)	31	(5.5)
Native Hawaiian	1	(0.3)	0	(0.0)	1	(0.2)
White	301	(80.7)	161	(83.9)	462	(81.8)
Missing	1	(0.3)	0	(0.0)	1	(0.2)
Age (Years)						
Mean	50.8		50.8		50.8	
Range	18.0 to 75.0		19.0 to 78.0		18.0 to 78.0	
65 to 74	55	(14.7)	30	(15.6)	85	(15.0)
≥ 75	1	(0.3)	2	(1.0)	3	(0.5)
Weight (Kg)						
Mean weight	77.6		74.5		76.6	
Range	35.1 to141.5		40.9 to 113.1		35.1 to 141.5	
Mean BMI	26.5		25.5		26.2	
Range	17.0 to 49.0		16.6 to 44.7		16.6 to 49.0	

Region						
Asia-Pacific	37	(9.9)	16	(8.3)	53	(9.4)
Latin America	7	(1.9)	2	(1.0)	9	(1.6)
Europe	185	(49.6)	97	(50.5)	282	(49.9)
North America	144	(38.6)	77	(40.1)	221	(39.1)
High Risk Stratum	121	(32.4)	54	(28.1)	175	(31.0)
Primary Reason for Transplant‖						
Acute lymphocytic leukaemia	35	(9.4)	17	(8.9)	52	(9.2)
Acute myeloid leukaemia	142	(38.1)	72	(37.5)	214	(37.9)
Aplastic anaemia	9	(2.4)	11	(5.7)	20	(3.5)
Chronic lymphocytic leukaemia	10	(2.7)	4	(2.1)	14	(2.5)
Chronic myeloid leukemia	17	(4.6)	6	(3.1)	23	(4.1)
Lymphoma	47	(12.6)	28	(14.6)	75	(13.3)
Myelodysplastic syndrome	63	(16.9)	22	(11.5)	85	(15.0)
Myelofibrosis	9	(2.4)	6	(3.1)	15	(2.7)
Plasma cell myeloma	14	(3.8)	10	(5.2)	24	(4.2)
Other	27	(7.2)	16	(8.3)	43	(7.6)
Positive Donor CMV Serostatus	229	(61.4)	114	(59.4)	343	(60.7)
Donor Type						
Matched related	127	(34.0)	64	(33.3)	191	(33.8)
Mismatched related	57	(15.3)	22	(11.5)	79	(14.0)
Matched unrelated	138	(37.0)	80	(41.7)	218	(38.6)
Mismatched unrelated	51	(13.7)	26	(13.5)	77	(13.6)
Stem Cell Source						
Peripheral blood	279	(74.8)	134	(69.8)	413	(73.1)
Bone marrow	82	(22.0)	47	(24.5)	129	(22.8)
Cord blood	12	(3.2)	11	(5.7)	23	(4.1)
Days from Transplantation to Randomization						
< 2 Weeks	237	(63.5)	121	(63.0)	358	(63.4)

Numbers analysed

Table 26 Subject Accounting for Efficacy Analyses (All Randomized Subjects)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	**376**		**194**		**570**	
Included in All Randomized and Treated	**373**	**(99.2)**	**192**	**(99.0)**	**565**	**(99.1)**
Excluded from All Randomized and Treated	**3**	**(0.8)**	**2**	**(1.0)**	**5**	**(0.9)**
Did not receive study medication	3	(0.8)	2	(1.0)	5	(0.9)
Included in FAS population	**325**	**(86.4)**	**170**	**(87.6)**	**495**	**(86.8)**
Excluded from FAS population	**51**	**(13.6)**	**24**	**(12.4)**	**75**	**(13.2)**
Not in All Randomized and Treated	3	(0.8)	2	(1.0)	5	(0.9)
Subjects with detectable CMV DNA on Day 1	48	(12.8)	22	(11.3)	70	(12.3)
Included in PP population	**295**	**(78.5)**	**156**	**(80.4)**	**451**	**(79.1)**
Excluded from PP population	**81**	**(21.5)**	**38**	**(19.6)**	**119**	**(20.9)**
Not in FAS	51	(13.6)	24	(12.4)	75	(13.2)
< 75% compliant with study therapy	8	(2.1)	4	(2.1)	12	(2.1)
> 7 consecutive days of study drug interruption	8	(2.1)	2	(1.0)	10	(1.8)
Wrong treatment administered	2	(0.5)	1	(0.5)	3	(0.5)
Did not have documented seropositivity for CMV	1	(0.3)	0	(0.0)	1	(0.2)
Had a history of CMV end-organ disease within 6 months prior to randomization	0	(0.0)	0	(0.0)	0	(0.0)
Was CMV viremic before randomization	2	(0.5)	1	(0.5)	3	(0.5)
Prohibited medication[†]	14	(3.7)	7	(3.6)	21	(3.7)
Had previously participated in this study or any other study involving letermovir	0	(0.0)	0	(0.0)	0	(0.0)
Had previously participated or is currently participating in any study involving administration of a CMV vaccine or another CMV investigational agent during the course of this study	0	(0.0)	0	(0.0)	0	(0.0)

[†] Use of prohibited medication with anti-CMV activity.

Note: Each criterion for the PP population was evaluated for each subject. As such, a subject may have met more than one of the exclusion criteria for the PP population and will be counted once for each exclusion that they met. Therefore , the sum of the reasons for exclusion may not equal the total number of subjects excluded from the PP population.

FAS = Full Analysis Set, PP = Per Protocol.

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

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

In addition to patients who were excluded at screening due to a positive CMV DNA, 12.8% and 11.3% of randomised subjects in the letermovir and the placebo group respectively were excluded from the FAS population due to positive CMV DNA at Day 1. The proportion of patients with detectable CMV DNA at Day 1 was hence fairly balanced and slightly less than expected and accounted for in the estimation of the sample size (i.e. 15%). See further below regarding this subset of patients

Outcomes and estimation

Letermovir showed superior efficacy over placebo in the primary endpoint analysis, as well as in several secondary endpoints closely related to the primary endpoint. A lower proportion of subjects in the letermovir

group (37.5%) developed clinically significant CMV infection compared to the placebo group (60.6%) through Week 24 post-transplant (FAS population, NC=F approach). The estimated difference (95% CI) of -23.5% (-32.5%, -14.6%), adjusted for the stratification factor of high versus low risk for CMV reactivation, was statistically significant (1-sided p value <0.0001).

Overview of primary and secondary endpoints

Table 27 P001: Summary of the Efficacy Analyses for Primary and Secondary Endpoints (FAS Population)

	Letermovir (N=325)		Placebo (N=170)		Difference[†]	
	n	%	n	%	Difference(95% CI)	p-value
Primary Endpoint						
Clinically significant CMV infection through Week 24 post-transplant[‡]	122	37.5	103	60.6	-23.5 (-32.5, -14.6)	<0.0001
Secondary Endpoints						
Clinically significant CMV infection through Week 14 post-transplant[‡]	62	19.1	85	50.0	-31.3 (-39.9, -22.6)	<0.0001
CMV End-organ Disease through Week 14 post-transplant[§]	1	0.4	2	1.4	-1.0 (-3.5, 1.5)	0.2258
CMV End-organ Disease through Week 24 post-transplant[§]	5	2.0	3	2.4	-0.4 (-4.0, 3.2)	0.4056
Initiation of PET for documented CMV viremia through Week 24 post-transplant[‡]	119	36.6	101	59.4	-23.3 (-32.3, -14.3)	<0.0001
Initiation of PET for documented CMV viremia through Week 14 post-transplant[‡]	61	18.8	84	49.4	-31.0 (-39.6, -22.4)	<0.0001

[†] 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A 1-sided p-value ≤0.0249 was used for declaring statistical significance for primary analysis of the primary endpoint. Nominal two-sided p-values (not adjusted for multiplicity) are provided for other analyses as a measure of the strength of the relationship between treatment and response.

[‡] Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24/Week 14 post-transplant visit window.

[§] Approach to handling missing values: Data-as-Observed (DAO) approach. With DAO approach, any subject with missing value for a particular endpoint was excluded from the analysis.

N = Number of subjects in analysis population.

n = Number of subjects with outcome.

Primary endpoint

Table 28 P001: Analysis of Proportion of Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant (NC=F Approach, FAS Population)

Parameter	Letermovir (N=325) n (%)	Placebo (N=170) n (%)
Failures[†]	**122 (37.5)**	**103 (60.6)**
Clinically significant CMV infection by Week 24[‡]	57 (17.5)	71 (41.8)
Initiation of PET based on documented CMV viremia	52 (16.0)	68 (40.0)
CMV end-organ disease	5 (1.5)	3 (1.8)
Discontinued from study before Week 24	56 (17.2)	27 (15.9)
Adverse Event	6 (1.8)	1 (0.6)
Death	28 (8.6)	11 (6.5)
Lost To Follow-up	1 (0.3)	3 (1.8)
Physician Decision	3 (0.9)	3 (1.8)
Withdrawal By Subject	18 (5.5)	9 (5.3)
Missing outcome in Week 24 visit window	9 (2.8)	5 (2.9)
Stratum-adjusted treatment difference (Letermovir-Placebo)[§]		
Difference (95% CI)	-23.5 (-32.5, -14.6)	
p-value	<0.0001	

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

[‡] Clinically significant CMV infection was defined as CMV end organ disease or initiation of PET based on documented CMV viremia and the clinical condition of the subject.

[§] 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A 1-sided p-value ≤0.0249 was used for declaring statistical significance.

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

N = number of subjects in each treatment group.

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

Subjects excluded from the FAS population due to detectable CMV DNA on Day 1

The subjects that were excluded in the primary analysis due to detectable CMV viral DNA on Day 1 have been analysed separately. A lower proportion of subjects with detectable CMV viral DNA on Day 1 developed clinically significant CMV infection in the letermovir group (64.6%) compared to the placebo group (90.9%) through Week 24 post-transplant. The estimated difference (95% CI for the difference) was -26.1% (-45.9%, -6.3%), with a nominal one-sided p-value <0.0048.

Table 29 Analysis of Proportion of Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant Only Subjects with Detectable CMV Viral DNA on Day 1(NC=F Approach

Parameter	Letermovir (N=48) n (%)	Placebo (N=22) n (%)
Failures[†]	**31 (64.6)**	**20 (90.9)**
Clinically significant CMV infection by Week 24[‡]	22 (45.8)	17 (77.3)
Initiation of PET based on documented CMV viremia	21 (43.8)	17 (77.3)
CMV end-organ disease	2 (4.2)	1 (4.5)
Discontinued from study before Week 24	8 (16.7)	3 (13.6)
Missing outcome in Week 24 visit window	1 (2.1)	0 (0.0)
Stratum-adjusted treatment difference (Letermovir-Placebo)[§]		
Difference (95% CI)	-26.1 (-45.9, -6.3)	
p-value	0.0048	

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

[‡] Clinically significant CMV infection was defined as CMV end organ disease or initiation of PET based on documented CMV viremia and the clinical condition of the subject. In one instance in both the letermovir and placebo arm, 1 subject is counted as both a case of initiation of PET and as a case of CMV end-organ disease.

[§] 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A nominal one-sided p-value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

N = number of subjects in each treatment group.

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

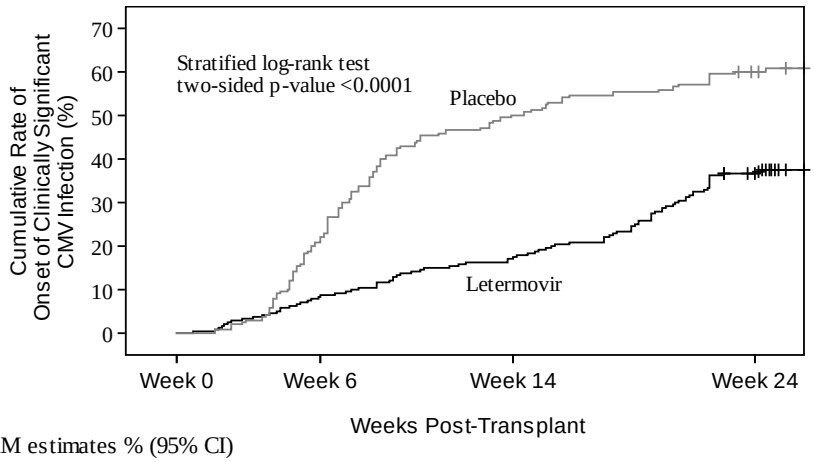
The difference between treatment groups regarding the primary endpoint is driven by a difference in the rate of PET initiation, showing the ganciclovir-saving potential of letermovir. This could have a direct impact for patients, reducing the need for re-hospitalization as PET is most commonly initiated with intravenous ganciclovir. A lower use of ganciclovir could also result in a total reduction of CMV-treatment-related adverse events, given that the safety profile of letermovir is more beneficial when used in a prophylactic regimen compared to ganciclovir-based PET.

The analysis based on all randomised and treated subjects, i.e. nd including those with detectable CMV Viral DNA on Day 1 showed a very similar outcome. The proportion of failures was 41.0% (153/373) and 64.1% (123/192) in the letermovir and placebo arm respectively. The stratum-adjusted difference between the two arms was; -23.6 (-31.9, -15.2); p>0.0001.

In clinical practice some patients will end up in a similar situation to those that had started letermovir prophylaxis but were excluded from the FAS population due to a positive CMV DNA screening result in a

sample taken before initiation of letermovir. Of note, the absolute efficacy of letermovir in subjects with positive CMV-DNA on Day 1 is clearly lower than in those without Day 1 viremia but the numerical relative difference to placebo is similar. Confounding by factors related to immune status cannot be excluded.

Figure 7 Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection Through Week 24 Post-Transplant (FAS Population)



No. at risk: KM estimates % (95% CI)				
Letermovir	325	299: 8.6 (5.6, 11.7)	270: 17.2 (13.1, 21.3)	204: 36.6 (31.4, 41.9)
Placebo	170	135: 21.8 (15.6, 28.0)	85: 50.0 (42.5, 57.5)	66: 60.0 (52.6, 67.4)
No. of events, Letermovir				
Initiation of PET	0	11	20	49
CMV End-organ Disease	0	1	1	5
Discontinued from Study	0	16	35	56
Missing Week 24 Outcome	0	0	0	9
No. of events, Placebo				
Initiation of PET	0	29	64	67
CMV End-organ Disease	0	1	2	3
Discontinued from Study	0	7	19	27
Missing Week 24 Outcome	0	0	0	5

The KM plot shows a clear difference in time to onset of CMV infection between letermovir and placebo until Week 14, with some catch-up when letermovir is discontinued. However, the clinical implication of CMV reactivation is depending on the immune status of the patient. Most, if not all, CMV R+ patients are expected to present with CMV DNAemia at some time point post-transplant, but the de-escalation of CMV PCR monitoring within this study (and in current clinical practice) means that not all subjects (mostly low-risk) will be tested when this occurs.

Subgroup analyses

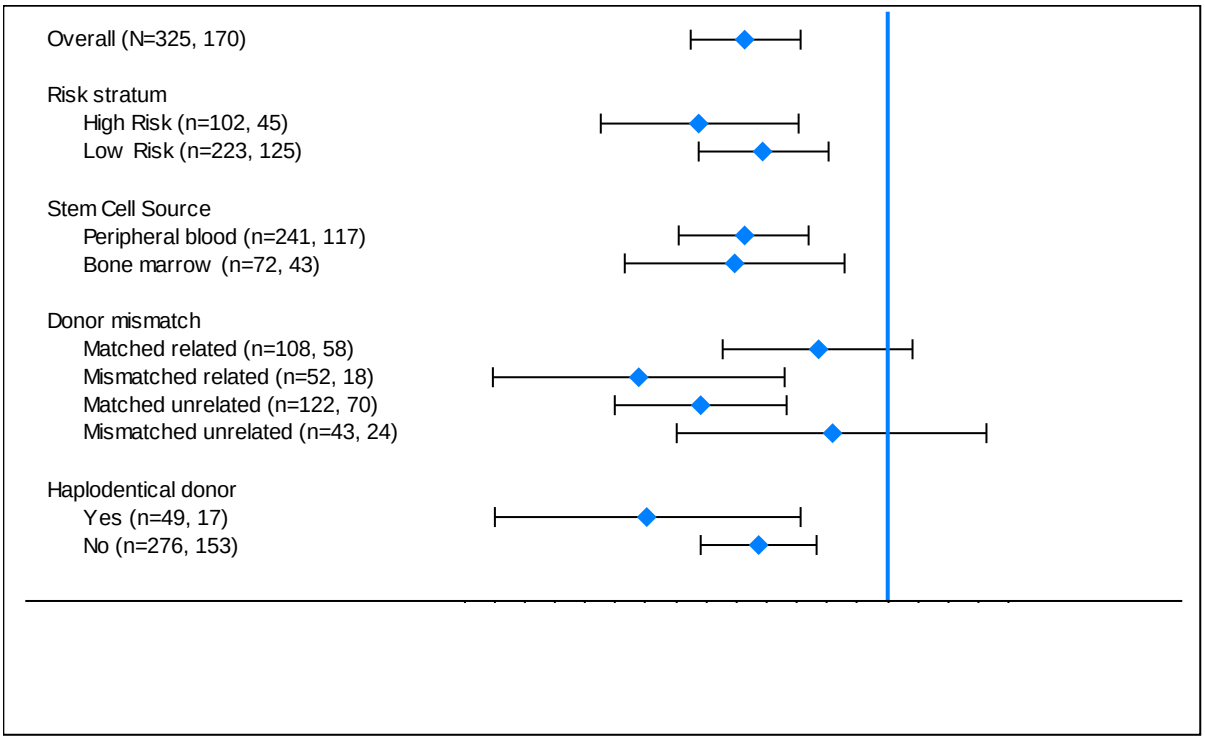
Forest plots were used to assess the consistency of the treatment effect of letermovir in P001 across various subgroups (FAS population) based on risk categories for CMV reactivation (risk stratum, stem cell source,

degree of donor mismatch, haploidentical transplantation), subject characteristics (age, gender, weight, region, time of randomization from the day of transplantation), and conditioning and concomitant immunosuppressive regimen (CsA-containing and tacrolimus-containing) used.

Overall, the treatment effect consistently favored letermovir across subgroups based on subject baseline, epidemiological and clinical characteristics.

Note: The Forest plots below illustrate the treatment difference (letermovir minus placebo) in the proportion of subjects with clinically significant CMV infection through Week 24 post-transplant by subgroup.

Figure 8 Proportion of Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant by Risk factor Subgroups (NC=F Approach, FAS Population)



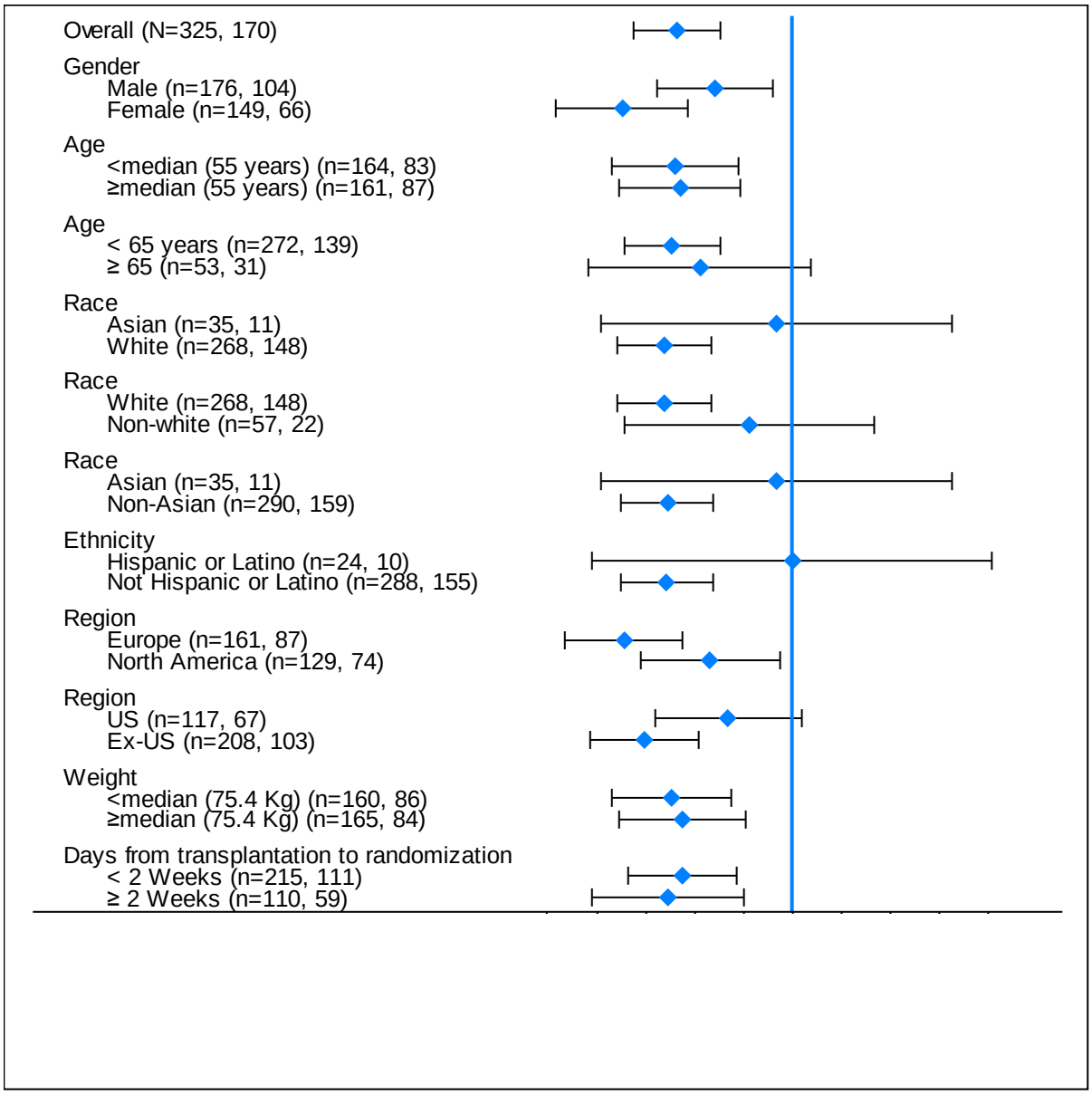
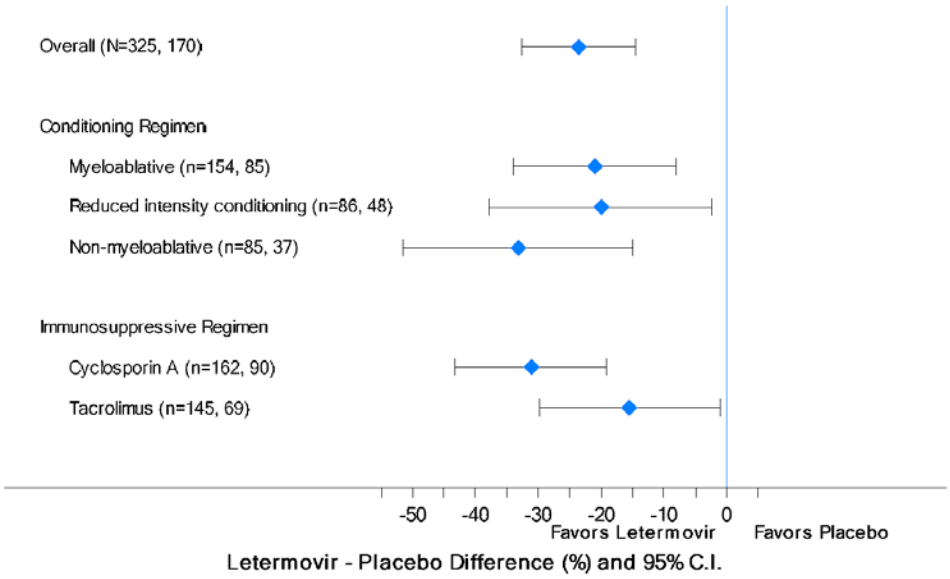

Overall (N=325, 170)
Gender
Male (n=176, 104)
Female (n=149, 66)
Age
<median (55 years) (n=164, 83)
≥median (55 years) (n=161, 87)
Age
< 65 years (n=272, 139)
≥ 65 (n=53, 31)
Race
Asian (n=35, 11)
White (n=268, 148)
Race
White (n=268, 148)
Non-white (n=57, 22)
Race
Asian (n=35, 11)
Non-Asian (n=290, 159)
Ethnicity
Hispanic or Latino (n=24, 10)
Not Hispanic or Latino (n=288, 155)
Region
Europe (n=161, 87)
North America (n=129, 74)
Region
US (n=117, 67)
Ex-US (n=208, 103)
Weight
<median (75.4 Kg) (n=160, 86)
≥median (75.4 Kg) (n=165, 84)
Days from transplantation to randomization
< 2 Weeks (n=215, 111)
≥ 2 Weeks (n=110, 59)

Figure 9 Proportion of Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant by Conditioning Regimen and Immunosuppressive Therapy Subgroups (NC=F, FAS Population)



Differences between letermovir and placebo groups were overall consistent across clinical and epidemiological subgroups, although confidence intervals widen in groups with limited data.

Factors associated with CMV DNAemia up to week 14 (in 13 of 25 cases more than 2 weeks after cessation of letermovir) included high risk for CMV reactivation at baseline and absence of GVHD but number are to limited to draw conclusions regarding on-treatment failures. Factors associated with CMV DNAemia after cessation of letermovir prophylaxis up to Week 24 post-transplant among letermovir-treated subjects included high risk for CMV reactivation at baseline, GVHD, use of corticosteroids and CMV positive donor serostatus. Besides a partial correlation to CMV donor serostatus no other factors were identified that could explain the apparent moderate difference in treatment effect between men and women.

CMV donor serostatus has previously been identified as an important risk factor for CMV viremia post HSCT also in CMV R+ subjects. In the P001 study, receiving an HSCT from a CMV seropositive donor was correlated to a lower the risk for CMV DNAemia in the range of 10-15% in both letermovir and placebo groups. Although not formally related to letermovir treatment, this baseline factor is of clinical importance and is described in section 5.1 of the SmPC.

Table 30 Subjects with Clinically Significant CMV Infection Through Week 24 Post Transplant by Donor CMV serostatus (NC=F Approach, FAS Population)

	Letermovir		Placebo		Letermovir vs. Placebo Difference in
Subject Characteristic	n/N	% (95% CI)	nN	% (95% CI)	% (95% CI)[†]

Subgroup					
Donor CMV Serostatus					
Positive	64/199	32.2 (25.7, 39.1)	55/98	56.1 (45.7, 66.1)	-24.4 (-36.2, -12.6)
Negative	57/123	46.3 (37.3, 55.6)	48/72	66.7 (54.6, 77.3)	-20.6 (-34.7, -6.6)
Unknown	1/3	33.3 (0.8, 90.6)	NA	NA	NA

[†] Treatment difference and 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk).

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study of Week 24 post-transplant visit window.

N = number of subjects in each treatment group.

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

NA = Not Applicable.

Efficacy in relation to exposure and mode of administration

When comparing letermovir subgroups with immunosuppressive regimens based on CsA vs tacrolimus, there is a notable numerical difference in risk reduction. Also, exposure is clearly lower in subjects receiving per oral letermovir without CsA. For the 240 mg and 480 mg tablet groups, AUC is approximately 61% and 34% of that generated by the 480 mg iv formulation, respectively.

Table 31 Proportion of Subjects with Clinically Significant CMV Infection On-Treatment by Route and Dose of Administration (DAO Approach, FAS Population)

	Letermovir	
Subgroup	n/N	% (95% CI)
Total	**12/288**	**4.2 (2.2, 7.2)**
Route and Dose of Administration		
Oral 480 mg, no CsA[‡]	5/92	5.4 (1.8, 12.2)
Other	7/196	3.6 (1.4, 7.2)

Note: Approach to handling missing values: Data-as-Observed (DAO) approach. With DAO approach, any subject with missing value for a particular endpoint was excluded from the analysis.

N = number of subjects in each treatment group.

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

‡ Subjects only with oral 480 mg, no subjects receiving concomitant cyclosporine (CsA) were counted in this category.

Table 32 Summary of the Proportion of subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant by Route of Dose Administration (NC=F Approach, FAS Population)

	Letermovir	
Subgroup	n/N	% (95% CI) †
Total	**122/325**	**37.5 (32.3, 43.1)**
Route and Dose of Administration		
Oral 480 mg, no CsA‡	40/103	38.8 (29.4, 48.9)
Other	82/222	36.9 (30.6, 43.7)

† Treatment difference and 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk).

‡ Only subjects who received oral 480 mg, no CsA exclusively throughout their treatment course were counted in this category.

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

N = number of subjects in each treatment group.

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

Table 33 Proportion of Subjects with Clinically Significant CMV Infection On-Treatment by Letermovir AUC Quartiles (DAO Approach, FAS Population)

	Letermovir	
Subgroup	n/N	% (95% CI)

Total	**12/288**	**4.2 (2.2, 7.2)**
Letermovir AUC Quartile		
AUC 1st quartile	4/76	5.3 (1.5, 12.9)
AUC 2nd quartile	4/73	5.5 (1.5, 13.4)
AUC 3rd quartile	3/67	4.5 (0.9, 12.5)
AUC 4th quartile	1/72	1.4 (0.0, 7.5)
Note: Approach to handling missing values: Data-as-Observed (DAO) approach. With DAO approach, any subject with missing value for a particular endpoint was excluded from the analysis. N = number of subjects in each treatment group. n (%) = Number (percent) of subjects in each sub-category. AUC quartiles: Q1= 36732 (ng.hr/mL), median=49478 (ng.hr/mL), Q3= 63898 (ng.hr/mL). AUC= AUC (ng.hr/mL) at steady state.		

Table 34 Proportion of Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant by Letermovir AUC Quartile (NC=F Approach, FAS Population)

	Letermovir	
Subgroup	n/N	% (95% CI)
Total	**122/325**	**37.5 (32.3, 43.1)**
Letermovir AUC Quartile		
AUC 1st quartile	25/82	30.5 (20.8, 41.6)
AUC 2nd quartile	36/85	42.4 (31.7, 53.6)
AUC 3rd quartile	28/77	36.4 (25.7, 48.1)
AUC 4th quartile	33/81	40.7 (29.9, 52.2)
Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window. N = number of subjects in each treatment group. n (%) = Number (percent) of subjects in each sub-category. AUC quartiles: Q1= 36732 (ng.hr/mL), Q2=49478 (ng.hr/mL), Q3= 63898 (ng.hr/mL).		

AUC= AUC (ng.hr/mL) at steady state.

When looking at the individual modes of administration, all 12 on-treatment failures were receiving letermovir orally.

Table 35 Listing of Subjects with Virologic Failure on Letermovir

Subid	Route of Administration	Total Daily Dose (mg)	Day of last exposure to letermovir	Day of Clinically Significant CMV infection
102186	oral administration	480	43	43
100335	oral administration	240	18	18
101760	oral administration	240	10	10
101917	oral administration	240	7	7
101625	oral administration	240	61	62
101911	oral administration	240	27	29
100045	oral administration	480	14	11
100224	oral administration	240	13	12
101804	oral administration	480	14	16
102024	oral administration	480	35	37
100346	oral administration	480	16	17
100347	oral administration	480	3	4

It is noted that all subjects with virologic failure were receiving letermovir orally. However, this was also the dominating route of administration in the study.

The clinical efficacy of the 480 mg oral regimen (without CsA) is numerically lower when comparing the primary endpoint during the treatment phase using a data-as-observed approach, which would be the most relevant measure of the risk for virologic failure. However, when comparing the primary endpoint at 24 Weeks post-transplant, efficacy is similar to all other regimens. With only 12 on-treatment failures to analyse, random effects cannot be excluded.

When analysing the primary endpoint in relation to AUC quartiles during the on-treatment phase, using a data-as-observed approach, the failure rate in the 4th quartile is numerically lower. This could point towards a dynamic dose-response trend in the exposure interval observed in the P001 study, but given the low number of true on-treatment failures it is difficult to draw any definitive conclusions. When analysing the primary endpoint at 24 weeks post-transplant, there are no obvious differences between AUC quartiles with regards to the primary endpoint. Given the unexpectedly low AUC generated by the 480 mg tablet, limitations in modelling predictions and the relative complicated interaction profile of letermovir, it might be that not all

patients receiving the 480 mg tablet (without CsA) will be above EC90 for an adequate time in clinical practice. This could be of particular importance in a situation with DDI perpetrators lowering the letermovir AUC.

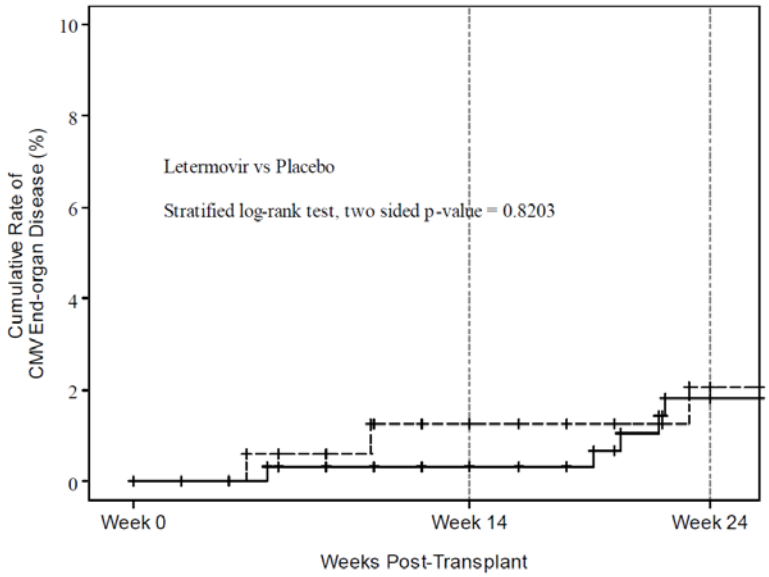
Whether the low exposure could still be associated with an increased risk of treatment-associated RAVs cannot be formally excluded until the phenotypic resistance testing is completed.

Secondary endpoints

Due to the very limited numbers of subjects with CMV end-organ disease, the group with "Initiation of PET for documented CMV viremia" is very closely related to the subjects with "Clinically significant CMV infection" and are therefore not presented in further detail.

Overall, the incidence of CMV end-organ disease in the FAS population was low through both the Week 14 and Week 24 post-transplant time points, with only 8 cases of confirmed end-organ disease through Week 24 post-transplant.

Figure 10 Kaplan-Meier Plot of Time to Onset of CMV End-organ Disease Through Week 24 Post-Transplant (FAS Population)



No. at risk: KM estimates % (95% CI)			
Letermovir	325	287: 0.3 (0.0, 1.0)	256: 1.8 (0.2, 3.4)
Placebo	170	145: 1.3 (0.0, 3.0)	118: 2.1 (0.0, 4.4)

Three subjects developed CMV end-organ disease through Week 14 post-transplant: 1 subject in the letermovir group and 2 subjects in the placebo group. All 3 subjects had gastrointestinal (GI) disease. The estimated difference (95% CI) in treatment groups was -1.0% (-3.5%, 1.5%) with a nominal 1-sided p-value of 0.2258.

An additional 5 subjects developed CMV end-organ disease through Week 24 post-transplant for a total of 8 subjects (5 [2.0%] in the letermovir group and 3 [2.4%] in the placebo group). The additional 5 subjects had GI CMV end-organ disease. The estimated difference (95% CI) between treatment groups was 0.4% (-4.0%, 3.2%), with a nominal 1-sided p value of 0.4056.

The low incidence of subjects with CMV end-organ disease was expected in P001 since subjects who developed “clinically significant CMV infection” (mostly low-grade CMV DNAemia) were treated with PET and hence not expected to progress to developing CMV disease. Although numbers are limited and differences non-significant, the rate of CMV end-organ disease were numerically lower in the letermovir group at week 14.

There is an apparent catch-up in the letermovir group between weeks 14 and 24, both in terms of CMV DNAemia and CMV disease, when prophylaxis is discontinued. GVHD, use of corticosteroids, high risk classification at baseline and negative CMV donor serostatus were identified as independent factors for meeting the primary endpoint during weeks 14-24. However, as the clinical consequences of CMV reactivation in general are decreasing with time post HSCT (and most, if not all, R+ patients will experience CMV DNAemia at some time before cellular immunity is sufficiently restored) this is not fully translatable into clinical benefit and the lack of efficacy and safety data for extended use of letermovir beyond Day 100 post HSCT must be clear to the prescribers.

Ancillary analyses

Table 36 P001: Summary of the Efficacy Analyses for Non-Mortality Exploratory Endpoints (FAS Population)

	Letermovir (N=325)		Placebo (N=170)	
Exploratory Endpoints	n	% (95% CI)	n	% (95% CI)
Bacterial and/or Fungal opportunistic infection through Week 14 post-transplant	78	24.0 (19.5, 29.0)	37	21.8 (15.8, 28.7)
Bacterial and/or Fungal opportunistic infection through Week 24 post-transplant	87	26.8 (22.0, 31.9)	43	25.3 (19.0, 32.5)
GVHD through Week 14 post-transplant	126	38.8 (33.4, 44.3)	71	41.8 (34.3, 49.6)
GVHD through Week 24 post-transplant	159	48.9 (43.4, 54.5)	93	54.7 (46.9, 62.3)
Re-hospitalization through Week 14 post-transplant	118	36.3 (31.1, 41.8)	81	47.6 (39.9, 55.4)
Re-hospitalization for CMV infection/disease through Week 14 post-transplant	2	0.6 (0.1, 2.2)	12	7.1 (3.7, 12.0)
Re-hospitalization through Week 24 post-transplant	158	48.6 (43.1, 54.2)	94	55.3 (47.5, 62.9)

Re-hospitalization for CMV infection/disease through Week24 post-transplant	10	3.1 (1.5, 5.6)	13	7.6 (4.1, 12.7)
Documented CMV viremia through Week 14 post-transplant	103	31.7 (26.7, 37.1)	118	69.4 (61.9, 76.2)
Documented CMV viremia through Week 24 post-transplant	186	57.2 (51.7, 62.7)	124	72.9 (65.6, 79.5)
N = Number of subjects in analysis population. n = Number of subjects with outcome.				

All-cause mortality

Table 37 Vital Status for All Subjects Through Week 48 post-transplant (Full Analysis Set)

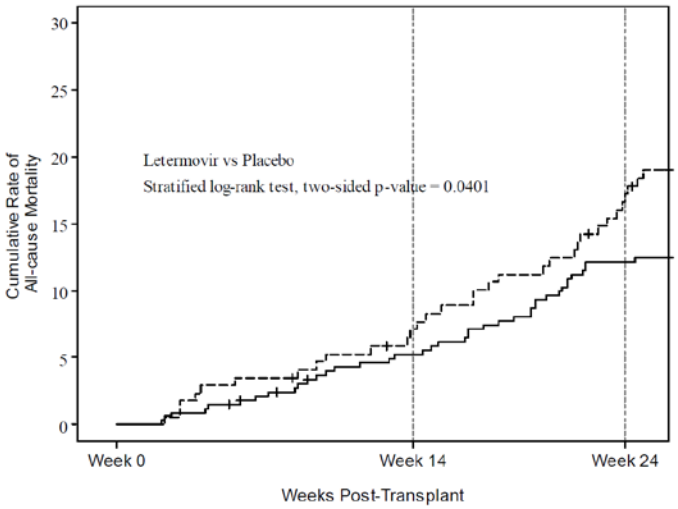
	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	325		170		495	
Vital Status for All Subjects in Trial Through 24 Weeks Post-transplant						
Alive	281	(86.5)	135	(79.4)	416	(84.0)
Dead	40	(12.3)	32	(18.8)	72	(14.5)
Unknown	4	(1.2)	3	(1.8)	7	(1.4)
Vital Status for All Subjects in Trial Through 48 Weeks Post-transplant						
Alive	239	(73.5)	120	(70.6)	359	(72.5)
Dead	76	(23.4)	46	(27.1)	122	(24.6)
Unknown	10	(3.1)	4	(2.4)	14	(2.8)
Note: Week 48 post-transplant is defined as 350 days post-transplant (2 weeks post Week 48 visit). Any death <=350 days post-transplant was counted as death, and any death >350 days post-transplant was counted as alive at Week 48 post-transplant. n (%) = Number (percent) of subjects in each sub-category.						

Mortality data is available for 97.2% of the FAS population. This is acceptable, although it is noteworthy that vital status could not be clarified for all subjects included in the study.

All-cause mortality was an exploratory endpoint and no approach to the statistical analysis was pre-specified. The observed cumulative incidence of death week 24 was 12.3% (40/325) in the letermovir group and 18.8% (32/170) in the placebo group; at week 48, it was 23.4% (76/325) in the letermovir group and 27.1% (46/170) in the placebo group.

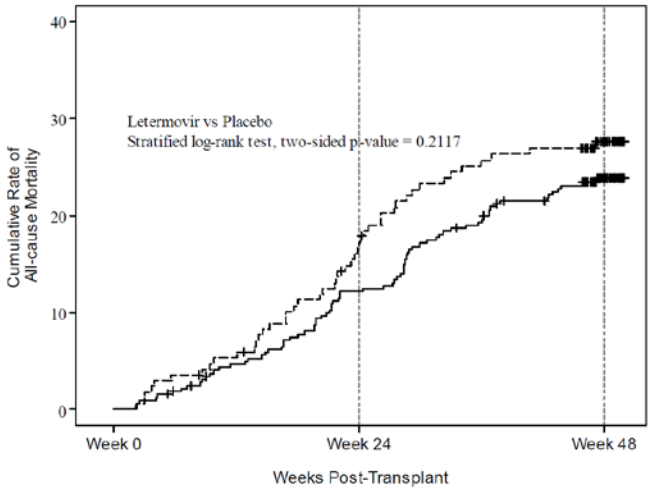
The distribution of time to all-cause mortality through Week 24 (nominal two-sided log-rank p-value=0.0401, not controlled for multiplicity) was slightly different between the letermovir and placebo groups, but the difference was not significant at Week 48 (nominal two-sided log-rank p-value=0.2117, not controlled for multiplicity).

Figure 11. Kaplan-Meier Plot of Time to All-cause Mortality Through Week 24 Post-Transplant (FAS Population)



No. at risk: KM estimates % (95% CI)			
Letermovir	325	304: 5.3 (2.8, 7.7)	282: 12.1 (8.6, 15.7)
Placebo	170	156: 7.1 (3.2, 11.0)	139: 17.2 (11.5, 22.9)

Figure 12. Kaplan-Meier Plot of Time to All-cause Mortality Through Week 48 Post-Transplant (FAS Population)



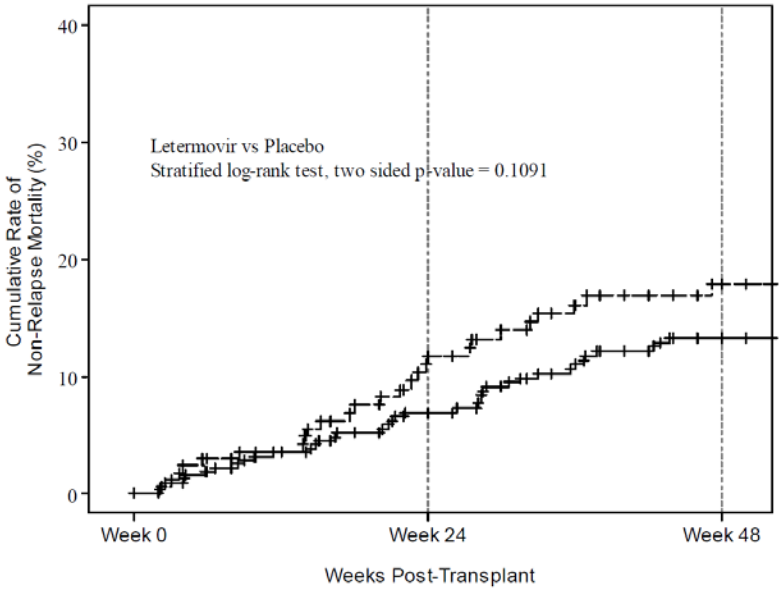
No. at risk: KM estimates % (95% CI)			
Letermovir	325	282: 12.1 (8.6, 15.7)	165: 23.8 (19.1, 28.5)
Placebo	170	139: 17.2 (11.5, 22.9)	81: 27.6 (20.8, 34.4)

Non-relapse mortality

At week 14 post-transplant (FAS population) the observed incidence of non-relapse mortality was 13/325 (4.0%) for the letermovir group compared with 9/170 (5.3%) for the placebo group. At week 24, the observed incidence of non-relapse mortality was 21/325 (6.5%) for the letermovir group compared to 18/170 (10.6%) for the placebo group in the FAS population. At 48 weeks, the non-relapse mortality was 38/325 (11.7%) in the letermovir group and 27/170 (15.9%) in the placebo group.

The K-M event rate for non-relapse mortality at Week 48 post-transplant was 13.3% for the letermovir group (95% CI: 9.3% to 17.3%) compared to 17.8% in the placebo group (95% CI: 11.5% to 24.1%). The distribution of time to non-relapse mortality through Week 48 was not significantly different between the letermovir and placebo groups (nominal two-sided p-value=0.1091, stratified log-rank test).

Figure 13 Kaplan-Meier Plot of Time to Non-Relapse Mortality Through Week 48 Post-Transplant (FAS Population)



No. at risk: KM estimates % (95% CI)			
Letermovir	325	262: 6.9 (4.1, 9.8)	138: 13.3 (9.3, 17.3)
Placebo	170	125: 11.7 (6.6, 16.8)	71: 17.8 (11.5, 24.1)

CMV-related mortality

It must be taken into consideration that all analyses of mortality in this single study phase 3 programme are exploratory. The mode of analysis as well as type 1 error control was not pre-specified.

The MAA has provided KM-plots regarding CMV-related mortality (data not shown). However, the definition used was “death due to any reason in subjects who met the primary endpoint”. In most cases the cause of death is unrelated to CMV infection. As the incidence of CMV infection is highly skewed between study groups, introducing unacceptable bias and connecting deaths with often unrelated CMV DNAemia, these data are not considered scientifically sound and are omitted from the assessment report.

A more interesting analysis of the impact of CMV reactivation on mortality is the post-hoc analysis of all-cause mortality through Week 48 post-transplant, in relation to whether the primary endpoint was met through Week 24. Among subjects with clinically significant CMV infection through Week 24 the mortality rate in the letermovir vs. placebo groups was 21.1% vs. 33.8%; and among subjects without clinically significant CMV infection, the mortality rate in the letermovir vs. placebo groups was 23.9% vs. 22.2%. Seemingly, subjects failing letermovir prophylaxis (often post Day 100) presents with an all-cause mortality rate comparable to study subjects without clinically significant CMV infection. This illustrates the potential benefit of letermovir, in delaying the onset of CMV reactivation to a phase where the patient is less fragile and

immunologically more competent. Subjects failing letermovir prophylaxis are expected to be selected on negative covariates compared to those failing placebo; hence, the comparison should if anything underestimate the benefit of letermovir.

Re-hospitalization

Table 38 Proportion of Subjects with Re-Hospitalization After Transplant Through Week 14 and 24 Post-Transplant (FAS Population)

Response Variable	Letermovir (N=325)			Placebo (N=170)		
	n	m	% (95% CI)	n	m	% (95% CI)
All Re-hospitalizations Week 14	118	168	36.3 (31.1, 41.8)	81	107	47.6 (39.9, 55.4)
Re-hospitalizations for CMV infection/disease Week 14	2	2	0.6 (0.1, 2.2)	12	12	7.1 (3.7, 12.0)
All Re-hospitalizations Week 24	158	278	48.6 (43.1, 54.2)	94	146	55.3 (47.5, 62.9)
Re-hospitalizations for CMV infection/disease Week 24	10	11	3.1 (1.5, 5.6)	13	13	7.6 (4.1, 12.7)

N = number of evaluable subjects in in each treatment group.
n = Number of subjects in each sub-category.
m = Number of unique episodes in each sub-category.
% = Percent of subjects in each sub-category.

Table 39 Total Duration of Rehospitalization(s) Per Subject Through Week 24 post-transplant (FAS Population)

Response Variable	Letermovir (N=325)		Placebo (N=170)	
	n(m) Days Mean	Days Median (min, max)	n(m) Days Mean	Days Median (min, max)
All Re-hospitalizations through Week 24	158 (278) 23.3	15 (1 ,127)	94 (146) 26.3	14 (1 ,159)

N = number of evaluable subjects in in each treatment group.

n = Number of subjects in each sub-category.

m = Number of unique episodes in each sub-category.

Median = median total number of days of rehospitalization for each subject

The cumulative rates of all-cause re-hospitalization at week 14 and 24 are numerically lower in the letermovir group compared to placebo. Also, the mean number of days in hospital is numerically lower in the letermovir group, while the median is however similar between groups. Given the variability of data, the overall differences are negligible and do not clearly indicate that letermovir prophylaxis will reduce the overall need

of in-patient care compared to a standard-of-care PET approach.

Resistance

In order to identify CMV variants that may be associated with a change in susceptibility to letermovir (compared to a reference strain) in subjects failing CMV prophylaxis, genotypic analyses were conducted on subjects who met the primary endpoint of clinically significant CMV infection through Week 24 post-transplant with documented CMV viremia, and had a plasma sample available for CMV UL56 / UL89 Genotypic Analysis.

Table 40 Prevalence of UL56 and UL89 Genotypic Variants for Subjects Who Received Letermovir or Placebo (Full Analysis Set; GAP)

Population	Entire coding Sequence Available (UL56)	UL56 Genotypic Variant Not Detected (n/N, %)	UL56 Genotypic Variant Detected (n/N, %)	Entire coding Sequence Available (UL89)	UL89 Genotypic Variant Not Detected (n/N, %)	UL89 Genotypic Variant Detected (n/N, %)
Overall	63	7/63 (11%)	56/63 (89%)	57	20/57 (35%)	37/57 (65%)
Subjects who received letermovir	22	2/22 (9%)	20/22 (91%)	19	7/19 (37%)	12/19 (63%)
Subjects who received placebo	41	5/41 (12%)	36/41 (88%)	38	13/38 (34%)	25/38 (66%)

GAP = Genotyping Analysis Population; GV = Genotypic Variant.

Note: Differences detected at a frequency of ≥5% of the total sequence data at a given position indicate the presence of a CMV genotypic variant (GV).

The number of letermovir subjects in the FAS GAP with previously characterized, letermovir-resistant GVs is listed below. There are 19 UL56 GVs that have previously been shown to shift the EC50 for letermovir ≥ 1.6-fold in cell-culture models of CMV infection. These characterized GVs map to 11 different amino acids between residues 231 to 369 of the UL56 protein; this region has been described as the letermovir resistance "hot spot".

The overall rate of UL56 and UL89 polymorphisms are comparable between study groups. However, given the length of the sequence this is a highly insensitive measure of resistance development.

Hitherto, two different RAVs have been identified in the GAP; UL56 V236M was detected in one subject, and UL56 C325W was detected in the other subject. These substitutions are both in the UL56 letermovir resistance "hot spot" (AA 231-369), and both are at residues where mutations were previously seen following resistance selection in cell-culture models of infection.

Given the novel mechanism of action and limited experience from virologic failure *in vivo*, also GVs outside the identified "hot spot" should be carefully assessed for potential impact on virologic control.

- V236M is a highly relevant RAV (fold change ~ 50).

- N446del, N446S and A464T are more common in subjects failing letermovir than placebo, but numbers are too limited to allow any conclusion without comparison to baseline CMV genotype and prior to phenotypic characterization of virologic failure strains.

- Deviations at UL56 positions 425 and 586 are highly frequent in both letermovir and placebo groups, illustrating that the reference CMV strain used is not completely representative of the clinical isolates, at least not those reactivating post HSCT.

The Applicant has clarified that there were no study protocol defined collection of baseline samples suitable for CMV isolation, but are analyzing those that are available. This, in adjunction with the phenotypic resistance data should be submitted to address CHMP recommendation.

Summary of main study

Letermovir demonstrated superior efficacy over placebo in the primary endpoint analysis, as a lower proportion of subjects in the letermovir group (37.5%) developed clinically significant CMV infection compared to the placebo group (60.6%) through Week 24 post-transplant (FAS population, NC=F approach). The estimated difference (95% CI) of -23.5% (-32.5%, -14.6%), adjusted for the stratification factor of high versus low risk for CMV reactivation, was statistically significant (1-sided p value <0.0001).

Clinical studies in special populations

There were a limited number of subjects above 65 years (n=55), and only one subject above 75. This is acceptable, given the currently proposed indication where local practice guidelines regarding age limits for allogenic HSCT are likely to limit the use of letermovir in elderly subjects. As the pharmacologic target is of viral origin the pharmacodynamic response is not expected to differ in the elderly population per se, given that exposure is similar.

2.5.3. Discussion on clinical efficacy

Letermovir introduces a completely new mechanism of action in the prophylaxis of CMV reactivation and disease, targeting the CMV UL56/UL89 terminase complex. Biochemical characterization and electron microscopy suggest that letermovir affects the formation of proper unit length genomes from viral DNA concatemers and interferes with virion maturation. According to the Applicant, letermovir administration leads to a cessation of the production of infectious viral particles but allows DNA synthesis to occur, thus providing DNA copies that could be detected by CMV DNA assays. It is not clear whether this is applicable to analyses of clinical plasma, as circulating virions are considered the major source of CMV DNA. However, as there are no validated alternative biomarkers or PET initiation thresholds, the use of CMV DNA for monitoring and standard-of-care PET criteria is endorsed although this could hypothetically be too conservative and result in unnecessary termination of letermovir prophylaxis.

Favourable safety data from studies in phase 1 and 2 allowed for a prophylactic approach in the phase 3 program, in contrast to current clinical practice where ganciclovir/valganciclovir is mainly used in pre-emptive and therapeutic settings due to safety issues. Patients with pre-existing viremia have however not been included in the study or excluded from the efficacy analysis population (FAS), depending on whether CMV DNA was detected before enrolment or after enrolment but prior to initiation of letermovir prophylaxis.

The phase 3 program consists of a single multicentre study (P001), enrolling a total of 570 CMV seropositive subjects planned for allogenic stem cell transplant, randomized in a 2:1 ratio to letermovir or placebo. The primary endpoint is “clinically significant CMV infection” at 24 weeks post-transplant, where letermovir provides a statistically significant reduction from 60.6 to 37.5% of subjects compared to placebo. The difference is consistent across epidemiological and clinical subgroups. However, the P001 study definition of

clinically significant CMV infection is liberal; in the vast majority of cases this criterion is fulfilled by patients initiating pre-emptive ganciclovir therapy based on low-level viremia, making the primary and secondary endpoints largely measures of the ganciclovir-saving potential of letermovir. This is expected to be of clinical importance due to the safety profile of ganciclovir, but is already to some extent mitigated by the currently used pre-emptive protocol where a majority of patients will have left the most critical period post-transplant (before and during engraftment, where myelotoxicity is a particular concern) before initiating pre-emptive therapy with ganciclovir. A reduction in the need of pre-emptive therapy could however reduce the need for re-hospitalization, as PET is most commonly initiated with iv ganciclovir, but there were no clear differences in total in-patient care between letermovir and placebo groups. See the discussion on clinical safety for further details.

The rates of CMV end-organ disease were overall low, though numerically lower in the letermovir arm while on-treatment (up to 14 weeks post-transplant). Although numbers are limited and differences non-significant, there is an apparent catch-up in the letermovir group between weeks 14 and 24 when prophylaxis is discontinued with the occurrence of a few new cases of gastrointestinal CMV disease in the letermovir group. Possibly, in a subset of patients, additional clinical benefit could be expected from prolonged letermovir prophylaxis beyond week 14 post-transplant but no clinical data from prolonged prophylaxis are available to make a recommendation.

It is noted that all subjects with virologic failure were receiving letermovir orally. However, this was also the dominating route of administration in the study. The clinical efficacy of the 480 mg oral regimen (without CsA) is numerically lower when comparing the primary endpoint during the treatment phase using a data-as-observed approach, which would be the most relevant measure of the risk for virologic failure. However, when comparing the primary endpoint at 24 Weeks post-transplant, efficacy is similar to all other regimens. With only 12 on-treatment failures to analyse, random effects cannot be excluded.

When analysing the primary endpoint in relation to AUC quartiles during the on-treatment phase, using a data-as-observed approach, the failure rate in the 4th quartile (highest exposure) is numerically lower. This could point towards a dynamic dose-response trend in the exposure interval observed in the P001 study, but given the low number of true on-treatment failures it is difficult to draw any definitive conclusions. When analysing the primary endpoint at 24 weeks post-transplant, there are no obvious differences between AUC quartiles with regards to the primary endpoint, but this analysis is less sensitive. Whether the low exposure could still be associated with an increased risk of treatment-associated RAVs cannot be formally excluded until the phenotypic resistance testing is completed.

In subjects failing letermovir prophylaxis where CMV DNA could be successfully sequenced, two patients presented with known resistance-associated polymorphisms. In addition, a number of genetic variants that has not been associated with reduced susceptibility to letermovir were found. The current presentation of the virologic dataset however lacks baseline sequencing and phenotypic resistance testing, limiting the conclusions that can be drawn, and this issue will not be completely resolved within this procedure but is referred to an post-authorization commitment.

All-cause mortality was an exploratory endpoint, with no statistical analysis plan pre-specified; furthermore, vital status data were not systematically gathered during the study.. The observed cumulative incidence of death week 24 was 12.3% (40/325) in the letermovir group and 18.8% (32/170) in the placebo group; at week 48, it was 23.4% (76/325) in the letermovir group and 27.1% (46/170) in the placebo group. The distribution of time to all-cause mortality through Week 24 was slightly lower in the letermovir group (nominal two-sided log-rank p-value=0.0401, not controlled for multiplicity), but the difference was not significant at Week 48.

An interesting finding is the impact of CMV reactivation on mortality in subjects who presented with a clinically significant CMV infection through week 24. Patients failing letermovir prophylaxis (or within 10 weeks after discontinuation) have an estimated mortality at 48 weeks that is numerically lower compared to those in the placebo group who present with clinically significant CMV infection (21.1 vs 33.8%). This results in a rate comparable to study subjects without clinically significant CMV infection in the letermovir arm, and may illustrate the potential benefit of letermovir in delaying the onset of CMV reactivation to a phase where the patient is less fragile and more immunocompetent. Subjects failing letermovir prophylaxis are expected to be selected on negative covariates compared to those failing placebo; hence, this comparison could underestimate the benefit of letermovir. On the other hand, as there is no demonstration that these differences were due to CMV disease, this line of reasoning remains speculative.

To summarise, it must be taken into consideration that all analyses of mortality in this single study phase 3 program are exploratory and neither the mode of analysis or type 1 error control were pre-specified in the statistical analysis plan.

2.5.4. Conclusions on the clinical efficacy

The use of letermovir prophylaxis until 14 weeks post allogenic stem cell transplant is effective in postponing CMV reactivation in CMV seropositive patients. However, the ultimate benefit to patients is currently less well-established but could, with regards to efficacy, potentially consist of a reduction of days in hospital post-transplant and decreased morbidity and mortality related directly or indirectly to CMV reactivation. This has however not been unambiguously shown in the P001 study, but as CMV reactivation is widely accepted as the cause of CMV-related disease during the first 100 days post-HSCT it can be concluded that letermovir provides a clinical benefit to this patient group.

2.6. Clinical safety

Patient exposure

The dose proposed for clinical use, i.e. 480 mg, or 240 mg when CsA is part of co-treatment, was given to 373 patients in phase 3 (14 weeks), 18 patients in study P020 (phase 2, 14 days treatment). In addition 362 phase 1 subjects received this dose, mostly as single dose.

A dose higher than 480 mg qd was given to 86 subjects in phase 1, of whom 17 received such a dose for >10 days.

The mean and median duration of letermovir treatment in the phase 3 study was 69 and 82 days for both formulations combined (around 2 weeks for the IV formulation).

Table 41 Summary of Subject Exposure in Letermovir Phase 1, 2, and 3 Trials

Treatment	Phase 1	Phase 2[†]	Phase 3[‡]	Total Number of Subjects
Letermovir	668	116	373	1157
Oral	538	116	367	1021
Intravenous	142	0	99	241
Placebo	138	33	192	363

Active Control[¶]	0	9	0	9
[†] The Phase 2 trials were P019 and P020; [‡] The Phase 3 trial is P001. Both oral and intravenous (IV) letermovir formulations were administered in P001. Subjects who received both oral and IV letermovir are counted in both groups; [¶] Subjects in the active control group of the Phase 2a trial (P019) received valganciclovir.				

Adverse events

Introduction

The focus of this section is the safety outcomes in the conducted phase 3 study. The All Subjects as Treated (ASaT) population was used for the analysis of safety data (all randomized subjects who received at least one dose of study medication). Short notes on some safety findings in the dose finding study are also provided (P020, phase 2, where letermovir dosing of 60 mg qd, 120 mg qd and 240 mg qd over 12 weeks was compared to placebo, with around 30 patients per arm).

In the phase 3 study patients were randomized to letermovir or placebo (2:1). The IV and oral route could be used, according to the need as deemed by the investigator.

Treatment was given for a maximum of 14 weeks, and had to be started within 28 days post-transplant at the latest. In the case of CMV infection/disease (see efficacy section), treatment with letermovir/placebo was stopped (and not re-initiated thereafter), and CMV treatment (valganciclovir, ganciclovir, cidofovir or foscarnet) was initiated in accordance with common clinical practice. The "treatment phase" applies to therapy with letermovir/placebo.

Monitoring of Adverse Events in the Phase 3 Trial (P001)

From the time informed consent was signed until randomization, the following AEs were reported: those resulting from protocol-specified procedures or intervention, those resulting in death, and those resulting in a subject not being randomized.

After randomization and initiation of study medication, AE monitoring included the collection of all AEs through Week 16 post-transplant in all subjects, *including those who discontinued study medication early but continued to be followed-up in the trial*. Thereafter, only drug-related SAEs and SAEs with a fatal outcome were collected through Week 48 post-transplant. The tabulated AE data after Week 16 post-transplant also contained any other types of AEs that were *passively* reported.

Presentation of AEs in CSR and Safety Summary (P001)

Safety analyses are presented *according to the protocol-specified time points and/or analysis definitions*, which were based on the timing of collection of AEs in P001 relative to dosing and the status of the study at the time of this Application.

Treatment Phase: All AEs collected from the time of initiation of study medication through 14 days following the last dose of study medication were considered as occurring during the Treatment Phase. These data are presented under subheading "AEs in treatment phase".

Through Week 24 Post-Transplant: AEs reported as described above up to week 24 post-transplant.

Through the Database Lock: AEs reported as described above up to week 48 post-transplant. At the time of database lock (DBL), a total of 431 subjects (75.6% of all randomized) had continued beyond Week 24 post-transplant and 302 (53.0%) of these subjects completed the trial.

Upon request, all AEs and graded lab toxicity up to week 16 were also presented during the procedure.

Adverse Events - Treatment Phase

Common AEs

Overall, the AE profile was similar in the letermovir and placebo groups, including proportions with serious AEs. AEs deemed drug-related were, overall, not more frequent with letermovir, and proportions of patients stopping therapy for potentially drug-related AEs were also similar between arms.

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	373		192		
with one or more adverse events	365	(97.9)	192	(100.0)	-2.1 (-4.2, -0.2)
- drug-related[‡]	63	(16.9)	23	(12.0)	4.9 (-1.4, 10.6)
with serious adverse events	165	(44.2)	90	(46.9)	-2.6 (-11.3, 6.0)
- drug-related	3	(0.8)	3	(1.6)	NA
who died	38	(10.2)	17	(8.9)	1.3 (-4.2, 6.2)
discontinued[§] due to AE	72	(19.3)	98	(51.0)	-31.7 (-39.7, -23.6)
- drug-related	18	(4.8)	7	(3.6)	1.2 (-2.9, 4.5)
discontinued due to serious AE	35	(9.4)	27	(14.1)	-4.7 (-10.9, 0.7)
-drug-related	3	(0.8)	3	(1.6)	NA

[†] Based on Miettinen & Nurminen method; [‡] Determined by the investigator to be related to the drug; [§] Study medication withdrawn; NA = Not Applicable.

Common AEs in this treatment population were-expectedly-very frequent (see following table). The most commonly reported AEs (letermovir vs. placebo) during the treatment phase were GVHD (39.1% vs. 38.5%), diarrhea (26.0% vs. 24.5%), nausea (26.5% vs. 23.4%), vomiting (18.5% vs. 13.5%), rash (20.4% vs. 21.4%), and pyrexia (20.6% vs. 22.4%). Overall, the frequency of AEs was similar between arms. To be noted, in protocol 020 (phase 2, numbers limited), there was no tendency for a higher frequency of AEs with higher dosing, regardless of the SOC term.

The incidence of the following AEs was higher in the letermovir group compared to the placebo group (CI_{95} values in brackets). These AEs are marked in the following table, and discussed further in this report.

- Cardiac Disorders: 12.6% vs. 6.3% [1.1, 11.1]
- Ear and Labyrinth Disorders: 4.6% vs. 1.0% [0.5, 6.3]
- Myalgia: 5.1% vs. 1.6% [0.2, 6.5]
- Hyperkalemia: 7.2% vs. 2.1% [1.4, 8.6]
- Dyspnea: 8.0% vs. 3.1% [0.8, 8.6]

The following were more common with placebo:

- CMV infection: 8.3% vs. 45.8% [-45.1%, -30.0]
- Upper abdominal pain: 4.0% vs. 8.3% [-9.4%, -0.3]
- Gastroesophageal reflux disease: 1.1% vs. 4.7% [-7.7%, -1.0]
- Myopathy: 0.5% vs. 2.6% [-5.5%, -0.1]
- Dehydration: 0.5% vs. 2.6% [-5.5%, -0.1]
- Presyncope: 0.3% vs. 2.1% [-5.0%, -0.2]

Of note, figures presented for SOC groups (e.g. Blood and lymphatic disorders), next table, would to the understanding of the Rapporteur concern the actual number of individuals reported to have had such AEs. When summing up individual terms, the numbers may exceed that presented for the SOC group, since patients may have had >1 type of AE within that group (e.g. both anemia and neutropenia). Numbers may also not add up to the total sum for the group, since only AEs seen in at least 4 subjects in either treatment arm are presented.

When looking at "Infections and Infestations" (reported in 64.4% in the letermovir arm vs 72.4 in the placebo arm) it would seem as if *non-CMV* infections would be considerable more common in the letermovir-arm, since CMV was reported as AE much more frequently in the letermovir arm (8.3% vs 45.8%). However, this seems to be an effect of how frequencies were reported (4 or more subjects with a specific AE, biasing results in favor of the smaller control group). When looking AEs reported in >0% of patients in either arm (table not presented in this report), *non-CMV* infections were reported in very similar frequencies when adjusting for the 25% difference in the duration of treatment phase (1.05 events per patient in the letermovir-arm vs 0.84 events per person in the placebo-arm; 1.05/0.84 =1.25).

Table 42 P001: AEs (≥4 Subjects in One or More Treatment Groups), Treatment Phase (ASaT Population)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	373		192		
with one or more adverse events	365	(97.9)	192	(100.0)	-2.1 (-4.2, -0.2)
Blood and lymphatic system disorders	**98**	**(26.3)**	**51**	**(26.6)**	**-0.3 (-8.2, 7.2)**
Anaemia	25	(6.7)	10	(5.2)	1.5 (-3.1, 5.4)
Eosinophilia	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Febrile neutropenia	31	(8.3)	18	(9.4)	-1.1 (-6.6, 3.6)
Leukopenia	11	(2.9)	7	(3.6)	-0.7 (-4.6, 2.2)
Neutropenia	14	(3.8)	7	(3.6)	0.1 (-3.9, 3.2)
Pancytopenia	7	(1.9)	6	(3.1)	-1.2 (-4.9, 1.3)
Thrombocytopenia	25	(6.7)	11	(5.7)	1.0 (-3.8, 4.9)
Cardiac disorders	**47**	**(12.6)**	**12**	**(6.3)**	**6.4 (1.1, 11.0)**
Atrial fibrillation	13	(3.5)	2	(1.0)	2.4 (-0.5, 5.0)
Atrial flutter	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Cardiac failure	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Sinus tachycardia	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Tachycardia	15	(4.0)	4	(2.1)	1.9 (-1.5, 4.8)
Ear and labyrinth disorders	**17**	**(4.6)**	**2**	**(1.0)**	**3.5 (0.5, 6.3)**
Ear pain	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)

Vertigo	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Endocrine disorders	**6**	**(1.6)**	**0**	**(0.0)**	**1.6 (-0.4, 3.5)**
Eye disorders	**62**	**(16.6)**	**32**	**(16.7)**	**-0.0 (-6.9, 6.2)**
Gastrointestinal disorders	**261**	**(70.0)**	**129**	**(67.2)**	**2.8 (-5.1, 11.0)**
Abdominal discomfort	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Abdominal distension	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Abdominal pain	44	(11.8)	18	(9.4)	2.4 (-3.3, 7.5)
Abdominal pain upper	15	(4.0)	16	(8.3)	-4.3 (-9.4, -0.3)
Angina bullosa haemorrhagica	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Aphthous ulcer	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Constipation	27	(7.2)	20	(10.4)	-3.2 (-8.8, 1.5)
Diarrhoea	97	(26.0)	47	(24.5)	1.5 (-6.3, 8.8)
Dry mouth	20	(5.4)	6	(3.1)	2.2 (-1.7, 5.6)
Dyspepsia	20	(5.4)	7	(3.6)	1.7 (-2.4, 5.1)
Dysphagia	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Flatulence	4	(1.1)	4	(2.1)	-1.0 (-4.2, 1.0)
Gastritis	6	(1.6)	1	(0.5)	1.1 (-1.4, 3.0)
Gastrooesophageal reflux disease	4	(1.1)	9	(4.7)	-3.6 (-7.7, -1.0)
Haematochezia	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Haemorrhoids	18	(4.8)	4	(2.1)	2.7 (-0.8, 5.8)
Nausea	99	(26.5)	45	(23.4)	3.1 (-4.6, 10.3)
Proctalgia	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Stomatitis	23	(6.2)	9	(4.7)	1.5 (-3.0, 5.2)
Tongue coated	4	(1.1)	4	(2.1)	-1.0 (-4.2, 1.0)
Toothache	6	(1.6)	1	(0.5)	1.1 (-1.4, 3.0)
Vomiting	69	(18.5)	26	(13.5)	5.0 (-1.7, 11.0)
General disorders and administration site conditions	**211**	**(56.6)**	**100**	**(52.1)**	**4.5 (-4.2, 13.1)**
Hepatobiliary disorders	**22**	**(5.9)**	**15**	**(7.8)**	**-1.9 (-7.0, 2.3)**
Hepatic function abnormal	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Hyperbilirubinaemia	6	(1.6)	2	(1.0)	0.6 (-2.2, 2.6)
Immune system disorders	**153**	**(41.0)**	**80**	**(41.7)**	**-0.6 (-9.3, 7.8)**
Drug hypersensitivity	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Graft versus host disease	146	(39.1)	74	(38.5)	0.6 (-8.0, 8.9)
Hypogammaglobulinaemia	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Infections and infestations	**241**	**(64.6)**	**139**	**(72.4)**	**-7.8 (-15.5, 0.4)**
Bacteraemia	20	(5.4)	4	(2.1)	3.3 (-0.3, 6.4)
Bronchopulmonary aspergillosis	9	(2.4)	2	(1.0)	1.4 (-1.5, 3.7)
Candida infection	11	(2.9)	4	(2.1)	0.9 (-2.5, 3.5)
Clostridium difficile colitis	9	(2.4)	4	(2.1)	0.3 (-3.0, 2.8)
Conjunctivitis	6	(1.6)	1	(0.5)	1.1 (-1.4, 3.0)
Cystitis	7	(1.9)	3	(1.6)	0.3 (-2.8, 2.6)
Cytomegalovirus infection	31	(8.3)	88	(45.8)	-37.5 (-45.1, -30.0)
Device related infection	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Epstein-Barr virus infection	14	(3.8)	6	(3.1)	0.6 (-3.2, 3.6)
Folliculitis	13	(3.5)	4	(2.1)	1.4 (-2.0, 4.2)
Herpes zoster	6	(1.6)	0	(0.0)	1.6 (-0.4, 3.5)
Human herpesvirus 6 infection	5	(1.3)	2	(1.0)	0.3 (-2.5, 2.2)
Nasopharyngitis	15	(4.0)	4	(2.1)	1.9 (-1.5, 4.8)
Oral candidiasis	12	(3.2)	2	(1.0)	2.2 (-0.7, 4.7)
Oral herpes	7	(1.9)	4	(2.1)	-0.2 (-3.5, 2.1)
Pharyngitis	8	(2.1)	6	(3.1)	-1.0 (-4.7, 1.7)
Pneumonia	20	(5.4)	5	(2.6)	2.8 (-1.0, 6.0)
Respiratory tract infection	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Rhinitis	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Rhinovirus infection	10	(2.7)	2	(1.0)	1.6 (-1.2, 4.0)

Sepsis	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Septic shock	4	(1.1)	5	(2.6)	-1.5 (-5.0, 0.6)
Sinusitis	7	(1.9)	2	(1.0)	0.8 (-2.0, 3.0)
Staphylococcal bacteraemia	10	(2.7)	6	(3.1)	-0.4 (-4.2, 2.3)
Upper respiratory tract infection	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Urinary tract infection	16	(4.3)	6	(3.1)	1.2 (-2.7, 4.3)
Urinary tract infection bacterial	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Viraemia	11	(2.9)	11	(5.7)	-2.8 (-7.2, 0.6)
Injury, poisoning and procedural complications	**42**	**(11.3)**	**27**	**(14.1)**	**-2.8 (-9.1, 2.8)**
Investigations (selected list)	**133**	**(35.7)**	**60**	**(31.3)**	**4.4 (-3.9, 12.4)**
Alanine aminotransferase increased	24	(6.4)	16	(8.3)	-1.9 (-7.1, 2.4)
Aspartate aminotransferase increased	19	(5.1)	13	(6.8)	-1.7 (-6.5, 2.2)
Blood alkaline phosphatase increased	9	(2.4)	2	(1.0)	1.4 (-1.5, 3.7)
Blood bilirubin increased	9	(2.4)	5	(2.6)	-0.2 (-3.7, 2.4)
Blood creatinine increased	36	(9.7)	13	(6.8)	2.9 (-2.3, 7.4)
Blood potassium increased	7	(1.9)	1	(0.5)	1.4 (-1.1, 3.4)
Blood testosterone decreased	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Electrocardiogram QT prolonged	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Gamma-GT increased	3	(0.8)	4	(2.1)	-1.3 (-4.5, 0.7)
Haematocrit decreased	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Haemoglobin decreased	6	(1.6)	0	(0.0)	1.6 (-0.4, 3.5)
Neutrophil count decreased	6	(1.6)	2	(1.0)	0.6 (-2.2, 2.6)
Platelet count decreased	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
White blood cell count decreased	8	(2.1)	2	(1.0)	1.1 (-1.7, 3.3)
Metabolism and nutrition disorders (selected list)	**134**	**(35.9)**	**63**	**(32.8)**	**3.1 (-5.3, 11.2)**
Hyperglycaemia	25	(6.7)	10	(5.2)	1.5 (-3.1, 5.4)
Hyperkalaemia	27	(7.2)	4	(2.1)	5.2 (1.4, 8.6)
Hypernatraemia	5	(1.3)	2	(1.0)	0.3 (-2.5, 2.2)
Hypokalaemia	22	(5.9)	11	(5.7)	0.2 (-4.5, 4.0)
Musculoskeletal and connective tissue disorders	**121**	**(32.4)**	**57**	**(29.7)**	**2.8 (-5.5, 10.6)**
Neoplasms benign, malignant and unspecified	**39**	**(10.5)**	**17**	**(8.9)**	**1.6 (-4.0, 6.5)**
Acute myeloid leukaemia	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Acute myeloid leukaemia recurrent	11	(2.9)	8	(4.2)	-1.2 (-5.3, 1.8)
Nervous system disorders	**137**	**(36.7)**	**64**	**(33.3)**	**3.4 (-5.0, 11.5)**
Dizziness	25	(6.7)	11	(5.7)	1.0 (-3.8, 4.9)
Dysgeusia	17	(4.6)	7	(3.6)	0.9 (-3.1, 4.2)
Headache	52	(13.9)	18	(9.4)	4.6 (-1.3, 9.8)
Hypoaesthesia	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Neuropathy peripheral	8	(2.1)	6	(3.1)	-1.0 (-4.7, 1.7)
Paraesthesia	7	(1.9)	3	(1.6)	0.3 (-2.8, 2.6)
Presyncope	1	(0.3)	4	(2.1)	-1.8 (-5.0, -0.2)
Tremor	27	(7.2)	8	(4.2)	3.1 (-1.3, 6.9)
Psychiatric disorders	**78**	**(20.9)**	**30**	**(15.6)**	**5.3 (-1.6, 11.6)**
Anxiety	20	(5.4)	5	(2.6)	2.8 (-1.0, 6.0)
Confusional state	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Delirium	4	(1.1)	4	(2.1)	-1.0 (-4.2, 1.0)
Depression	11	(2.9)	3	(1.6)	1.4 (-1.8, 3.9)
Insomnia	34	(9.1)	10	(5.2)	3.9 (-0.9, 8.1)
Mental status changes	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Renal and urinary disorders (selected list)	**81**	**(21.7)**	**46**	**(24.0)**	**-2.2 (-9.8, 4.9)**

Acute kidney injury	36	(9.7)	25	(13.0)	-3.4 (-9.5, 1.9)
Haematuria	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Renal failure	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Renal impairment	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)

AEs that had a higher frequency in the letermovir group (Cardiac Disorders, Ear and Labyrinth Disorders, Myalgia, Hyperkalemia, Dyspnea) were further analyzed for potential clinical relevance. According the applicant, the incidence of individual preferred terms within SOCs did not show a significant imbalance for mentioned SOCs apart from Cardiac disorders (discussed below). For the others, no such episodes led to discontinuation of study medication and these events were not further analyzed. Hyperkalemia is further discussed in the section on lab chemistry.

In addition to AEs just discussed, headache was numerically more common with letermovir, as well as psychiatric disorders (mainly driven by a higher frequency of insomnia). It summary it seems as if letermovir may not be fully free from CNS side effects – mild to moderate for the most. When looking at serious AEs (treatment phase), headache remains to be mentioned for letermovir, n=3 (0.8%), an AE that may of course be related to other factors than letermovir therapy per se. None of the psychiatric events were reported as serious AEs.

Cardiac SOC events were reported twice more frequently for patients treated with letermovir, overall. The difference mainly concerned events of various kinds of tachyarrhythmia, next table.

Table 43 Cardiac SOC AEs reported in Treatment phase, phase 3 study (all reported cases)

	Letermovir (373) n (%)	Placebo (192) n (%)
Any	47 (12.6)	12 (6.3)
Atrial fibrillation	13 (3.5)	2 (1.0)
Atrial flutter	4 (1.1)	0 (0.0)
Atrial hypertrophy	0 (0.0)	1 (0.5)
Atrioventricular block	1 (0.3)	0 (0.0)
Bradycardia	2 (0.5)	1 (0.5)
Cardiac failure	5 (1.3)	0 (0.0)
Cardiac failure acute	1 (0.3)	0 (0.0)
Cardiac failure congestive	1 (0.3)	0 (0.0)
Cardiogenic shock	0 (0.0)	1 (0.5)
Cardiomyopathy	1 (0.3)	0 (0.0)
Cardiovascular disorder	1 (0.3)	0 (0.0)
Left ventricular hypertrophy	0 (0.0)	1 (0.5)
Myocarditis	1 (0.3)	0 (0.0)
Palpitations	2 (0.5)	0 (0.0)
Pericardial effusion	3 (0.8)	1 (0.5)
Pericarditis	1 (0.3)	0 (0.0)
Sinus node dysfunction	1 (0.3)	0 (0.0)
Sinus tachycardia	4 (1.1)	3 (1.6)
Tachycardia	15 (4.0)	4 (2.1)
Torsade de pointes	1 (0.3)	0 (0.0)
Ventricular tachycardia	1 (0.3)	0 (0.0)

Source: Integrated analysis of safety , table 5.3.5.3.3

The table below shows that the difference in frequency of cardiac events is driven by patients with a history of cardiac disorder; in this group Cardiac SOC AEs were > 3 times more common in the letermovir-arm.

Table 44 Subjects with Cardiac Medical History and Cardiac AEs, Treatment Phase (ASaT Population)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	**373**		**192**		**565**	
With medical history of cardiac disorders	**112**	**(30.0)**	**49**	**(25.5)**	**161**	**(28.5)**
with Cardiac Disorder SOC AE	24	(21.4)	3	(6.1)	27	(16.8)
without Cardiac Disorder SOC AE	88	(78.6)	46	(93.9)	134	(83.2)
Without medical history of cardiac disorders	**261**	**(70.0)**	**143**	**(74.5)**	**404**	**(71.5)**
with Cardiac Disorder SOC AE	23	(8.8)	9	(6.3)	32	(7.9)
without Cardiac Disorder SOC AE	238	(91.2)	134	(93.7)	372	(92.1)
Every subject is counted a single time for each applicable row and column, n (%)= Number (percent) of patients in each sub-category						

Source: safety summary, Table 2.7.4: 49

The Cardiac SOC AE was graded serious for 8 subjects (letermovir group: 6 [1.6%]; placebo: 2 [1.0%]). Of the 6 subjects in the letermovir group, 5 had either pre-existing or active medical conditions associated with the cardiovascular system (not the case for the 2 in the placebo group). Letermovir was stopped as a consequence in 1 patient (fatal event, not considered drug related). This event occurred after 2 days of treatment, and the patient suffered from sepsis at this time point.

Preclinical studies did not identify a cardiac signal. Overall, ECGs and vital signs were similar with letermovir and placebo throughout phase 1-3. Further, there was no exposure dependency for Cardiac Disorders SOC AEs over the exposure range.

The applicant also notified that use of one or more cardiotoxic antineoplastic agents for pre-HSCT conditioning is a confounding factor for the analysis of Cardiac Disorders SOC AEs. The applicant concludes that there is no evidence for a causal association between intake of letermovir and Cardiac Disorders SOC AEs.

In the phase 2 study called P020 (stems cell recipients), letermovir (60, 120 or 240 mg) was compared to placebo during 12 weeks of treatment, with around 30 patients per arm. Here 1 treatment emergent cardiac case was seen with letermovir dosed 240 mg (pericarditis) and no cases in the other arms.

Drug-related AEs (treatment phase)

Overall, the incidence of AEs considered potentially drug-related was 17% for the letermovir group versus 12% with placebo [95% CI: -1.4, 10.6]. The 5% difference was driven by a higher frequency of gastrointestinal AEs, mainly nausea (7.2 vs 3.6 %).The majority of these events were mild or moderate in intensity. Of note, gastrointestinal AEs (possibly linked to letermovir) do not seem dose dependent. In

protocol 020 (the dose finding study) treatment emergent GI disorders were in fact more frequently reported in the lowest dose group, 60 mg qd, here with a frequency of such AEs similar to that seen with placebo. Gastrointestinal AEs were in fact the lowest in the highest dose group (240 mg qd).

AEs week 0-16

AEs and lab toxicity during the treatment phase was the main focus for the safety evalution, that is to say a comparison of safety for letermovir versus placebo. In order to understand potential safety advantages with letermovir versus that seen with present standard of care (i.e. the therapy that in practice was given in the placebo-arm), safety data seen week 0-16 was requested during the procedure. As a reminder, around 7% of those allocated to letermovir versus around 40% of those allocated to placebo initiated PET during that time frame.

No relevant difference in AEs or graded lab toxicity was seen between arms during this time frame. Having in mind that no main difference in safety was seen between letermovir and placebo in the treatment phase (prior section) this would indicate that available CMV agents are well tolerated the way they are used (short term) in pre-emptive therapy.

Serious adverse event / deaths / other significant events

Serious adverse events (treatment phase)

The proportion of subjects with at least one SAE reported was 44.2% in the letermovir group vs. 46.9% in the placebo group. SAEs most frequently concerned:

- GVHD (9.9% vs. 10.4%),
- recurrent acute myeloid leukemia (2.9% vs. 3.6%),
- CMV infection (2.7% vs. 6.8%),
- acute kidney injury (1.3 % vs. 4.7%)
- pneumonia (2.1% vs. 1.6%), and
- pyrexia (1.9% vs. 2.1%).

As mentioned, Cardiac Disorders SOC were reported as SAEs by 6 subjects (1.6%) in the letermovir group and 1 (0.5%) in the placebo group. A numerical imbalance was also noted in the percentage of subjects who experienced one or more SAEs of Nervous System Disorders (letermovir: 3.2%; placebo: 0.0%) and Vascular Disorders (1.6% vs. 0.5%).

Proportions stopping therapy due to (any) serious AE was 9.4% vs. 14.1%.

Deaths through week 48

Mortality data from the phase 3 study was provided both in the efficacy sections (CSR and Summary), here with a focus on the FAS population, where deaths (all cause, relapse and non-elapse mortality) at certain time points from day of transplant were summarized. In the safety summaries (CSR and Company Safety

Summary), the ASaT population was in focus with regards to AEs leading to death, with time points referring to onset of these AEs (study day).

In order to further understand the mortality data presented in the efficacy and safety sections, Excel data including all deaths in study P001 (ASaT population) was requested, with information on "Primary cause of deaths" (used in the efficacy analysis), time for death (post-transplant), "fatal AE(s) leading to death (presented in the safety sections of the application), and other relevant parameters. A complete table with this information is provided in an Appendix, section 11.

The mortality rates initially presented by the company did not include all deaths that occurred through week 48; patients who discontinued (and died) prior to week 48 were not included. According to the company, sites were not required to report the vital status of subjects after discontinuation from the study. Upon request this data was retrospectively collected, and the company has presented data for 97.2% of the population to date (next table), analyses on mortality (discussed in the efficacy section) have been updated accordingly. Patient details on all deaths (including those collected retrospectively) was provided in a separate report, and this data has been assessed (please refer to Appendix section 11.1 at the end of this report, "Deaths in the phase 3 study").

Table 45 Vital Status for All Subjects Through Week 48 post-transplant

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	325		170		495	
Vital Status for All Subjects in Trial Through 24 Weeks Post-transplant						
Alive	281	(86.5)	135	(79.4)	416	(84.0)
Dead	40	(12.3)	32	(18.8)	72	(14.5)
Unknown	4	(1.2)	3	(1.8)	7	(1.4)
Vital Status for All Subjects in Trial Through 48 Weeks Post-transplant						
Alive	239	(73.5)	120	(70.6)	359	(72.5)
Dead	76	(23.4)	46	(27.1)	122	(24.6)
Unknown	10	(3.1)	4	(2.4)	14	(2.8)

Note: Week 48 post-transplant is defined as 350 days post-transplant (2 weeks post Week 48 visit). Any death <=350 days post-transplant was counted as death, and any death >350 days post-transplant was counted as alive at Week 48 post-transplant. n (%) = Number (percent) of subjects in each sub-category.

Below is the safety summary around "fatal AEs" leading to death" (treatment phase followed by through week 24). None of these fatal events were considered related to study treatment. For reasons mentioned, sum figures do not match the mortality rate shown above (through week 24) since time periods in the coming tables refer to onset of event, not time of death. As a reminder, the treatment phase was also, on average, longer for patients treated with letermovir. With that in mind, no obvious difference in types of AEs leading to death is seen between arms.

Table 46 Subjects With Adverse Events that Lead to Fatal Outcomes (Incidence > 0% in One or More Treatment Groups) Treatment Phase (ASaT Population)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	373		192		565	
with one or more fatal adverse events	38	(10.2)	17	(8.9)	55	(9.7)
with no fatal adverse events	335	(89.8)	175	(91.1)	510	(90.3)
Blood and lymphatic system disorders	**1**	**(0.3)**	**1**	**(0.5)**	**2**	**(0.4)**
Immune thrombocytopenic purpura	0	(0.0)	1	(0.5)	1	(0.2)
Thrombocytopenia	1	(0.3)	0	(0.0)	1	(0.2)
Cardiac disorders	**1**	**(0.3)**	**1**	**(0.5)**	**2**	**(0.4)**
Cardiac failure	1	(0.3)	0	(0.0)	1	(0.2)
Cardiogenic shock	0	(0.0)	1	(0.5)	1	(0.2)
General disorders and administration site conditions	**0**	**(0.0)**	**1**	**(0.5)**	**1**	**(0.2)**
Multiple organ dysfunction syndrome	0	(0.0)	1	(0.5)	1	(0.2)
Hepatobiliary disorders	**2**	**(0.5)**	**2**	**(1.0)**	**4**	**(0.7)**
Acute hepatic failure	1	(0.3)	0	(0.0)	1	(0.2)
Hepatic function abnormal	0	(0.0)	1	(0.5)	1	(0.2)
Venoocclusive liver disease	1	(0.3)	2	(1.0)	3	(0.5)
Immune system disorders	**5**	**(1.3)**	**3**	**(1.6)**	**8**	**(1.4)**
Graft versus host disease	5	(1.3)	3	(1.6)	8	(1.4)
Infections and infestations	**9**	**(2.4)**	**6**	**(3.1)**	**15**	**(2.7)**
Bacterial sepsis	0	(0.0)	1	(0.5)	1	(0.2)
Bronchopulmonary aspergillosis	1	(0.3)	1	(0.5)	2	(0.4)
Klebsiella sepsis	1	(0.3)	0	(0.0)	1	(0.2)
Pneumocystis jirovecii pneumonia	0	(0.0)	1	(0.5)	1	(0.2)
Pneumonia	2	(0.5)	0	(0.0)	2	(0.4)
Sepsis	3	(0.8)	1	(0.5)	4	(0.7)
Septic shock	3	(0.8)	3	(1.6)	6	(1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**18**	**(4.8)**	**5**	**(2.6)**	**23**	**(4.1)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**18**	**(4.8)**	**5**	**(2.6)**	**23**	**(4.1)**
Acute lymphocytic leukaemia	1	(0.3)	0	(0.0)	1	(0.2)
Acute lymphocytic leukaemia recurrent	2	(0.5)	0	(0.0)	2	(0.4)
Acute myeloid leukaemia	2	(0.5)	1	(0.5)	3	(0.5)
Acute myeloid leukaemia recurrent	7	(1.9)	3	(1.6)	10	(1.8)
Diffuse large B-cell lymphoma recurrent	1	(0.3)	0	(0.0)	1	(0.2)
Mantle cell lymphoma	1	(0.3)	0	(0.0)	1	(0.2)
Mycosis fungoides	1	(0.3)	0	(0.0)	1	(0.2)
Mycosis fungoides recurrent	1	(0.3)	0	(0.0)	1	(0.2)
Myelodysplastic syndrome	0	(0.0)	1	(0.5)	1	(0.2)

Natural killer-cell leukaemia	1	(0.3)	0	(0.0)	1	(0.2)
Plasma cell myeloma recurrent	1	(0.3)	0	(0.0)	1	(0.2)
Respiratory, thoracic and mediastinal disorders	**2**	**(0.5)**	**0**	**(0.0)**	**2**	**(0.4)**
Respiratory failure	2	(0.5)	0	(0.0)	2	(0.4)
Vascular disorders	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.2)**
Venoocclusive disease	1	(0.3)	0	(0.0)	1	(0.2)

Every subject 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.

Through 24 Weeks Post-transplant (ASaT Population)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Infections and infestations	**20**	**(5.4)**	**10**	**(5.2)**	**30**	**(5.3)**
Pneumonia	6	(1.6)	0	(0.0)	6	(1.1)
Pneumonia bacterial	0	(0.0)	1	(0.5)	1	(0.2)
Pneumonia staphylococcal	0	(0.0)	1	(0.5)	1	(0.2)
Pulmonary tuberculosis	0	(0.0)	1	(0.5)	1	(0.2)
Sepsis	5	(1.3)	2	(1.0)	7	(1.2)
Septic shock	4	(1.1)	3	(1.6)	7	(1.2)
Metabolism and nutrition disorders	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.2)**
Failure to thrive	1	(0.3)	0	(0.0)	1	(0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**27**	**(7.2)**	**15**	**(7.8)**	**42**	**(7.4)**
Acute lymphocytic leukaemia	1	(0.3)	0	(0.0)	1	(0.2)
Acute lymphocytic leukaemia recurrent	3	(0.8)	1	(0.5)	4	(0.7)
Acute myeloid leukaemia	2	(0.5)	3	(1.6)	5	(0.9)
Acute myeloid leukaemia recurrent	12	(3.2)	8	(4.2)	20	(3.5)
Chronic myeloid leukaemia recurrent	1	(0.3)	0	(0.0)	1	(0.2)
Diffuse large B-cell lymphoma recurrent	1	(0.3)	1	(0.5)	2	(0.4)
Mantle cell lymphoma	1	(0.3)	0	(0.0)	1	(0.2)
Mycosis fungoides	1	(0.3)	0	(0.0)	1	(0.2)
Mycosis fungoides recurrent	1	(0.3)	0	(0.0)	1	(0.2)
Myelodysplastic syndrome	0	(0.0)	2	(1.0)	2	(0.4)
Natural killer-cell leukaemia	1	(0.3)	0	(0.0)	1	(0.2)
Plasma cell myeloma recurrent	2	(0.5)	0	(0.0)	2	(0.4)
Primary myelofibrosis	1	(0.3)	0	(0.0)	1	(0.2)
Nervous system disorders	**0**	**(0.0)**	**1**	**(0.5)**	**1**	**(0.2)**
Cerebral haemorrhage	0	(0.0)	1	(0.5)	1	(0.2)
Renal and urinary disorders	**0**	**(0.0)**	**1**	**(0.5)**	**1**	**(0.2)**
Chronic kidney disease	0	(0.0)	1	(0.5)	1	(0.2)
Respiratory, thoracic and mediastinal disorders	**2**	**(0.5)**	**1**	**(0.5)**	**3**	**(0.5)**
Lung disorder	0	(0.0)	1	(0.5)	1	(0.2)
Respiratory failure	2	(0.5)	0	(0.0)	2	(0.4)
Vascular disorders	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.2)**
Venoocclusive disease	1	(0.3)	0	(0.0)	1	(0.2)

Deaths in Protocol 020 (phase 2)

The study included 98 patients treated with letermovir (3 dose levels) and 33 treated with placebo. Five patients died during the trial, whereof 4 were treatment emergent (within 7 days after last dose of study medication):

Letermovir 60 mg: 2 patients: GVHD + pneumonia day 59; AML recurrent day 109
Letermovir 120 mg: 1 patient (non-treatment emergent): Pneumonia day 104
Letermovir 240 mg: 1 patient: Pneumonia day 37
Placebo: 1 patient: Pneumonia day 24.

Areas of special interest

Incidence of and time to engraftment
In P001, engraftment was defined as documented absolute neutrophil counts ≥500/mm3 on 3 consecutive days. At the time of randomization, 63.5% of subjects in the letermovir group and 59.9% of subjects in the placebo group had not engrafted. In these patients engraftment failed in 4.6% of those randomized to letermovir, as compared to compared to 8.7% of those allocated to placebo. Similar trends were seen in subjects at increased risk for delayed engraftment (e.g., cord blood or haploidentical transplant recipients) as well as those not at such risk.

Incidence of selected opportunistic infections other than CMV
A summary of infections that would be considered opportunistic in this population was provided without any marked difference between arms, next table. As discussed in pharmacodynamics section, it is still of interest to see complied data on DNA-emia of HHV-6 and EBV, having in vitro effects in mind.

Table 47 Proportion of Subjects with Selected Opportunistic Infections Other than CMV infection Through Week 14 Post-Transplant (FAS Population)

	Letermovir (N=325)		Placebo (N=170)	
	N	% (95% CI)	N	% (95% CI)
Subjects with one or more selected opportunistic infections	57	17.5 (13.6, 22.1)	31	18.2 (12.7, 24.9)
Bacterial	**37**	**11.4 (8.1, 15.3)**	**21**	**12.4 (7.8, 18.3)**
Bacteremia	39	12.0 (8.7, 16.0)	21	12.4 (7.8, 18.3)
Pneumonia	5	1.5 (0.5, 3.6)	1	0.6 (0.0, 3.2)
Sepsis	5	1.5 (0.5, 3.6)	8	4.7 (2.1, 9.1)
Fungal	**10**	**3.1 (1.5, 5.6)**	**3**	**1.8 (0.4, 5.1)**
Aspergillosis	9	2.8 (1.3, 5.2)	2	1.2 (0.1, 4.2)
PJP Pneumonia	1	0.3 (0.0, 1.7)	1	0.6 (0.0, 3.2)
Parasitic	**0**	**0.0 (0.0, 1.1)**	**1**	**0.6 (0.0, 3.2)**
Cerebral Toxoplasmosis	0	0.0 (0.0, 1.1)	1	0.6 (0.0, 3.2)
Viral	**16**	**4.9 (2.8, 7.9)**	**11**	**6.5 (3.3, 11.3)**
Adenovirus disease	1	0.3 (0.0, 1.7)	0	0.0 (0.0, 2.1)
BK virus infection	10	3.1 (1.5, 5.6)	7	4.1 (1.7, 8.3)
EBV Meningoencephalitis	0	0.0 (0.0, 1.1)	1	0.6 (0.0, 3.2)
HHV-6 Meningoencephalitis	2	0.6 (0.1, 2.2)	0	0.0 (0.0, 2.1)
Influenza	1	0.3 (0.0, 1.7)	0	0.0 (0.0, 2.1)
Parainfluenzae Virus Infection	3	0.9 (0.2, 2.7)	0	0.0 (0.0, 2.1)
RSV infection	0	0.0 (0.0, 1.1)	3	1.8 (0.4, 5.1)

Subjects with laboratory criteria for potential drug-induced liver injury (DILI)
The traditional algorithm, i.e. AST or ALT ≥3 x ULN, total bilirubin ≥2 x ULN and, at the same time, ALP < 2 x ULN was used to screen for potential DILI cases (treatment phase).

Overall, 11 subjects met these criteria, 8 (2.1%) in the letermovir group and 3 (1.6%) in the placebo group. None was considered related according to the investigators. These conclusions are supported by the Rapporteur on the basis of short narratives, since plausible alternative causes (AEs) are found in all 11 cases (venoocclusive liver disease (2), sepsis/pneumonia (3), other therapies in patient with Gilbert (1), engraftment syndrome (1), severe heart failure (1). In those 5 in the letermovir-arm who survived surviving these AEs, liver function tests normalized with continuous letermovir therapy.

ECGs

Thorough QT study
Study P004 evaluated QT effects of single doses of iv letermovir dosed 480 mg or 960 mg (supratherapeutic), placebo or 400 mg moxifloxacin (positive control). Treatment was double-blinded with respect to letermovir, while moxifloxacin was administered open-label. The study (single center) randomized 38 healthy subjects in a 4-period, 8-sequence crossover design, with a 7 days wash-out period between treatments, and a 14 day follow-up after the last treatment. The design was in line with the ICH E14 guidance.

The upper limits of the 90% CI for the true mean difference from placebo of the both letermovir doses were <10 msec at all time points. The mean difference from placebo of moxifloxacin was 12 msec, in line with the expected. In summary, the letermovir did not show a potential for clinically relevant QT effects, including the supratherapeutic dose which yielded a 2-fold Cmax and a 2.7-fold AUC as compared to the 480 mg IV dose.

Phase 3 outcomes.
ECGs were collected at screening visit, at study Week 2 and at the EOT visit. Subjects were not excluded from the study if they had abnormal ECG findings at screening visit. Medications known to prolong QT were allowed.

There was no tendency of QTc prolongation with letermovir (treatment phase), tables next page. Similarly, no relevant differences in median PR or QRS-intervals, or beats per minute overtime were seen at these time points.

Laboratory findings

Graded lab toxicity

Descriptive statistics for protocol-specified laboratory tests were presented from baseline and Study Weeks 2, 4, and 8, end of treatment (EOT), Study Week 16, and at the last observed time point (LOTTR). This concerned Hematology, common blood chemistry, urinalyses and FSH, LH, testosterone and inhibin B levels in males (testicular toxicity seen in rats).

Overall, the frequency of graded toxicity (grade 1-4) for the hematology (Hemoglobin, White blood cell count, neutrophils) and chemistry laboratory values were comparable in the letermovir and placebo groups, with the exception of the Grade 4 ALT (6 vs 0 cases) and platelet count:

- Five out of six with ALT grade 4 had alterative explanations or had a negative re-challenge. The sixth case (ALT high around week 10) lacked such data, and here the event resolved post treatment.

- Grade 4 decrease in platelets was somewhat more frequent with letermovir than with placebo (13.5 vs 9.5%). However, the treatment phase was 25% longer for those allocated to letermovir. Further, the proportion of subjects with an "AE of decreased platelet count" during the treatment phase was similar between groups (2.9 vs 2.6 %). In addition, mean change from baseline in platelets over time does not indicate lower values during therapy with letermovir (next section). Finally, there was no tendency for worsened engraftment with letermovir, and the results in other hematology lab parameters (HB, LPK, neutrophils) were fully similar between arms. In summary, it seems unlikely that letermovir therapy per se carries a risk for thrombocytopenia.

For creatinine, changes (including the most reported, grade 3) were comparable between groups, consistent with the similar incidence of Renal Disorders AEs during the Treatment Phase.

The table below shows parameters just mentioned. In addition potassium is shown, since hyperkalemia (AE) was reported more frequently with letermovir as mentioned in previous section.

Table 48 Selected Laboratory Findings (P001, ASaT Population, Treatment Phase)

Criterion[†]	Letermovir		Placebo		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Platelet (10[3]/microL)						
Grade 1: 100 - <124.999	8/371	(2.2)	3/191	(1.6)	11/562	(2.0)
Grade 2: 50 - <100	12/371	(3.2)	11/191	(5.8)	23/562	(4.1)
Grade 3: 25 - <50	20/371	(5.4)	8/191	(4.2)	28/562	(5.0)
Grade 4: <25	50/371	(13.5)	19/191	(9.9)	69/562	(12.3)
ALT (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	42/371	(11.3)	23/191	(12.0)	65/562	(11.6)
Grade 2: 2.5 - <5.0 x ULN	14/371	(3.8)	16/191	(8.4)	30/562	(5.3)
Grade 3: 5.0 - <10.0 x ULN	7/371	(1.9)	3/191	(1.6)	10/562	(1.8)
Grade 4: ≥10.0 x ULN	6/371	(1.6)	0/191	(0.0)	6/562	(1.1)
AST (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	31/371	(8.4)	26/191	(13.6)	57/562	(10.1)
Grade 2: 2.5 - <5.0 x ULN	11/371	(3.0)	9/191	(4.7)	20/562	(3.6)
Grade 3: 5.0 - <10.0 x ULN	6/371	(1.6)	2/191	(1.0)	8/562	(1.4)
Grade 4: ≥10.0 x ULN	2/371	(0.5)	0/191	(0.0)	2/562	(0.4)
Creatinine (mg/dL)						
Grade 1: 1.1 - 1.3 x ULN	4/371	(1.1)	0/191	(0.0)	4/562	(0.7)
Grade 2: >1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above BL	43/371	(11.6)	17/191	(8.9)	60/562	(10.7)
Grade 3: >1.8 - <3.5 x ULN or Increase of 1.5 - <2.0 x BL	102/371	(27.5)	55/191	(28.8)	157/562	(27.9)
Grade 4: ≥3.5 x ULN or Increase of ≥2.0 x Baseline	75/371	(20.2)	31/191	(16.2)	106/562	(18.9)
Potassium (mmol/L)						
Grade 1: 5.6 - <6.0	4/371	(1.1)	6/191	(3.1)	10/562	(1.8)
Grade 2: 6.0 - <6.5	3/371	(0.8)	0/191	(0.0)	3/562	(0.5)
Grade 3: 6.5 - <7.0	0/371	(0.0)	1/191	(0.5)	1/562	(0.2)
Grade 4: ≥7.0	0/371	(0.0)	0/191	(0.0)	0/562	(0.0)

The prior table shows data for the treatment phase it does not capture potential toxic effects of pre-emptive therapy prior to week 14 (such patients are no longer in the treatment phase).

To better understand whether letermovir seem to result in less toxicity than does present standard procedure (which in practice includes PET given at an earlier stage), graded lab toxicity up to week 16 is of interest (discussed in a prior section). As a reminder, during that time period PET was started in around 7% of patients in the letermovir arm versus around 40% of those in the placebo arm. No relevant difference in graded lab toxicity was seen between arms during that time period.

It is noted that there was no difference between arms in graded worsening of potassium between arms, a bit odd since hyperkalemia (as AE) was more frequently reported for those treated with letermovir than with placebo (7% vs 2% of ASaT population, treatment phase). The company could not provide an explanation to this mismatch in AE reporting and reports in graded lab toxicity. Further, potassium concentrations over time were fully similar between ams. Further, it was shown that reported AEs on hyperkalemia were not linked to reports on Cardiac SOC AEs. It is concluded that there is no evidence for hyperkalemia as a letermovir drug effect.

Mean change from baseline in lab chemistry
No relevant difference in mean change from baseline was seen for pre-specified lab parameters, including paramters of particular interest (hematology, creatinine and transaminases).

Laboratory Evaluation of Testicular Function in Males

Profound and irreversible effects on testicular function were seen in rats (not in other species). Markers of testicular toxicity were therefore monitored in male subjects in the phase 3 study (Serum inhibin B, LH, FSH, and testosterone levels at baseline, EOT (max week 14), and at week 24.
No clinically relevant effects of letermovir on male sex hormones were seen. While this is the present target population, these patients may not be the most sensitive population to demonstrate a lack of effect, having in mind prior cancer treatment and frequently abnormal baseline values.
Since no mechanistic explanation on why testicular toxicity would be species specific have been provided (i.e. seen in rats but not in other species, including humans), testicular toxicity remains a concern that has to be closely monitored. Biomarkers for testicular toxicity will be studied in an ongoing/coming placebo-controlled study in renal transplant patients. Results from this study will be more informative for the issue, since those patients have not received the types of other toxic treatment used in the patients in the present study.

Safety in special populations

Renal impairment

In a phase 1 renal impairment study, a modest elevation of letermovir exposure (1.5-2 fold) was observed in subjects with moderate and severe renal impairment (eGFR ≥30 to 59 and < 30 mL/min/1.73 m2). In phase 3, a limited number of patients with renal impairment were treated with letermovir (n=6 with a eGFR <50 ml/min (MDRD equation), none with a clearance <30. A slightly higher number had a baseline clearance < 60 ml/min (letermovir-arm 32, placebo-arm 19). Out of the 32 in the letermovir-arm, only 5 received letermovir IV (highest exposure). When looking at SOC term Blood creatinine increased (treatment phase) for these 51

patients, this term was (numerically) more common in the LTV-arm, 7/32 (22%) vs 1/19 (5%). Increases were mild to moderate, and seemed to resolve without stopping letermovir. Confounding baseline parameters naturally complicates the comparison.

On the basis of this data, the company does not see a need for dose adjustment.

Hepatic impairment

The effect of hepatic impairment on letermovir pharmacokinetics was evaluated in moderate (Child-Pugh B) and severe (Child-Pugh C) hepatically impaired female subjects in a Phase 1 trial (P015). The exposure (AUC) was 1.6- and 3.8-fold higher than in healthy subjects.

In the phase 3 study, subjects with severe (Child-Pugh C) hepatic impairment or with moderate (Child-Pugh B) hepatic impairment and moderate renal impairment (creatinine clearance < 50 mL/min by Cockcroft-Gault equation) were excluded. Numbers actually treated with Child Pugh A (mild) or Child Pugh B (moderate) hepatic (but normal renal function) in phase 3 is unclear. In a subgroup analysis on the issue, the company defined hepatic impairment as AST/ and or ALT ≥3 times ULN, which certainly would not be parameters with adequate sensitivity/specificity for the task. Indeed, patients with severe hepatic impairment may have normal or just slightly raised transaminases, and patients with high transaminases may indeed have a normal hepatic function. With the use of the chosen definition, only a handful of patients were categorized as having hepatic impairment (7 in the letermovir-arm, ASaT population).

On the basis of this data, the company concludes that letermovir can be given without dose adjustment to patients other than those with severe (Child-Pugh C) hepatic impairment, or with moderate (Child-Pugh B) hepatic impairment and moderate renal impairment (i.e. the same rule as chosen for the phase 3 study).

Elderly

Of the 373 subjects treated with letermovir in the phase 3 study, 56 (15.0%) subjects were 65 years of age or older. Safety was similar across older and younger subjects.

Paediatric population

No data are available for patients below 18 years of age.

HIV and hepatitis co-infection

HIV and or hepatitis B/C co-infection was part of exclusion criteria in the phase 2 and 3 studies. Hence, there is no data on such patients. To have the combination of prior stem cell transplant and these infections would be rare. The issue for the use of letermovir in such patients would be potential drug interactions (i.e. HIV and HBV therapy). Having epidemiology in mind it does not seem reasonable to request specific DDI studies. Pharmacology expertise may be used in cases where letermovir would be considered (rather than PET).

Safety related to drug-drug interactions and other interactions

Letermovir is relatively prone to interactions, both as a perpetrator and a victim. Important drug interactions for the target population include e.g. effects of CsA on letermovir exposure (half dose to be given), substantial effects by OATP-inhibitors (contraindicated, letermovir plasma exposure increased) and lowered voriconazole exposures (inducing effect of letermovir). This is listed in the RMP.

No specific safety issues related to drug drug interactions were captured in the phase 3 study.

2.6.1. Discussion on clinical safety

In the blinded comparison of letermovir versus placebo given during maximum 14 weeks in a fair number of stem-cell transplant patients (373 vs 192) there was no obvious difference in the pattern and frequencies of AEs (in the so-called "*treatment"* phase).

It should be taken into account that these patients suffer from problems related to the prior cancer treatment, as well as the transplantation, and the assessment of AEs of an antiviral against such a background is naturally a challenge. A somewhat lower mortality (around 5% lower at weeks 24 and 48) in patients who received letermovir was noted in the study. The difference versus placebo was driven by a lower rate in non-relapse mortality, and further by patients who *did* reactivate the CMV infection. As discussed in the efficacy section, the mortality rate was around twice as high in patients who did reactivate CMV-infection during treatment with placebo, as compared to the rate in those who reactivated CMV as a "breakthrough" during therapy with letermovir, for whom the mortality rate was similar to that seen in those who did not reactive the CMV-infection at all. The finding is in line with what has been shown in several studies, namely, that early reactivation of CMV (where day 100 has been claimed to be a cut-off) is associated with a higher mortality in HSCT recipients, and where letermovir prophylaxis may lower the risks associated with CMV reactivation, by deferring this event to a later time point. However, data are not sufficiently strong to claim this effect.

None of the AEs leading to death were considered related to therapy by the investigators (either arm).

For other issues of particular interest such as failure to engraft the transplant and incidence/severity of GVHD there was no tendency for higher frequencies in those treated with letermovir. The incidence of infections other than CMV, a main problem for this treatment population, did not seem to be affected. Among common AEs mild to moderate GI side effects were somewhat more common during therapy with letermovir (treatment phase).

Cardiac events, mainly rhythm disturbances (atrial fibrillation, flutter and tachycardia) were seen more frequently during therapy with letermovir than with placebo. This was driven by patients with a prior cardiac history. In these patients such AEs were reported 3 times more frequent during therapy with letermovir (difference not significant in the total population). The events were not reported as serious. A time to event analysis was presented, where it was shown that the numerical difference in the frequency of these AEs occurred during the first 2 weeks or so, followed by a parallel incidence with letermovir and placebo. A thorough analysis on any link to certain cardiac medications was undertaken, without any such finding, ruling out unexplained drug drug interactions as a potential cause of the finding. . No cardiac signals were seen in pre-clinical studies, and no relevant QT effects were seen in a thorough QT study and the events were not related to letermovir exposures (i.e. not higher in patients with events as compared to those without). . Following these further analyses it was concluded that there was no suggestive evidence for letermovir as a cause of cardiac AE, and that no specific warnings or recommendations are needed in the SmPC.

A trend for a higher frequency of headache and insomnia was also noted, where the evidence for causality to letermovir is somewhat weak, having the disease state of these patients in mind. The signal was weakened in an exposure-adjusted analysis, and a difference was only seen during early visits. In summary, at present there are no signs of problematic CNS side effects.

There were no obvious findings in graded toxicity in lab chemistry.

When looking at all AEs and graded lab toxicity *through study week 16*, there were still no relevant difference between arms. During this time period PET was initiated in around 7% of those allocated to letermovir and in around 40% of those in the placebo arm. The lack of differences between arms, both during treatment phase and during weeks 0-16, implies that PET with available CMV agents (i.e. standard of care) in fact is well tolerated.

2.6.2. Conclusions on the clinical safety

The safety profile of letermovir is considered acceptable. No relevant difference in AEs or graded lab toxicity was seen during treatment with letermovir and placebo (i.e. treatment phase). However, the same is true when looking at weeks 0-16, where PET was initiated in around 7% vs 40% of patients. Hence, according to the data presented, the safety profile of letermovir prophylaxis per se seems similar to that of present standard of care (i.e. PET with available agents).

2.7. Risk Management Plan

Safety concerns

Important identified risks	Pharmacokinetic Drug Interactions (effects on drug transporters and several CYP enzymes)
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Study (Type and Study Number)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date of submission of final study report
Drug interaction study of the effect of SD/MD rifampicin on letermovir (category 3)	To evaluate effects of induction and OATP inhibition by rifampicin on letermovir	Potential risk of pharmacokinetic drug interaction via induction potentially resulting in decreased concentration of letermovir or OATP inhibition leading to increased letermovir concentrations	Planned	31 December 2019
Drug interaction study of the effect of a strong P-gp/BCRP inhibitor on letermovir *(category 3)*	To evaluate the potential effect of P-gp/BCRP inhibition on letermovir concentrations	Potential risk of pharmacokinetic drug interaction via P-gp/BCRP inhibition potentially resulting in increased letermovir concentrations	Planned	31 March 2020

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risk: Pharmacokinetic Drug Interactions (effects on drug transporters and several CYP enzymes)	**Listed under SmPC:** 4.3 Contraindications 4.4 Special Warnings and Precautions for Use 4.5 Interaction with other medicinal products and other forms of Interaction 5.2 Pharmacokinetic properties **Package Leaflet:** 2. What you need to know before you use **PREVYMIS** Do not use PREVYMIS Warnings and precautions Other medicines and PREVYMIS	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.6 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 1 November 2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of letermovir with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers letermovir to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

2.10.2. Labelling exemptions

A request of translation exemption of the blister foil label as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The company estimates a very small number of patients affected in the EU (20 to 25 patients per 1 million). The rest of the labelling components, including the PL, will be provided in the national languages of the MSs concerned.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

A request of translation exemption of the vial label as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found unacceptable by the QRD Group for the following reasons:

The request for the English vial label was rejected because the dilution steps were considered too critical for the safe administration of the product.

A request to omit certain particulars from the 30 ml vial label (minimum particulars) as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

To enable the launch of the intravenous product in two different doses for an extremely low number of patients and also to provide it to patients beyond the Western Europe, the company is developing multilingual labels for the immediate packaging. However, showing the full set of particulars in this vial label profile would heavily impair the readability of the provided information to healthcare professionals, in particular in the case of multilingual artworks.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Prevymis (letermovir) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant is seeking an indication for the" prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT)".

Cytomegalovirus is ubiquitous and generally acquired early in life, with the majority of the adult population being CMV-seropositive in most countries worldwide. Allogeneic hematopoietic stem cell transplant (HSCT) recipients are immune-compromised, which increases the risk for CMV infection, mostly due to reactivation of latent CMV infection. Hematopoietic stem cell transplant recipients with prior CMV infection (R+) are at highest risk for developing CMV reactivation and disease, especially during the first 100 days post-transplant.

3.1.2. Available therapies and unmet medical need

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

1. prophylaxis with antivirals
2. pre-emptive therapy (PET), the practice of active surveillance for viral replication and initiating treatment with anti-CMV agents when CMV viremia is detected.

The most widely used agents ganciclovir (GCV) and valganciclovir (VGCV) are more effective than acyclovir and its prodrug valaciclovir. However, GCV/VGCV is associated with myelotoxicity, which is particularly problematic in the post-HSCT setting. Due to the concerns of the toxicities associated with anti-CMV agents, PET is currently the preferred preventive approach in the majority of centres worldwide, especially during the first 100 days post-transplant. Consequently, patients need to be monitored for CMV-DNA very frequently, a burden both to patients and prescribers. In fact, CMV reactivation will, over time, in practice occur in all these patients, but is less clinically relevant at later time points. However, CMV viremia is associated with an increased risk of overall mortality even after adjustment for PET.

Considering the challenges for PET as well as the toxicities associated with current anti-CMV agents, there is a role for an effective and well-tolerated antiviral agent for the prevention of CMV reactivation and disease in allogeneic HSCT recipients.

3.1.3. Main clinical studies

Letermovir is a new anti-CMV medicine with a new target, the viral DNA terminase, which plays a key role in cleavage and packaging of viral progeny DNA. CMV terminase minimally consists of a large and a small subunit that are encoded by two viral genes (UL56 and UL89): Cross-resistance to other CMV drugs is not anticipated.

P001 was a single pivotal, randomized, double-blind, placebo-controlled Phase 3 trial designed to evaluate the safety and efficacy of letermovir at a dose of 480 mg QD, adjusted to 240 mg QD when co-administered with CsA, versus placebo in adult, CMV-seropositive allogeneic HSCT recipients (R+). Treatment was administered through Week 14 (~100 days) post-transplant. Overall, 570 subjects were randomized with 376 in the letermovir group and 194 in the placebo group. This trial assessed prophylaxis with letermovir (compared to placebo) in the prevention of CMV reactivation.

3.2. Favourable effects

The primary efficacy endpoint of P001 was the incidence of “clinically significant CMV infection” through Week 24 post-transplant in the “FAS population”, that is to say patients who received therapy and had a negative CMV-DNA test in plasma on day 1 of treatment. Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV PET based on documented CMV DNA-emia.

Letermovir demonstrated superior efficacy over placebo in the analysis of the primary endpoint, with 37.5% versus 60.6% of patients in the letermovir and placebo group failing prophylaxis up to 24 weeks. The estimated treatment difference was -23.5% (95%CI: -32.5, -14.6; one-sided p-value <0.0001). The proportions with “clinically significant CMV-infection up to week 14 was 19.1% with letermovir and 50.0% with placebo; 16% versus 40% of patients in the letermovir and placebo arms initiated PET. 1.5% versus 1.8% of patients developed end-organ CMV disease. Efficacy consistently favoured letermovir across subgroups including low and high risk for CMV reactivation, conditioning regimens, and concomitant immunosuppressive regimens.

All-cause mortality was described as an exploratory endpoint without a prespecified statistical analysis plan. The proportion for all-cause mortality in the letermovir vs. placebo groups was 12.3% vs. 18.8% at Week 24 post-transplant, and 23.4% vs. 27.1% at Week 48 post-transplant. The distribution of time to all-cause mortality through Week 24 (nominal two-sided log-rank p-value=0.0401, not controlled for multiplicity) was slightly different between the letermovir and placebo groups, but the difference was not significant at Week 48 (nominal two-sided log-rank p-value=0.2117, not controlled for multiplicity).

3.3. Uncertainties and limitations about favourable effects

All analyses of mortality in this single phase 3 study are exploratory The mode of analysis was not pre-specified and there was no plan for type 1 error control. The statistical strength of evidence for this effect is weak. Therefore, there is uncertainty on the magnitude of any impact on mortality through letermovir prophylaxis rather than a standard PET approach with (val)ganciclovir

There is a relative increase in the incidence of initiation of PET in the letermovir group between weeks 14 and 24 when prophylaxis is discontinued. Furthermore, although differences are small and statistically non-significant, there is also the occurrence of a few new cases of gastrointestinal CMV disease in the letermovir group. Traditionally, in the prophylactic setting, drugs have been studied during the first 100 days post-transplant, when the risk of serious CMV infection is highest. However, it is possible that additional clinical benefit could be expected in a subset of patients, from prolonged letermovir prophylaxis beyond week 14 post-transplant. Thus there is an uncertainty whether treatment up to 100 days post-transplant is most appropriate in all cases. There is an interesting finding in the phase 3 study, which seems supportive of the limited 14 weeks treatment duration. Namely, all-cause mortality in patients treated with letermovir and who still met the primary endpoint was fully similar to the mortality in those patients (both arms) who did not reactivate CMV-infection (around 21%). In contrast, the mortality was notably higher in patients allocated to placebo and who met the primary endpoint. Although numbers are limited, these figures could be taken to be supportive for a beneficial effect of letermovir (direct and indirect) on the basis of preventing early CMV reactivation. However, it is not clear that the causes of death would be CMV-related, wherefore the interpretation of this finding is fraught with uncertainty.

Patients with pre-existing CMV viremia, regardless of level, were not included in the study. Further, patients who reactivated CMV between screening and baseline (i.e. day for start of therapy) stopped therapy and

continued with PET, and were not part of the efficacy analyses. However, such patients are not explicitly excluded in the current labelling.

In subjects failing letermovir prophylaxis where CMV DNA could be successfully sequenced (n=22), only one presented with a known resistance-associated polymorphism. In addition, a number of genetic variants that have not been associated with reduced susceptibility to letermovir were found. Baseline target gene sequencing, as well as phenotypic resistance testing at failure is not available at present, limiting the conclusions that can be drawn. Phenotypic data, which may be interpretable without paired baseline CMV-DNA samples (not readily available) will be analysed and will be submitted though a post-authorization commitment, as recommended by CHMP.

Of note, PET was initiated according to treatment guidelines, that is to say at very low CMV-DNA levels. Having the mechanism of action in mind, where letermovir blocks the CMV life cycle "downstream" DNA replication, it is in fact unclear whether the DNA-emia seen in around 20% of patients treated with letermovir actually represents true viremia. In the single phase 2 study where letermovir was given to viraemic patients it was noted that viral load decay was much slower than that seen with control therapy (ganciclovir); however, after 14 days of therapy a similar viral load decay was seen with letermovir and ganciclovir. Hence, it is uncertain to what extent letermovir prophylaxis could indeed continue without going to PET also in case of "breakthrough" CMV-DNA, and for the same reason it may be that CMV-DNA is not the optimal parameter to monitor during letermovir prophylaxis. To some extent requested phenotypic data may shed some light on this issue that would be of high interest to study in coming clinical trials.

It is presumed that an important benefit of letermovir could be a better safety profile compared to what is seen with GCV/VGCV or other medicines used for PET (the PET-sparing effect being the main documented effect). However, the way safety data was collected, with a focus on a comparison to placebo during the treatment phase, does not capture the potential toxicity associated with PET, not allowing for this potential benefit to be shown.

3.4. Unfavourable effects

The dose proposed for clinical use, i.e. 480 mg, or 240 mg when CsA is part of co-treatment, was given to 373 patients in phase 3 (14 weeks), 18 patients in study P020 (phase 2, 14 days treatment). In addition 362 phase 1 subjects received this dose, mostly as single dose. A dose higher than 480 mg qd was given to 86 subjects in phase 1, of whom 17 received such a dose for >10 days. The mean and median duration of letermovir treatment in the phase 3 study was 69 and 82 days for both formulations combined (around 2 weeks for the IV formulation).

Overall, the safety profile seems acceptable Six (1.1%) subjects experienced a serious adverse reaction through Week 24 post-transplant, with 3 (0.8%) in the letermovir group and 3 (1.6%) in the placebo group. Overall, similar proportions of subjects in each group discontinued study medication due to an adverse reaction (4.8% letermovir vs. 3.6% placebo). The most frequently reported adverse reactions that led to discontinuation of letermovir were nausea (1.6%), vomiting (0.8%), and abdominal pain (0.5%).

The most commonly reported AEs (letermovir vs. placebo) during the treatment phase were GVHD (39.1% vs. 38.5%), diarrhea (26.0% vs. 24.5%), nausea (26.5% vs. 23.4%), vomiting (18.5% vs. 13.5%), rash (20.4% vs. 21.4%), and pyrexia (20.6% vs. 22.4%).

The following AEs were more common in the letermovir arm: Cardiac Disorders: 12.6% vs. 6.3% [1.1, 11.1]; Ear and Labyrinth Disorders: 4.6% vs. 1.0% [0.5, 6.3]. Myalgia: 5.1% vs. 1.6% [0.2, 6.5]. Hyperkalemia: 7.2% vs. 2.1% [1.4, 8.6]; Dyspnea: 8.0% vs. 3.1% [0.8, 8.6]

3.5. Uncertainties and limitations about unfavourable effects

Cardiac events, mainly rhythm disturbances (atrial fibrillation, flutter, tachycardia that was supraventricular to the extent that this has been specified) were seen more frequently during therapy with letermovir than with placebo. This was driven by patients with a prior cardiac history, in whom such AEs were reported 3 times more frequent during therapy with letermovir (difference not significant in total population). The events were not reported as serious. However, no cardiac signals were seen in pre-clinical studies, and no relevant QT effects were seen in a thorough QT study and events were not exposure dependent. Furthermore, there was no impact of letermovir over placebo on vital signs. Thorough analyses of concomitant cardiac medications in patients with and without events ruled out an association to any particular cardiac medication or class of cardiac medication. In summary, the totality of evidence did not indicate that these events were caused by letermovir, and no specific actions or SmPC wordings are deemed necessary. The issue can be readdressed in future controlled studies. Similarly, the causal relation with the other AEs seen more frequently in the letermovir is unclear, as the pharmacological mechanism is not fully understood.

There is little data on safety when used in patients with r hepatic impairment or severe renal impairment.

In rat, major irreversible testicular toxicity and decreased fertility of exposed males were observed and no rat-specific mechanism for these findings has been presented. In study P001 no clinically relevant effects of letermovir on male sex hormones were seen. However, these patients may not be the most sensitive population to verify a lack of effect, having in mind prior cancer treatment, pre-transplantation conditioning and frequently abnormal baseline values. The issue is not deemed relevant in the present target population (subject to other very toxic agents) and is therefore not considered a safety concern for the present indication.

The applicant is proposing the use of sterile filtration in combination with aseptic processing instead of terminal sterilization. Further development work is required to confirm whether the latter option is feasible for this product or not. While the former method is considered sufficient to ensure a positive benefit-risk balance, with a low risk of residual contamination, the latter is the state of the art method with respect to ensuring no microbial contamination, and should be used whenever possible. In order to optimise the sterility assurance level (SAL) of the manufacturing process, the marketing authorisation holder should be requested to implement the measures outlined in the Post Approval Change Management Protocol (PACMP), which has been agreed with the CHMP, concerning development, validation and introduction of terminal sterilisation.

3.6. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Reduction of CMV DNAemia during prophylaxis	Proportion of subjects with CMV DNAemia and/or CMV end-organ disease	%	Letermovir 37.5%	Placebo 60.6%	This is a surrogate marker for efficacy.
Overall, the AE profile was similar for letermovir and placebo in the phase 3 study. Liver and kidney target organs of toxicity in pre-clinical studies. No signal for such toxicity in humans with the dose studied.					
Cardiac events	Mainly tachy arrhythmias (atrial fibrillation/flutter, tachycardia)	Reported in 12.6% vs 6.3%			Difference in frequency fully driven by subjects with prior cardiac history (events reported in 21.4 vs 6.1%). Causality unclear. No overall effects on vital signs and no QT-effects seen.
Ear and labyrinth disorders		Reported in 4.1 vs 1.0%			Mild, causality unclear. Summing up individual SOC terms not supportive of causality.
Myalgia		Reported in 5.1 vs 1.6%			Causality unclear. Frequencies of similar individual SOC terms not supportive of causality. CK graded toxicity similar between arms.
Headache		Reported in 9.1 vs 5.2%.			Differences not statistically significant in safety analysis.
Insomnia		Reported in 9.1 vs 5.2%			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

CMV reactivation and, potentially, subsequent end-organ disease, is an important complication post HSCT. In the early days of transplantation, death due to CMV infection was a very considerable risk, which was subsequently reduced due to the introduction of prophylaxis, PET and treatment of CMV disease, using various agents. The most used agent in this setting is GCV/VGCV; however, due to myelotoxicity this use is somewhat complicated, prompting the routine use of PET rather than prophylaxis post HSCT. Apart from toxicity, the present use of PET also calls for frequent monitoring of CMV-DNA; a robust prophylaxis could

lessen the need for this burden. As long as it is unclear to what extent CMV-DNA breakthrough during letermovir prophylaxis is clinically relevant (i.e represents true viremia), this activity would have to be maintained also during letermovir prophylaxis.

Efficacy has been shown for letermovir as prophylaxis against CMV-DNAemia post HSCT. The incidence of CMV end-organ disease was similarly low in both arms. The side effect profile of letermovir appears overall not distinctly different from placebo, and thus favourable within the relatively complex treatment context. The safety profile, with due respect to uncertainties, is the key benefit that has been shown.

With regard to the interesting finding from an exploratory analysis according to which it appears that there is a trend towards lower mortality at week 24 (which is attenuated at week 48), CHMP agreed that this finding, from a single pivotal trial, is considered weak from the statistical point of view and is not explained by a direct impact on CMV- or ganciclovir-related mortality. CHMP therefore did not agree to introduce this information in section 5.1. of the SmPC, as the applicant had proposed.

3.7.2. Balance of benefits and risks

The benefits shown with letermovir outweigh the risks. The benefit-risk balance of Prevymis in the claimed indication is positive.

3.8. Conclusions

The overall benefit-risk of Prevymis is positive for the claimed indication.

4. Recommendations

Outcome

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

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

The 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.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to optimise the sterility assurance level (SAL) of the manufacturing process, the marketing authorisation holder should implement the measures outlined in the Post Approval Change Management Protocol (PACMP) agreed with the CHMP concerning development, validation and introduction of terminal sterilisation.	31 August 2018 (PACMP Step 1)

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that letermovir is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.