15 September 2022
EMA/792160/2022
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Livtencity

International non-proprietary name: maribavir

Procedure No. EMEA/H/C/005787/0000

## Note

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

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# List of abbreviations

| | |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| β-HCG | beta-human chorionic gonadotropin |
| BCS | Biopharmaceutics Classification System |
| BE | bioequivalence |
| BID | twice daily |
| BLQ | below the lower limit of quantification |
| CI | confidence interval |
| CHMP | Committee for Medicinal Products for Human use |
| CMH | Cochran-Mantel-Haenszel |
| $C_{min}$ | predose maribavir concentration |
| CMA | critical material attributes |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| COVID-19 | coronavirus disease 2019 |
| CPP | critical process parameter |
| CRO | contract research organisation |
| CQA | critical quality attribute |
| CSR | clinical study report |
| CTCAE | common terminology criteria for adverse events |
| CV | coefficient of variation |
| DMC | data monitoring committee |
| DNA | deoxyribonucleic acid |
| DoE | design of experiments |
| DSC | differential scanning calorimetry |
| EAC | Endpoint Adjudication Committee |
| EC | European Commission |
| $EC_{50}$ | concentration that gives half maximal response |

| | |
|---|---|
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eDiary | electronic diary |
| eGFR | estimated glomerular filtration rate |
| EOS | end of study |
| EOT | end of treatment |
| EQ-5D-5L | EuroQoL Group 5-Dimension 5-Level |
| FT-IR | Fourrier transform infrared spectroscopy |
| GC | gas chromatography |
| GC-FID | gas chromatography with flame ionisation detection |
| GCP | good clinical practice |
| GERD | gastroesophageal reflux disease |
| GGT | gamma-glutamyltransferase |
| GI | gastrointestinal |
| GVHD | graft-versus-host disease |
| GMP | good manufacturing practice |
| HCV | hepatitis C virus |
| HDPE | high density polyethylene |
| HIV | human immunodeficiency virus |
| HPLC | high performance liquid chromatography |
| HPLC-UV | High-performance liquid chromatography-Ultraviolet |
| HPLC-PDA | High-performance liquid chromatography/photodiode array |
| HRQoL | health-related quality of life |
| HSCT | haematopoietic stem cell transplant |
| HSV | herpes simplex virus |
| IAT | investigator-assigned anti-CMV treatment |
| IB | investigator brochure |
| ICH | International Council for Harmonisation |
| IEC | independent ethics committee |
| IRB | institutional review board |
| IRT | interactive response technology |
| IV | intravenous(ly) |
| LDPE | l density polyethylene |

| | |
|---|---|
| KPS | Karnofsky performance status |
| LC-MS/MS | liquid chromatography tandem mass spectrometry |
| LLOQ | lower limit of quantification |
| LOCF | last-observation-carried-forward |
| MDRD | modification of diet in renal disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MO | major objection |
| MRS | maribavir resistance set |
| MS | mass spectrometry |
| NCI | National Cancer Institute |
| NMR | nuclear magnetic resonance |
| OR | odds ratio |
| OVAT | one-factor-at-a-time |
| PAR | proven acceptable range |
| PCR | polymerase chain reaction |
| PCS | potentially clinically significant |
| PD | pharmacodynamic(s) |
| P-gp | P-glycoprotein |
| Ph. Eur. | European Pharmacopoeia |
| PK | pharmacokinetic(s) |
| PI | principal investigator |
| PP | per-protocol |
| PPQ | process performance qualification |
| PRO | patient-reported outcomes |
| PRS | primary resistance set |
| PSD | particle-size distribution |
| q12h | every 12 hours |
| qPCR | quantitative polymerase chain reaction |
| QbD | quality by design |
| QTc | corrected QT interval |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| QTTP | quality target product profile |
| RAP | resistance analysis plan |

| | |
|---|---|
| RAS | resistance-associated amino acid substitution |
| RBC | red blood cell |
| REC | recommendation |
| RH | relative humidity |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SDV | source document verification |
| SF-36v2 | short form-36 version 2 |
| SOC | system organ class |
| SOT | solid organ transplant |
| TdP | torsade de pointes |
| TAMC | total aerobic microbial count |
| TEAE | treatment-emergent adverse event |
| TGA | thermo-gravimetric analysis |
| TYMC | total combined yeasts/moulds count |
| UL27 | CMV UL27 gene |
| UL54 | CMV UL54 gene |
| UL97 | CMV UL97 gene |
| ULN | upper limit of normal |
| US | United States |
| USP | United States Pharmacopoeia |
| UV | ultraviolet |
| VAS | visual analogue scale |
| XR(P)D | X-ray (powder) diffraction |
| WBC | white blood cell |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Shire Pharmaceuticals Ireland Limited submitted on 31 May 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Livtencity, 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 15 October 2020.

Livtencity was designated as an orphan medicinal product EU/3/07/519 on 18 December 2007 in the following condition: Prevention of cytomegalovirus (CMV) disease in patients with impaired cell mediated immunity deemed at risk.

Livtencity was designated as an orphan medicinal product EU/3/13/1133 on 7 June 2013 in the following condition: Treatment of cytomegalovirus disease in patients with impaired cell mediated immunity.

The applicant applied for the following indication:

*Treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease who are resistant and/or refractory to one or more prior therapy including ganciclovir, valganciclovir, cidofovir or foscarnet.*

With their response to Day 120 List of Questions, the MAA was transferred to Takeda Pharmaceuticals International AG Ireland Branch.

## *1.2. Legal basis, dossier content*

**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 test(s) or study(ies).

## *1.3. Information on Paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0335/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0335/2020 was not yet completed as some measures were deferred.

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. Similarity

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

## *1.5. Applicant's request(s) for consideration*

### 1.5.1. Accelerated assessment

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

### 1.5.2. New active Substance status

The applicant requested the active substance maribavir 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.

## *1.6. Protocol assistance*

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

| **Date** | **Reference** | **SAWP co-ordinators** |
|---|---|---|
| 21 January 2010 | EMEA/H/SA/1193/2/2009/III | *Thomas Lang, Mira Pavlovic* |
| 9 April 2014 | EMEA/H/SA/1193/3/2014/PA/III | *Walter Janssens, Mair Powell, Brigitte Blöchl-Daum* |
| 25 September 2014 | EMEA/H/SA/1193/3/2014/PA/III | *Walter Janssens, Mair Powell, Brigitte Blöchl-Daum* |
| 28 January 2016 | EMEA/H/SA/1193/3/FU/2015/PA/II | *Mair Powell, Kerstin Wickström, Armando Magrelli* |
| 14 September 2017 | EMEA/H/SA/1193/4/2017/PA/I | *Christian Gartner, Odoardo Olimpieri* |

The protocol assistance pertained to the following *quality, non-clinical, and clinical* aspects:

- *API starting materials*
- *Non-clinical safety studies*
- *Dose regimen selection*
- *Inclusion of adolescents in clinical studies*
- *Design of phase 2 and phase 3 studies*
- *Patient population and definition of resistant and refractory populations*
- *Primary and secondary endpoints for phase 2 and Phase 3 studies*
- *Safety database to support approval*
- *Indication statement*
- *In vitro and in vivo virological evaluations for maribavir*

- *Design of the newly proposed phase 3 study in resistant/refractory CMV population [SHP620 303]*
- *Long-term FU extension study*
- *Agreement with the proposed evidence base to support conditional marketing authorisation and for conversion to full MA*
- *Evidence base to maintain the orphan designation*

## *1.7. Steps taken for the assessment of the product*

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

Rapporteur: Janet Koenig Co-Rapporteur: Filip Josephson

| | |
|---|---|
| The application was received by the EMA on | 31 May 2021 |
| The procedure started on | 17 June 2021 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 6 September 2021 |
| The CHMP Co-Rapporteur's Critique was circulated to all CHMP and PRAC members on | 20 September 2021 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 16 September 2021 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 14 October 2021 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 16 February 2022 |
| A GCP inspection at two investigator sites (one in Belgium and one in Germany) and at the sponsor site in the US between 22/11/2021 and 28/01/2022. The outcome of the inspection carried out was issued on | 17 March 2022 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on | 28 March 2022 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 07 April 2022 |
| The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on | 22 April 2022 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 20 May 2022 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 9 June 2022 |

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|---|---|
| The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on | 21 June 2022 |
| The CHMP agreed on a second list of outstanding issues to be sent to the applicant on | 23 June 2022 |
| The applicant submitted the responses to the CHMP second List of Outstanding Issues on | 15 August 2022 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP and PRAC members on | 30 August 2022 |
| 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 Livtencity on | 15 September 2022 |
| The CHMP adopted a report on similarity of Livtencity with Prevymis on (see Appendix on similarity) | 15 September 2022 |
| Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS) | 15 September 2022 |

# 2. Scientific discussion

## *2.1. Problem statement*

Drug-resistance to currently available anti-CMV agents such as ganciclovir, foscarnet and cidofovir is an emerging problem which may lead to graft loss and even be fatal for some transplant patients due to limited treatment options. Moreover, there are severe treatment-limiting toxicities with existing agents. Thus, there is an unmet medical need for CMV therapies with substantial benefit (e.g. in regard to efficacy, including lack of relevant cross-resistance and/or safety profile) over current therapeutic options in transplant patients.

### 2.1.1. Disease or condition

Human Cytomegalovirus (CMV), also known as human herpes virus 5, is a double-stranded DNA virus in the herpesvirus family. Human cytomegalovirus (CMV) infection is common, with serologic evidence of prior infection in 40% to 100% of various adult populations, and mostly acquired early in life. Primary CMV infection may be asymptomatic or manifest as self-limited febrile illness in immunocompetent individuals. However, serious HCMV disease occurs almost exclusively in individuals with compromised or immature immune systems, including transplant recipients, patients with acquired immunodeficiency syndrome (AIDS), immunosuppressed cancer patients, and neonates. Disease manifestations include retinitis, colitis, esophagitis, pneumonia, hepatitis, and meningoencephalitis.

As with other herpesviruses, CMV can persist as a latent virus after primary infection. Among individuals with intact immune system, reactivation of CMV infection is uncommon and generally asymptomatic. However, CMV reactivation in immunocompromised patients including solid organ

transplant (SOT) recipients and haematopoietic stem cell transplant (HSCT) recipients is associated with serious disease and increased mortality risk.

Uncontrolled CMV replication leads to dissemination to multiple organs and end-organ diseases such as pneumonitis, retinitis or hepatitis. Moreover, CMV infection is associated with indirect effects including increased risk of secondary bacterial or fungal infections or graft-versus-host disease in HSCT recipients or allograft loss in SOT recipients.

Development of antiviral resistance to currently available anti-CMV agents is a clinical challenge in SOT and HSCT recipients, leading to graft loss, and even death in some patients.

The initially proposed indication was as follows:

"Treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease who are resistant and/or refractory to one or more prior therapy, including ganciclovir, valganciclovir, cidofovir or foscarnet."

Thus, the indication pertains to SOT and HSCT recipients who have a detectable CMV viral load (CMV viraemia) with (CMV syndrome or CMV end-organ disease) or without (CMV infection) accompanied symptoms and who are genotypically resistant to available anti-CMV drugs.

### 2.1.2. Epidemiology

CMV is globally disseminated. Human cytomegalovirus (CMV) infection is common, with serologic evidence of prior infection in 40% to 100% of various adult populations. For the general population a global CMV seroprevalence of 83% and for Europe a CMV seroprevalence of 66% were recently estimated (Zuhair et al., 2019).

CMV infection in transplant recipients can result either from the transmission of CMV from donor tissue or from reactivation of a latent CMV infection in the transplant recipient. The risk of CMV infection is influenced by a number of factors, such as the CMV serostatus of the donor and recipient, the transplant types (SOT or HCST), the type of SOT organ transplanted, the net state of the host immunosuppression, and viral factors. Despite CMV prevention strategies (prophylaxis or preemptive therapy) in high-risk transplant populations, clinically significant CMV infection occurs in up to 35% of transplant patients (Boeckh et al., 2003; Legendre and Pascual, 2008). In the absence of prophylaxis or pre-emptive therapy the rate of CMV infection occurs in up to 40-80% (Ljungmann et al., 2011; Takenaka et al, 2015).

Post-transplant CMV infection is associated with substantial morbidity, a higher mortality risk, and increased cost of care compared to transplant recipients who do not develop post-transplant CMV infection (Biron, 2006; Falagas et al., 1998; San Juan et al., 2008; Yoo et al., 2011). Both directly and indirectly, CMV infection is the leading viral cause of morbidity and mortality among solid organ transplant (SOT) recipients (Biron, 2006). Untreated CMV pneumonia, for example, has a mortality rate of >50% among haematopoietic stem cell transplant (HSCT) recipients (Boeckh et al., 1996; Konoplev et al., 2001).

Development of antiviral resistance to currently available anti-CMV agents is a clinical challenge in SOT and HSCT recipients, leading to graft loss, and even death in some patients. Ganciclovir resistance developed in 7% donor-positive/recipient-negative kidney, liver, and pancreas recipients who were prophylaxed with approximately 3 months of oral GCV (Limaye et al., 2000). GCV-resistant disease accounted for 20% of CMV disease, occurred late (a median of 10 months after transplantation), was associated with higher intensity of immunosuppression, and was considered a clinically serious concern

(Avery, 2007). Ganciclovir resistant CMV infections were shown to be associated with a longer hospitalisation, serious toxicities from other treatments and increased mortality (Limaye et al., 2002)

Furthermore, refractory CMV infection, defined as detection of CMV for 2 or more weeks despite anti-CMV treatment, developed in 50% of HSCT recipients receiving standard anti-CMV therapy. Refractory CMV infection occurring within the first 100 days after HSCT was associated with increased risk of CMV organ disease and treatment-related mortality (Liu et al., 2015).

### 2.1.3. Biologic features

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

### 2.1.4. Clinical presentation, diagnosis and prognosis

CMV infection is defined as virus isolation or detection of viral proteins or nucleic acid in any body fluid or tissue specimen regardless of symptomatology whereas CMV disease is accompanied by clinical signs or symptoms. The clinical manifestations range from viraemia to CMV syndrome (fevers, malaise) to invasive disease (e.g. pneumonitis, colitis, pneumonitis, retinitis, hepatitis, esophagitis and menigoencephalitis). CMV disease typically occurs between Day 30 and Day 100 post-transplant (de la Hoz et al., 2002). The indirect effects of CMV comprise opportunistic infections, an association between CMV and graft dysfunction and failure, acute rejection and reduced patient survival.

There are two main methods used to diagnose CMV infection: the pp65 antigenaemia assay and real-time PCR. The latter can be used for early detection of viral replication. The 1st WHO International Standard for Human Cytomegalovirus for Nucleic Acid Amplification Techniques (CMV WHO IS; NIBSC) can be used to unify the reporting of CMV viral loads. For proven CMV end-organ disease the presence of characteristic clinical symptoms and/or signs are required together with documentation of CMV in tissue from the relevant organ e.g. by histopathology, virus isolation, rapid culture, immunohistochemistry, or DNA hybridisation (Ljungman et al., 2017).

### 2.1.5. Management

Management of post-transplant CMV infection focuses on preventing disease progression and development of complications during the period of immunosuppression by reducing CMV viraemia to undetectable levels. The current standard of care involves empiric use of available anti-CMV agents such as ganciclovir, valganciclovir, foscarnet, and cidofovir. However, with the exception of ganciclovir (indicated for the treatment of cytomegalovirus (CMV) in adults and adolescents ≥ 12 years of age), none of these agents is authorised for treatment of CMV disease in transplant patients in the EU. The total exposure and duration of use of these agents, relative to the period in which a transplant recipient is immunosuppressed and therefore at risk of breakthrough CMV infection/reactivation, could be limited in some patients due to their respective toxicities: bone marrow suppression caused by ganciclovir/valganciclovir and renal impairment caused by foscarnet or cidofovir (Boeckh et al., 2003;

Ljungman et al., 2001; Reusser et al., 2002; Salzberger et al., 1997). These toxicities are of particular concern in transplant patients, in whom the bone marrow has been ablated or significantly suppressed (HSCT patients), who continue to receive immunosuppressants to prevent organ rejection (SOT patients), who develop graft vs host disease (GVHD) (in HSCT patients), or patients who may require the use of other therapies that are potentially toxic to the kidneys or other organs (SOT and HSCT patients). The shared mechanism of action (i.e., inhibition of viral DNA polymerase activity encoded by gene locus UL54) among these agents also makes them susceptible to the development of cross-resistance (Avery, 2007; Limaye et al., 2000). The development of resistance to existing anti-CMV agents may be overcome or reduced (by increasing the dose [e.g., val/ganciclovir], decreasing immunosuppression, combining, or switching among the available antiviral drugs), and toxicity may be ameliorated (by administering growth factors to combat haematotoxicity or lowering the dose to minimise renal toxicity), some patients exhaust treatment options and ultimately lose their graft or die as a result of CMV infection or disease (Zafrani L. et al., 2009; Razonable, 2010). In addition, the trade-off of immunosuppression reduction as a therapeutic strategy for CMV infection in the setting of toxicity or the lack of efficacy of current anti-CMV agents, is the risk of organ rejection with fatal consequences for the patient.

## *2.2. About the product*

The current application concerns an antiviral film-coated tablet for oral administration of maribavir, an inhibitor of the human cytomegalovirus (HCMV) protein kinase UL97.

Maribavir is a benzimidazole riboside that inhibits HCMV replication. Maribavir antiviral activity is mediated by competitive inhibition of the HCMV protein kinase UL97 at the adenosine triphosphate (ATP) binding site, abolishing phosphotransferase, thereby interfering with viral DNA replication, encapsidation, and nuclear egress.

The following indication and posology are proposed (D0):

"Treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease who are resistant and/or refractory to one or more prior therapy, including ganciclovir, valganciclovir, cidofovir or foscarnet."

The recommended dose of maribavir is 400 mg (two 200mg tablets) with or without food twice daily resulting in a daily dose of 800mg.

## *2.3. Type of application and aspects on development*

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the strength of evidence that was presented which was not considered strong enough to support an accelerated assessment procedure. While it was considered that maribavir may turn out as a therapeutic advantage compared to available treatments, with improvements in both efficacy and safety, the claimed effects were not duly substantiated, i.e. it remained unclear, if maribavir resistant strains remain sensitive to other antivirals. The presented studies supporting the Applicant´s claims on efficacy and safety carried apparent methodological limitations, which cannot be overcome by the observed therapeutic effects.

The clinical development plan did not follow the CHMP advice concerning the statistical analysis of the primary efficacy endpoint and suffer from additional severe limitations due to the open-label study design of the single pivotal trial. Of the two supportive phase 2 studies brought forward by the Applicant, one lacks a control arm and the other does not cover the target population. The sustainability of viral clearance beyond week 8 remained unclear. Further, important data on

recurrence of CMV infection, all-cause mortality and development of resistance that could contribute to the strength of evidence were not provided. The commercial tablet formulation used in the pivotal clinical study is not identical to the formulation used in phase 2. These limitations were considered to potentially severely impact the study results. Hence, CHMP concluded that based on the currently available strength of evidence, an accelerated assessment of the medicinal product was not warranted.

## *2.4. Quality aspects*

### 2.4.1. Introduction

The finished product is presented as film-coated tablets containing 200 mg of maribavir as an active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose (E460(i)), sodium starch glycolate, magnesium stearate (E470b)

Film-coat: poly(vinyl alcohol) (E1203), macrogol (polyethylene glycol) (E1521), titanium dioxide (E171), talc (E553b), brilliant blue FCF aluminium lake (E133).

The product is available in high-density polyethylene (HDPE) bottles with child-resistant closure as described in section 6.5 of the SmPC.

### 2.4.2. Active Substance

#### *2.4.2.1. General information*

The chemical name of maribavir is 5,6-Dichloro-2-(isopropylamino)-1-β-L-ribofuranosyl-1H-benzimidazole, corresponding to the molecular formula C15H19Cl2N3O4. It has a molecular mass of 376.24 g/mol and the following structure:

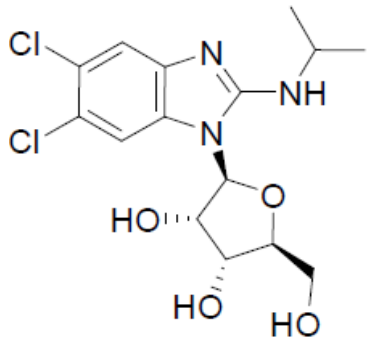



Figure 1: active substance structure

The chemical structure of maribavir was elucidated by a combination of nuclear magnetic resonance spectroscopy ($^{1}$H NMR, $^{13}$C NMR), mass spectrometry (MS), Fourier-transform infrared spectroscopy (FT-IR), UV-VIS spectroscopy, elemental analysis, and single crystal X-ray crystallography. The solid state properties of the active substance were measured by thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and dynamic vapour sorption (DVS).

Maribavir contains four chiral centres within the L-ribofuranosyl ring and shows polymorphism.

#### *2.4.2.2. Manufacture, characterisation and process controls*

Maribavir is synthesised in 4 main steps using well defined starting materials with acceptable specifications.

During the procedure, two major objections (MO1 and MO2) were raised in relation to acceptability of the starting materials. All the concerns related to the MO1 and MO2 were satisfactorily resolved, the applicant has provided sufficiently detailed justification for choice of the starting materials and applied adequate and suitable controls to ensure the routine quality. The starting materials are considered justified according to ICH Q11 guideline. Nevertheless, the CHMP recommended and the applicant agreed (REC 1-4):

1. to conduct further experimental investigations for further support of an impurity limit in a starting material, and to update a dossier section with method validation of the purity method.
2. to include derivatives of impurities in the specification of a starting material as specified impurities
3. to further evaluate the suitability of the purity method for a starting material related to an impurity and derivative
4. to re-evaluate the acceptance criterion for single unknown impurities in the specification of an intermediate when additional number of batches have been manufactured

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. A major objection (MO 3) was raised during the procedure requesting the applicant to provide a discussion on origin, levels, and carry-over of the impurity. The major objection was resolved, as the applicant provided additional clarification and justification.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. The manufacturing process has undergone several modifications. A sufficiently detailed description of the development of the manufacturing process is presented. 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 manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment, design of experiment (DOE) and one variable at a time (OVAT) studies. Based on these studies, proven acceptable ranges (PAR) have been defined for the manufacturing process of the active substance. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. Critical process parameters (CPP), critical in-process controls, and critical material attributes (CMA) for the manufacturing process of the active substance necessary to ensure consistent quality were identified based on a quality risk assessment. The related critical quality attributes (CQA) of the active substance are listed under the section Specification. Appropriate controls have been established to ensure the routine production of the active substance with consistent quality.

The active substance package complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

#### *2.4.2.3. Specification*

The active substance specification includes tests for description, identification, solid form, assay, related substances, sulphated ash, residual solvents, water content, particle size and microbial limits tests.

The active substance specifications are based on the active substance CQA, Parameters included in the specification cover all the critical aspects for ensuring the quality of the active substance. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. An assessment of potential genotoxic impurities has been performed in conformance with ICH M7.

PSD data were adequately presented and justified, however the applicant is recommended to finalise the PSD testing through the active substance shelf life (REC 5). 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 from three production-scale batches manufactured with a synthetic route equivalent to the commercial route of synthesis (PPQ batches) were provided. The results are within the specifications and consistent from batch to batch. Additionally, representative number of batches used in clinical studies and as stability batches were provided as supportive data.

#### *2.4.2.4. Stability*

Stability data from three primary production-scale batches of active substance from the proposed manufacturer stored in the intended commercial package in a container closure system representative of that intended for the market under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Additional supportive stability data were provided.

All tested parameters were within the specifications, no significant changes were observed for any parameter. Photostability testing following the ICH guideline Q1B was performed. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable.

### 2.4.3. Finished Medicinal Product

#### *2.4.3.1. Description of the product and pharmaceutical development*

The finished product is an immediate release tablet including 200 mg maribavir for oral administration. Maribavir 200 mg is a blue, film-coated, oval-shaped, convex tablet that is de-bossed with 'SHP' on one side and '620' on the other side.

Pharmaceutical development of the finished product contains QbD elements. The quality target product profile (QTPP) was defined as an immediate release dosage form that meets compendial and other relevant quality standards.

The manufacturing development has been evaluated through the use of criticality analysis to identify the CQA and the CPP of the finished product. Material attributes and process parameters were reviewed and classified as potentially critical or non-critical based on their potential to impact finished product CQA. The formulation development is sufficiently described.

Major objections (MO4 – MO6) were raised regarding the dissolution comparability and batch to batch consistency. Based on the additional submitted data and provided justification, the CHMP considered that it has been sufficiently proven that the differences in dissolution profiles between the commercial and relevant pivotal clinical batches are not clinically relevant. The MOs related to dissolution comparability were resolved, the commercial and clinical batches are considered comparable. The choice of the dissolution method has been justified.

The discriminatory power of the dissolution method has been demonstrated. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. For the non-compendial excipient, an adequate in-house specification is given. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report. The compatibility of the active substance and the excipients was sufficiently investigated. No overages are used in the formulation of maribavir 200 mg tablet.

The primary packaging is high-density polyethylene (HDPE) bottle with child resistant cap. The material complies with Ph. Eur. and EC requirements. The child resistant closure test results comply with 16 CFR 1700.20, which has been shown to be equivalent to ISO 8317:2015 requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

### *2.4.3.2. Manufacture of the product and process controls*

The manufacturing process consists of following steps: blending, sifting, lubrication, compression and coating.

Process validation data for three consecutive production batches (PPQ batches) manufactured by the current manufacturer using the proposed commercial manufacturing process were provided showing compliance with in-process controls, proven acceptable ranges and the release specification. The in-process and batch characterisation data of the three PPQ batches were consistent to each other. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner and that the in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Proven acceptable ranges (PAR) have been defined. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

### *2.4.3.3. Product specification*

The finished product release and shelf-life specifications shown include appropriate tests for this kind of dosage form including description, identification, assay, uniformity of dosage units, related substances, dissolution and microbiological examination.

The finished product specifications are in line with ICH Q6A. Limits for impurities are acceptable according to ICH Q3B.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

Following the first round of assessment, a major objection (MO7) was raised in relation to the potential risk of presence of nitrosamines in the finished product. Based on the additional data presented in

response, a MO was successfully resolved. A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

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 three PPQ batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Furthermore, batch analysis data are given for representative number of production scale batches used as clinical, primary or stability batches.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

#### *2.4.3.4. Stability of the product*

Stability data from three production scale primary batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH) and intermediate conditions (30°C / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The stability batches were packaged in a configuration that is representative of the commercial finished product packaging configuration.

The analytical procedures used are stability indicating. The stability study results showed no significant changes or trending. The storage conditions were endorsed as "Do not store above 30°C."

No significant changes were observed after freeze-thaw cycling study and in the in-use study. One batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not photosensitive.

Based on available stability data, the proposed shelf-life of 30 months and storage conditions "Do not store above 30°C." as stated in the SmPC (section 6.3 and 6.4) are acceptable.

#### *2.4.3.5. Adventitious agents*

No excipients derived from animal or human origin have been used.

### 2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product 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 applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

All major objections raised during the evaluation (acceptability of the starting materials, lack of discussion on origin, levels, and carry-over of the impurity, dissolution comparability between commercial batches and batches used during the clinical development, potential risk of presence of nitrosamines) have been resolved by provision of the relevant additional information and data or by applying additional control strategy.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These points are put forward and agreed as recommendations for future quality development.

## 2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

## 2.4.6. Recommendations 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:

1. to conduct further experimental investigations for further support of an impurity limit in a starting material, and to update a dossier section with method validation of the purity method.
2. to include derivatives of impurities in the specification of a starting material as specified impurities
3. to further evaluate the suitability of the purity method for a starting material related to an impurity and derivative
4. to re-evaluate the acceptance criterion for unknown impurities in the specification of an intermediate when additional number of batches have been manufactured
5. to conduct further particle size testing of the on-going long-term stability study.

The recommendations concerning the active substance should be fulfilled within the framework of a variation procedure since an update of module 3 will be required.

# *2.5. Non-clinical aspects*

## 2.5.1. Introduction

## 2.5.2. Pharmacology

### *2.5.2.1. Primary pharmacodynamic studies*

In vivo pharmacodynamics effects on HCMV were analysed in different animal models (transplanted human tissue or surrogate animal viral strains) in comparison to ganciclovir a two other benzimidazole nucleosides.

### *2.5.2.2. Secondary pharmacodynamic studies*

Maribavir showed no significant effects in a PharmaScreen profiling panel (PANLABS, Inc.) of in vitro and in vivo tests to identify possible off-target activity of maribavir, including its broad pharmacological effects on the CNS, CV, and GI systems, as well as on metabolic, inflammation and allergy, microbiological activity. However, due to the poor quality of the study report a thorough assessment of this report is not possible. The maribavir concentrations (3, 10 and 30 µg/mL) used in in vitro assays are approximately 10 to 100 fold higher than the unbound clinically Cmax level of 0.344 µg/mL and the majority of the oral doses used in the in vivo studies (except the 300 mg/kg dose in mice) were below, in the range of or slightly above the clinical exposure at the Cmax, when deduced from the TK-studies of the repeat-dose toxicity studies. Pharmacokinetic data of maribavir after IP administration are not available.

In a further study, effects of maribavir on the autonomic nervous system in vitro were evaluated in Dunkin Hartley guinea pig ileum and rabbit aorta. Maribavir does not modify alpha-adrenoreceptor activity in rabbit aorta but showed anticholinergic and antihistaminergic activity in vitro at 10 µM (3.76 µg/mL) in guinea pig ileum. However, antihistaminergic and anti-cholinergic effect by maribavir was not pointed out as an adverse issue in the toxicological studies.

### *2.5.2.3. Safety pharmacology programme*

A core battery of in vivo and in vitro safety pharmacology studies was performed with maribavir. These included studies on effects on central nervous, cardiovascular (in vivo and in vitro) and respiratory systems. The in vivo safety pharmacology studies were conducted in 1996 and are therefore of older origin. Whereas the in vitro hERG assay was performed under GLP, the in vivo safety pharmacology studies have not been performed under GLP. As outlined in the ICH S7A guideline, the safety pharmacology core battery should ordinarily be conducted in compliance with GLP. The applicant justifies that except for the hERG study, the safety pharmacology studies were conducted prior to the introduction of ICH S7A guidance and were therefore not Good Laboratory Practice (GLP-) compliant. However, the studies were conducted in reputable laboratories, using suitable group sizes to allow adequate statistical analysis of the results.

Considering that the in vivo safety pharmacology studies have been performed prior to introduction of the ICH S7A guideline and in view of the available GLP-compliant single-and repeated dose toxicity studies and the clinical studies, the lack of GLP compliance is acceptable.

CNS effects of maribavir were investigated in a behavioural study in CD-1 male mice at oral single doses of 250, 500 and 100 mg/kg. Pronounced effects on the CNS (hypoactivity, hypothermia, blepharospasm, tremors, ataxia and variable changes in respiration rate) were seen in this study at a dose ≥250 mg/kg.

Cardiovascular effects were investigated in vitro using HEK293 cells stably transfected with hERG.

Maribavir had no effect on the hERG current at concentrations of up to 1500 µg/mL (measured concentration 1250 µg/mL), providing a wide safety margin of more than 4000-fold the anticipated clinical plasma unbound Cmax of 0.344 µg/mL (0.91 µM), at the maximum proposed clinical dose of 400 mg BID.

Effects of maribavir on cardiovascular and respiratory function was investigated in anaesthetised closed chest beagle male dogs after IV administration of 3, 10 and 30 mg/kg as ascending dose. Transient increase in heart rate and respiratory rate were observed in dogs after IV administration of maribavir. No exposure data are available in dogs for maribavir. Using the HED dose calculation based on body surface area (according to FDA-Guidance for Industry: Estimating the Maximum Safe Starting Dose in

Adult Healthy Volunteer. Rockville, MD: US Food and Drug Administration; 2005.), the human equivalent dose to 30 mg/kg in dogs is 16.7 mg/kg which corresponds to a daily dose of 1000 mg in a 60 kg person.

In repeat-dose toxicity studies of up to 52 weeks duration in cynomolgus monkeys, maribavir had no effect on electrocardiography parameters at doses up to 400 mg/kg/day, the highest dose tested, corresponding approximately to total and free Cmax values of 11.6 and 1.9 µg/mL, respectively. To be compared with the clinical total and free clinical Cmax values of 17.2 and 0.344 µg/mL, respectively.

In a clinical thorough QT study, maribavir demonstrated no adverse CV effects at 100 or 1200 mg.

#### *2.5.2.4. Pharmacodynamic drug interactions*

See in Clinical Pharmacology

## 2.5.3. Pharmacokinetics

A detailed non-clinical programme on maribavir pharmacokinetics has been conducted. An overview is given below.

Table 1 Overview of non-clinical programme for PK

| **Scientific Report/ Study ID** | **Test system** | **Main results** |
|---|---|---|
| **Absorption** | | |
| V9053M-SHP620 (VP 1334) | Caco-2 cell bi-directional permeability assay | **Permeability**: $P_{app}$ >1 and efflux ER >3 at 10 µM → **high absorption potential and significant efflux** |
| M9059M-SHP620 (VP 1164) | CD-1 mouse (PO, IV) | oral bioavailability 69%, $t_{1/2}$ = 0.14-1.18 h |
| R9067M-SHP620 (VP 1232) | SD rat (PO, IV) | oral bioavailability 88-92%, $t_{1/2}$ = 0.38 h |
| R8574M-SHP620 | SD rat (PO, IV) | oral bioavailability 98.3%, $t_{1/2}$ = 2.74 h |
| R11505M-SHP620 | SD rat juvenile (PO) | $t_{1/2}$ (M/F) = 8.4/9.3 (PND7); 10.7/11.2 (PND14); 2.4/2.5 (PND21); 2.6/1.8 (PND28) → **age-dependent decrease in exposure (AUC)** |
| P8189M-SHP620 | Cyno monkey (PO) | PK of 4 different oral formulations:<br>$t_{1/2}$ = 9.46-20.7h<br>AUC (400 mg/animal) capsule with fluid bed granulation < capsules with shear granulation < capsules with pellet < tablets |
| P9068M-SHP620 (VP 1235) | Cyno monkey (PO, IV) | oral bioavailability 41.7-57.8%<br>constant level between 4 and 12 h postdose → **recirculation** |
| P9077M-SHP620 (VP 1177) | Cyno monkey (PO, IV) | oral bioavailability 71-184%, $t_{1/2}$ = 1.1 h |
| P8575M-SHP620 | Cyno monkey (PO, IV) | oral bioavailability 66.1%, $t_{1/2}$ = 11.5 h |
| **Distribution** | | |
| V9144M-SHP620 | ex vivo brain binding in monkey brain homogenates | estimated mean **brain-tissue-bound fraction** of maribavir (0.5, 5 µM) = 97.5 - 97.4% |
| M9059M-SHP620 (VP 1164) | CD-1 mouse | **brain distribution**: concentrations in brain homogenate <5% of those in plasma |
| V11009M-SHP620 | human hepatocytes | ***in vitro* distribution** – uptake into hepatocytes without saturation up to 100 µM |

| | | |
|---|---|---|
| V9072M-SHP620 (VP 1608) | *in vitro* maribavir binding to FBS | 48% binding of maribavir to FBS at 5% and 32% binding at 10% FBS |
| V9057M-SHP620 (VP 1135) | human serum proteins | higher binding to HSA as to AAG in plasma, Kd lower for |
| V9071M-SHP620 (VP 1585), V8540M-SHP620, V9054M-SHP620 (VP 1233) | mouse, rat, rabbit, monkey, human plasma | **moderate binding of maribavir to animal plasma proteins**: mouse (93.8%) > rabbit (89.7%) > monkey (89.5%) > rat (87.8%);<br>**VP 44469 less protein bound** than maribavir: rabbit (90.9%) > monkey (78.3%) > mouse (76.1%) > rat (71.4);<br>**free fractions higher at higher concentrations extensive (98%) protein binding in human plasma** |
| N11363M-SHP620 (VP 1552) | human plasma | binding to HSA ~90%, lower and concentration-dependent AAG binding (61.6% at 1 µg/mL and 0% at 80 µg/mL) |
| N11364M-SHP620 (VP 1551) | human plasma | ex vivo protein binding (plasma from CT):<br>**no differences in protein binding in plasma of renal or hepatic impaired patients** |
| TKD-BCS-00974-R1 | mouse, rat, monkey, human liver microsomes | **covalent binding of reactive metabolites to liver microsomes**: mouse (87.1) > monkey (79.6) > rat (53.9) > human (43.6 pmol equiv/mg protein) |
| V8540M-SHP620, V8198M-SHP620 | rat, monkey, human whole blood | **blood/plasma partitioning**: partitioning coefficient (Kp) = 4.16 (rat), 7.41 (monkey) and 1.37 (human) |
| R7646M-SHP620 | rat (pigmented and non-pigmented) | **QWBA**: **binding and long retention (>504 h post-dose) in melanin-containing tissues**; distribution into male reproductive organs and seminal vesicles; poor penetration of BBB; **highest concentrations in the kidney cortex, kidney, and liver; high concentrations also in urine and blood** |
| **Metabolism** | | |
| V8010M-SHP620 | rat, monkey and human hepatocytes and microsomes | **metabolism *in vitro*:**<br>3 primary pathways: N-dealkylation (VP 44469 = M4; major human metabolite) followed by glucuronidation (M1); direct glucuronidation (M7a, M7b, and M7c); N-glycosidic bond cleavage (M9, M13); no human specific metabolite identified, but **VP 44469 = human disproportionate metabolite**; high levels of parent drug |
| V9084M-SHP620 (VP 1509) | human fibroblasts ± HCMV | **no phosphorylated anabolites or metabolites of maribavir due to HCMV** |
| M9085M-SHP620 (VP 1618) | CD-1 mouse | **metabolism *in vivo*:**<br>extensive metabolism; 6 metabolites identified |
| R10949O-SHP620 | 28 d repeat-dose juvenile rats | **metabolism *in vivo*:**<br>limited metabolism: unchanged parent (major CRM), oxidation, N-dealkylation, N-glycosidic bond hydrolysis, and glucuronidation; lower metabolite levels on PND 34 vs. PND 7 |
| V8538M-SHP620 | Cyno monkey | **metabolism *in vivo*:**<br>*in vitro* identified metabolites confirmed (VP 44469, several glucuronides and others) |
| N12009M-TAK-620,<br>CSR 1263-106 | human plasma from ADME studies | **human *in vivo* metabolism:**<br>24h post-dose: remaining $^{14}$C-radioactivity was related to 88% maribavir + 12% VP 44469 (30-fold lower as $C_{max}$); 5 metabolites identified; long-lived radioactivity, not related to the main metabolites |
| V8537M-SHP620, V9086M-SHP620 (VP 1626) | human liver microsomes | **CYP phenotyping:**<br>CYP3A4 (70-85%), CYP1A2 (15-30%) |
| V8573M-SHP620 | human liver microsomes | **UGT phenotyping:**<br>UGT1A1, 1A3, 1A9 and 2B7 involved in glucuronide formation |
| **Excretion** | | |

| | | |
|---|---|---|
| M11988M-SHP620 (VP 1622), M9085M-SHP620 (VP 1618), R9078M-SHP620 (VP 1234), R7646M-SHP620, P9055M-SHP620 (VP 1236), P8177M-SHP620 | mice, rats, BDC rats, Monkeys, BDC monkeys | **Excretion of $^{14}$C-maribavir:**<br>**fecal excretion** – primary route (rat > mouse > monkey)<br>**urinary excretion** – minor route (sex differences only in mice with greater urinary excretion in F vs. M)<br>**biliary excretion** – major route in BDC monkeys/rats (>80%)<br>→ **significant enterohepatic recirculation**<br>→ maribavir = major excreted DRM in feces; metabolites excreted in urine |
| **Pharmacokinetic Drug Interaction** | | |
| V9079M-SHP620 (VP 1263), V7678M-SHP620, V8576M-SHP620 | human liver microsomes with marker substrates | **CYP inhibition** by maribavir (up to 100 µM):<br>CYP3A4 (weak + time-dependent, $IC_{50}$ = 50 µM), 1A2 (weak, $IC_{50}$ = 40 µM), 2C9 (weak; $IC_{50}$ = 18 µM), 2C19 (weak, $IC_{50}$ = 35 µM)<br>CYP inhibition by VP 44469 (up to 30 µM):<br>CYP3A4 (weak, $IC_{50}$ ~30 µM) |
| V7676M-SHP620, V8648M-SHP620 | human hepatocytes | **CYP3A4 mRNA induction** ($EC_{50}$ = 4.9-17.9 µM) without increase in activity;<br>**CYP1A2 and CYP2B6 with inconclusive results** (not conc. dependent induction of mRNA and activity, donor-differences) |
| V8573M-SHP620 | human liver microsomes | **UGT inhibition:**<br>UGT1A1 ($IC_{50}$ = 32.3 µM); poor inhibitor of UGT1A3, 1A9 and 2B7 ($IC_{50}$ = 184, 123, and 153 µM) |
| **Transporters** | | |
| V9052M-SHP620 (BB 1698) | MDCK and MDR1-MDCK cells; Caco-2 cells | **P-gp:**<br>**substrate + inhibitor** ($IC_{50}$ = 33.8 µM) |
| V7317M-SHP620, V317O-SHP620 | HEK293, C2BBe1, MDCK, BCRP-MDCK cells and BSEP vesicles | **Inhibition and substrate and potential of efflux and uptake transporters:**<br>moderate inhibitor of BCRP ($IC_{50}$ = 7.05),<br>weak inhibitor of BSEP ($IC_{50}$ = 46.5 µM), OATP1B1 ($IC_{50}$ = 45.5), OATP1B3 ($IC_{50}$ = 49.4), OAT3 ($IC_{50}$ = 33.3), MATE1 ($IC_{50}$ = 20.4);<br>VP 44469 $IC_{50}$ >15.5 µM for renal transporters → no relevant inhibition;<br><br>maribavir is substrate of OCT-1, BCRP and P-gp transport |
| **Other studies** | | |
| P9087M-SHP620 [VP 1174] | monkey | bioequivalence of 3 different capsule forms shown |

The amounts of maribavir and the main metabolite VP 44469 were analysed in several validated and in two non-validated assays.

Maribavir demonstrated moderate oral bioavailability in monkeys and high oral bioavailability in rodents. A gender difference in plasma concentration of maribavir and VP 44469 was observed in rodents. In the 2-year carcinogenicity study, the systemic concentration of maribavir and VP 44469 was greater for most dose levels in male mice. Contrary to mice, female rats exhibited higher plasma concentrations of maribavir and VP44469 than males (approximately x2 for maribavir), with evidence of slight accumulation after repeated administration. VP 44469 concentrations were lower than those for maribavir and barely detectable in the 2-year carcinogenicity study performed in rat. No obvious gender differences were observed in cynomolgus monkey of maribavir or VP 44469 exposure, however, indications of inter-animal variability was reported despite relatively consistency in exposure levels. The apparent $T_{½}$ after 5 -10mg/kg IV and oral (10 mg/kg) doses was highly variable between non-clinical species, ranging between 0.14 to 1.18 hours in mice, 0.38 to 2.74 hours in rats, and 11.5

hours in monkeys. Volume of distribution at steady state after single dose administration was 2 L/kg in mice, 7.3 L/kg in rat and 5.7-9.4 L/kg in cynomolgus monkey, respectively.

In mice, rats and monkeys, plasma concentrations were greater for maribavir than for the metabolite VP 44469, the main human metabolite. According to a human ADME study, the monkey absorption parameters are more similar to humans than to rodents.

Moderate binding of maribavir to animal plasma proteins occurred in animals in the range of: mouse (93.8%) > rabbit (89.7%) > monkey (89.5%) > rat (87.8%). VP 44469 less protein bound than maribavir in the following range: rabbit (90.9%) > monkey (78.3%) > mouse (76.1%) > rat (71.4%). In contrast, the protein binding in human plasma was high (98%). In all analysed samples, the free fractions were higher at higher concentrations. High binding to human serum albumin (84.3% to 90.6%) and a lower binding to α1-acid glycoprotein (AAG) was observed. Due to the lower abundance of AAG in plasma, AAG is not considered to contribute relevantly to high extent of protein binding in plasma. Therefore, further binding to lipoproteins is assumed. Maribavir was also determined to undergo moderate covalent binding to liver microsomal proteins due to NADPH-dependent bioactivation, which was lowest in human with 43.6 pmol equiv/mg protein < rat (53.9) < monkey (79.6) < mouse (87.1). Maribavir was significantly distributed into the cellular fraction of the blood with higher blood-plasma-ratios in rats (4.2) and monkeys (7.4) than in humans.

*In vivo* tissue distribution was analysed after oral administration of $^{14}$C-maribavir (10 mg/kg) to pigmented and non-pigmented rats followed by quantitative whole-body autoradiography (QWBA). Extensive distribution to GI that remained high to day 7 after PO administration was observed, indicative of enterohepatic recirculation which was confirmed by biliary excretion into small intestine after IV administration. Maribavir was widely distributed throughout the body with highest levels of radioactivity found in the liver, kidney, kidney cortex, kidney medulla, and GI tract. Significant binding to melanin and long retention in the respective tissues was shown in the QWBA study. Maribavir was also distributed into the testes and seminal vesicles. In this QWBA study in rats, maribavir did not cross the blood-brain-barrier to a measurable extent but was present in the choroid plexus. Further evaluations in mice and especially monkeys showed a variable amount of maribavir in the brain and the CSF. *In vitro* studies with monkey brain homogenates indicated a high binding of ~97% to brain proteins.

*In vitro* metabolism studies in pooled liver microsomes and primary hepatocytes of rat, monkey, and human indicated that the primary pathways for biotransformation include N-dealkylation to form VP 44469 (2 amino-5, 6-dichloro-1-β-L-ribofuranosyl-1Hbenzimidazole) and direct glucuronidation. Species differences were observed: glucuronidation is the primary metabolic pathway in rat and monkey hepatocytes, while human hepatocytes showed only little glucuronidation. N-dealkylation appearing to be the major metabolic *in vitro* pathway in humans. The formation of all metabolites except M7 (both parent + glucuronide) were almost completely inhibited by incubation with a pan-CYP inhibitor. VP 44469 was the major metabolite in humans (12%) and pharmacodynamic inactive.

In human liver microsomes and hepatocytes, the metabolism of maribavir is catalyzed principally by CYP3A4 and to a minor extent by CYP1A2; the CYP-driven pathways include N-dealkylation to form VP 44469 and deribosylation to M9. An *in vitro* study was conducted to further evaluate the role of CYP3A4 in the metabolism of maribavir in the formation of VP 44469. Maribavir conversion to VP 44469 was inhibited by ketoconazole (a CYP3A4 inhibitor) and CYP3A4 neutralizing antibody suggesting that CYP3A4 is the principal CYP isoenzyme responsible for conversion of maribavir to VP 44469. Further *in vivo* studies were undertaken to evaluate especially this DDI. Multiple UGT enzymes, namely UGT1A1, UGT1A3, UGT2B7, and possibly UGT1A9, were involved in the glucuronidation of maribavir in human.

The major metabolites of maribavir observed *in vivo* were also seen following incubation in HLM. *In vivo* studies show that biliary excretion and metabolism are the major routes of elimination in mice, rats, and monkeys. Oxidation, N-dealkylation, N-glycosidic bond hydrolysis, and glucuronidation were the major metabolic pathways of maribavir *in vivo* in all species with quantitative differences. VP 44469 (N-dealkylation of the isopropyl group) has been shown to be a metabolite in all species evaluated but with significant quantitative differences which were most obvious *in vitro* in microsomes and hepatocytes, where VP 44469 was the major metabolite in human in contrast to rat and monkey. The safety of VP 44469 has been assessed based on systemic exposure in mouse, rat and monkey toxicology studies and low exposure multiples of VP 44469 relative to NOAEL/LOAEL in toxicology were reached.

Investigations of excreta consisting $^{14}$C-labelled maribavir up to 96-168 hours were performed and the recovery of drug-related radiolabelled material (DRM) was incomplete.

Further investigation was performed in bile duct cannulated (BDC) and intact male cynomolgus monkey in 2018, (IV, 13 mg/kg, P8177M-SHP620). In intact animals, total recovery was 95.3% after 336 hours post-dose. 14.1% and 75.2% of the administered dose was recovered in urine and faeces, respectively. The majority of the radioactivity was eliminated by 96 hours, but low levels were still detectable by 312-336 hour post-dose.

In BDC animals, total recovery was 97% at 168 hours post-dose. Elimination via bile was 84% while 5.16% and 2.36% was eliminated via urine and faeces, respectively. However, low levels of radioactivity were still detectable in urine and faeces by 168 hours suggesting a low level of retention in tissues with slow release over time.

In monkeys, the major route of elimination was direct glucuronidation, whereas N-dealkylation to form VP 44469 was a comparatively minor pathway. After biliary secretion into the GI tract lumen, maribavir glucuronides were subsequently converted to the parent drug and reabsorbed, leading to apparent enterohepatic recirculation similar to the observations in rats.

The *in vitro* DDI related experiments are further discussed in relation to the *in vivo* data below.

## 2.5.4. Toxicology

The non-clinical safety of maribavir was investigated according to ICH-M3 (R2) requirements. Mice, rats and monkeys were chosen for single and repeat-dose toxicity studies because the main human metabolite of maribavir, VP 44469 was present in all of them and these species are common species for toxicity testing.

### *2.5.4.1. Single dose toxicity*

Single dose toxicity studies performed in mice and rats with oral and IV application of maribavir showed lethality and clinical signs like prostration, convulsions and decreased activity. No gross treatment related findings were observed in mice that died moribund or were sacrificed. In decedent rats, pathology findings related to the stomach/intestines, lungs and heart.

### *2.5.4.2. Repeat dose toxicity*

Repeat-dose toxicity studies were performed in mice, rats and monkeys. Maribavir was applied orally once a day to mice and rats, and according to the clinical treatment schedule twice a day to monkeys. In general, dose range finding studies preceded the pivotal studies. Pivotal studies were performed according to GLP. Toxicokinetic data for maribavir and the main metabolite VP 44469 were collected

within most of the repeat-dose studies. Table 2 shows a summary of repeat-dose toxicity studies performed.

Table 2 Summary of repeat-dose toxicity studies

| Study Type | Dose (oral gavage) mg/kg/day | GLP | Report Number |
|---|---|---|---|
| **Mice** | | | |
| 14-day DRF in CD-1 mice | Week 1: 0, 250, 350, 500<br>Week 2: 0, 500, 700, 1000 | No | M9583M-SHP620 (VP 1597) |
| 13-week in CD-1 mice with 12 - week recovery | 0, 50, 150, 300, 500 | Yes | M9582M-SHP620 (BB 1596) |
| **Rats** | | | |
| 28-day DRF in SD-rats | 0, 100, 200, 400 | No | R9554M-SHP620 (VP 1205) |
| 30-day in SD-rats with a 4-week recovery period | 0, 100, 200, 400 | Yes | R9568M-SHP620 (VP 1225) |
| 26-week in Han Wistar rats with a 4-week recovery period | 0, 25, 100, 400 | Yes | R9549M-SHP620 (VP1196) |
| **Monkeys** | | | |
| 28-day DRF in cynomolgous monkeys with a 39-day recovery period | 0, 10, 30, 90 BID<br>(0, 20, 60, 180 qd) | No | P9537M-SHP620 (VP 1178) |
| 30-day in cynomolgous monkeys with a 14-day recovery period | 0, 10, 30, 90 BD<br>(0, 20, 60, 180 qd) | Yes | P9559M-SHP620 (VP 1211) |
| 26-week in cynomolgous monkeys with a 4-week recovery period | Weeks 1-3: 0, 25, 50, 100 BID<br>(0, 50, 100, 200 qd)<br>Weeks 4-26: 0, 50, 100, 200 BID<br>(0, 100, 200, 400 qd) | Yes | P9539M-SHP620 (VP 1182) |
| 52-week in cynomolgous monkeys with a 4- or 8-week recovery period | 0, 50, 100, 200 BID<br>(0, 100, 200, 400 qd)<br>High dose not dosed weeks 10-13, then dose reduced to 150 BID (300 qd) at week 14 | Yes | P9538M-SHP620 (VP 1181) |
| DRF: dose range finding, qd: once a day, SD: Sprague Dawley | | | |

**Mice -** In the pivotal 13-week study in mice, doses of 300 and 500 mg/kg/day were not very well tolerated. The high dose group was therefore terminated early. Clinical signs associated with gastrointestinal effects were observed in decedents and surviving animals. Haematological changes in the form of higher platelet and reticulocyte counts and relative increase in spleen weights associated with splenic haematopoiesis were noticed. Gastrointestinal lesions included mucosal hyperplasia and inflammation of the cecum and/or colon and the non-/glandular stomach. Findings showed reversibility. The NOAEL was established at 150 mg/kg/day resulting in a margin of exposure of 0.4-times for total and 3-times for free unbound maribavir to the therapeutic exposure based on AUC.

According to toxicokinetic data obtained in mice, systemic exposure to both, maribavir and VP 44469 was approximately dose-proportional with no evidence of accumulation. No gender differences in exposure were noticed for maribavir whereas for VP 44469 exposure was higher in males than in females. Exposure to maribavir was in general greater than to VP 44469.

**Rat -** In the rat, two pivotal studies were performed; a 30-day and a 26-week study. Mucosal hyperplasia in the GI-tract at all doses was the main finding observed in the 30-day study. Dose-dependent haematology changes (increases in white blood cells and reticulocytes) and splenic erythropoiesis contributing to increases in erythropoietic foci in the liver of high dose females were also noticed. No NOAEL could be established. The exposure at the LOAEL was below the human therapeutic

exposure for total and around 2-times the human therapeutic exposure for free unbound maribavir based on AUC.

In the 26-week study, several animals were found dead or had to be sacrificed moribund. Although a relation to treatment was not excluded, the cause of death could not be determined. Histopathological findings concerned mucosal hyperplasia and mucosal lymphocyte infiltrates in different segments of the small and large intestine. Renal cortical tubule pigment deposition which did not impact renal function was also noticed in treated animals. Hepatocellular cytoplasmic alterations accompanied by increases in liver weights were attributed to induction in drug metabolizing liver enzymes which was shown by liver microsome analysis. Furthermore, changes in haematological parameters, which indicate a regenerative anaemia, and changes in clinical parameters were not considered clinically significant. Changes were slight and did not increase or decrease over time. The NOAEL was set at 25 mg/kg/day resulting in exposures below human therapeutic exposures for total (approximately 0.1-times) and free unbound (approximately 0.5-times) maribavir based on AUC.

Toxicokinetics in rats showed that exposure to maribavir (approximately 2-fold) and VP 44469 (up to 10-times) was higher in females compared to males and increased in proportion with dose. There was some evidence of maribavir accumulation after repeat-dosing. Exposure to maribavir was much higher than to VP 44469.

**Monkey -** Altogether, three pivotal repeat-dose toxicity studies were performed in the cynomolgus monkey. In the 30-day study, no treatment related changes were noticed at all up to the highest dose of 90 mg/kg BID applied. However, margins of exposure at the NOAEL were below (0.2-times for total) or slightly above (1.8 times for free) therapeutic maribavir exposures based on AUC.

Relating to the toxicokinetic data of the 30-day and two pharmacokinetic studies, doses for the subsequently performed 26-week study were chosen. However, exposure data from day 1 indicated lower exposures than expected. Therefore, doses were doubled after the first three weeks of treatment. Severe diarrhoea associated with poor condition of some mid and high dose animals was counteracted with dosing holidays of 11 up to 30 days until recovery. Reversible decreases in red blood cell counts with increases in reticulocytes were observed, which can be attributed to regenerative anaemia. Histopathology findings concerned the GI-tract with mucosal hyperplasia of the cecum, colon and rectum. A NOAEL could not be established. The LOAEL of 25/50 mg/kg BID results in a margin of exposure below or at human therapeutic maribavir exposures based on AUC.

In the 52-week repeat-dose toxicity study, again severe diarrhoea resulting in dehydration occurred with a dose-related incidence and severity. Maribavir administration was therefore discontinued for the high dose group for weeks 10 to 13 and the dose was reduced. However, at the end of 8 months of study, treatment was completely discontinued for high dose animals and animals were euthanised. Furthermore, dose administration was temporarily suspended for selected animals of all dose groups. Epithelial hyperplasia of the cecum, colon and rectum was noticed for animals of all dose groups. Haematological alterations noticed were considered to be secondary to diarrhoea and dehydration. Furthermore, a treatment-related decrease in alkaline phosphatase was seen in high dose animals. No NOAEL could be established. Maribavir exposure at the LOAEL of 50 mg/kg BID was below (0.3-times) for total and approximately 2-times for unbound at the therapeutic levels based on AUC.

High inter animal variability was noticed for toxicokinetics in monkeys. Maribavir exposure increased in a less than dose proportional manner in the 52-week study and showed no sex-related difference. VP 44469 exposure values seem to increase in proportion with dose for low and mid dose, but not for the high dose group. AUC and Cmax values for VP 44469 demonstrated a statistically significant trend towards higher values in females than in males.

Altogether, the main target organ for maribavir toxicity observed across animal species is the gastrointestinal tract leading to severe diarrhoea and dehydration with secondary erythroid haematological changes. Haematological changes in monkeys, rats and mice can be attributed to regenerative anaemia. In the longer-term studies in monkeys, maribavir toxicity resulted in dose reductions, dosing holidays and/or earlier termination of severely affected dose groups. Margins of exposure to the established NOAELs or LOAELs were in general either below or only slightly above human therapeutic exposures for maribavir based on AUC for all animal species.

#### *2.5.4.3. Genotoxicity*

Maribavir was negative in in vitro Ames tests, weakly positive in the L5178Y/tk+/- mouse lymphoma test without metabolic activation (- S9) and equivocal with metabolic activation (+ S9). Without metabolic activation a small increase in small colony mutant frequency was observed caused probably by chromosome damage effects (clastogenic). No cytotoxicity or increased mutagenicity at exposures > 3 x Cmax were observed with metabolic activation. In an in vivo micronucleus test performed in > 3 x the clinical exposure (Cmax unbound), maribavir showed no statistically significant increase in the number of micronucleated PCE's as compared to the vehicle and no cytotoxicity (bone marrow) could be observed in any treatment group. Maribavir showed no clastogenic effects in vivo.

In conclusion, maribavir is not considered to be genotoxic under the conditions of the studies. An appropriate wording was implemented in section 5.3 in the SPC.

#### *2.5.4.4. Carcinogenicity*

According to the current guideline ICH S1 long-term carcinogenicity testing of maribavir was carried out in two 2-year lifespan studies in rodents [mouse Crl:CD1(ICR) M9526M-SHP620 and rat Crl:WI(Han) R9581M-SHP620] in compliance with GLP. Toxicokinetic data for maribavir and the main metabolite VP 44469 were collected for both studies.

Neoplastic findings of both rodents were reported in the literature and generally, the incidence of each neoplasm was within historical control ranges with the exception of vascular neoplasms (haemangiosarcomas) detected in male mice (12.9 % to historical control). Further, the incidence of combined haemangiomas/haemangiosarcomas in multiple organs in male mice was 4/60 (6.7%), 1/60 (1.7%), 4/60 (6.7%), 5/78 (6.4%) and 14/77 (18%) at 0, 0, 25, 75 and 150 mg/kg/day, respectively, indicating an increased incidence at 150 mg/kg/day. The Applicant is of the opinion that the result was considered an equivocal test article-related biological effect for the following reasons: (1) the incidence of haemangiosarcoma only marginally exceeded that reported for CD-1 historical controls; (2) the difficulty in assessing the impact of adding at risk mice to Groups 4 and 5 after one year, (3) there was no increase in vascular neoplasms in female test article groups; (4) the morphology of the vascular neoplasms in male mice were similar to that seen in control mice of this study.

However, despite of the lack of any neoplastic proliferative effects in a chronic toxicity study (13 w) in mice, the absence of a genotoxic potential and a clear difference in duration of administration compared to the clinical dosing, the result was of uncertain relevance in terms of its translation to human risk and therefore considered equivocal. Neoplastic alterations in rat (age, strain) detected in control and treatment groups were not dose dependent or statistically significant and were expected in carcinogenicity studies of this duration.

Nevertheless, for both rodents, exposure margins obtained at the NOAEL for carcinogenicity are not existing (< 1 x) or rather low (1 – 2 x) with regard to the total concentrations or free concentrations of

maribavir based on AUC. Considering the proposed indication, the low exposure multiples should not be a concern. This information is indicated in the relevant section 5.3 of the SPC.

#### *2.5.4.5. Reproductive and developmental toxicity*

In line with the proposed indication "Treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease who are resistant and/or refractory to one or more prior therapy including ganciclovir, valganciclovir, cidofovir or foscarnet", a full range of reproductive toxicity studies was conducted in the late 1990s. All pivotal studies were carried out in accordance with the relevant guideline of that time (ICH Harmonised Tripartite Guideline 1993) and in compliance with GLP regulations.

In rats, male and female fertility was not affected at all by maribavir treatment at doses up to 400 mg/kg/day although in male rats, a decreased straight-line velocity of sperm was observed at all maribavir dose levels.

Embryofoetal and maternal toxicity was already evident at the lowest dose of 100 mg/kg/day. No substance related teratogenicity was observed up to the highest dose tested. In addition, prenatal and postnatal development was not affected by oral treatment of dams with maribavir at the low dose of 50 mg/kg/day during gestation and lactation. Treatment with higher dosages during these periods were associated with adverse effects on pups' body weights and correspondent delayed attainment of developmental milestones. Learning and memory as well as fertility and mating performance, the ability to maintain pregnancy and to deliver live offspring together with the survival of the offspring to day 4 postpartum, remained unaffected in the offspring up to the top dose of 400 mg/kg/day. Treatment of pregnant rabbits during the period of organogenesis induced no maternal and no embryofoetal toxicity up to the highest dose tested (100 mg/kg/day).

Exposure multiples obtained in the reproductive toxicity studies at the respective NOAELs/LOAELs are often < 1 when compared to the human exposure, at least with regard to the total maribavir concentrations. Comparison of the free and unbound concentrations at the NOEALs/LOAELs with the human free and unbound fraction revealed somewhat higher exposure multiples. Considering the proposed indication "Treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease who are resistant and/or refractory to one or more prior therapy, including ganciclovir, valganciclovir, cidofovir or foscarnet" as "last line therapy", the low exposure multiples are not considered a concern. The information provided in section 5.3 of the SmPC adequately reflects this fact. Regarding section 4.6 of the SmPC the wording is considered to be in line with the respective guideline.

#### *2.5.4.6. Toxicokinetic data*

Described in above sections.

#### *2.5.4.7. Local Tolerance*

According to the Guideline on non-clinical local tolerance testing of medicinal products (EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1*), local tolerance studies are considered unnecessary for medicinal products administered by oral route. In studies on dermal and ocular tolerance and skin sensitisation maribavir was not considered as a dermal irritant in rats and rabbits but as a slight ocular irritant in rabbits and was classified as a non-sensitiser to guinea-pig skin. These studies are of limited clinical relevance for the intended oral route of administration of maribavir.

#### *2.5.4.8. Other toxicity studies*

**Phototoxicity**

Maribavir was distributed in uveal tract of the eye and skin and exhibited affinity for melanin in pigmented rats with molar extinction coefficient (MEC) greater than the ICH S10 threshold (1000 Lmol-1/cm) in the UVB spectrum ( ~ 216, 270 and 300 nm). Maribavir was not phototoxic in the in vitro 3T3 NRU-PT study conducted according to standard conditions using a xenon arc solar simulator as the source of UVA exposure, equipped with a Schott WG 320 filter. Given that penetration of UVB light into human skin is mainly limited to the epidermis, while UVA can reach capillary blood, the clinical relevance of photochemical activation by UVB is considered less important than activation by UVA for systemic drugs as outlined in ICH S10. In conclusion, the risk for phototoxicity is considered low.

**Antigenicity**

No specific studies have been performed. Maribavir was classified as a non-sensitiser to guinea-pig skin.

**Immunotoxicity**

The potential immunotoxicity of maribavir was investigated in female Sprague-Dawley rats in an acute immunotoxicity study including a functional evaluation of the immunoglobulin antibody-forming cell (AFC) response to the T-dependent antigen and sheep red blood cells in the spleen at dosages of 10, 30 and 100 mg/kg/day (5, 15 and 50 mg/kg BID) for 7 days. Treatment with maribavir leads to significant increase in spleen weight at 100mg/kg. Furthermore, splenic specific and total IgM AFCs response significantly increased at ≥ 30 mg/kg. However, given the variability and overlap in individual animal data across all dose groups including the vehicle group, the lack of dose-response to the potential immunostimulatory responses in 30 and 100 mg/kg/day dose groups, and no specific immunomodulatory responses in the repeat-dose tox studies, the potential for maribavir-mediated immunotoxicity is deemed low.

**Dependence**

No specific dependence studies have been performed with maribavir.

## 2.5.5. Ecotoxicity/environmental risk assessment

The ERA provided for Maribavir is considered complete and acceptable.

The calculation of the predicted environmental concentration (PEC) in Phase I for the active substance Maribavir has been based on prevalences. The PECsurface water value exceeds the action limit of 10 ng/l. Consequently, a respective Phase II environmental risk assessment was performed by the applicant and submitted with an updated ERA.

Maribavir is not a PBT substance but should be classified as a vP substance.

PEC/PNEC calculation for surface water, groundwater, microorganisms and sediment revealed that maribavir does not pose a risk to the respective compartments.

As a result of the above considerations, Livtencity with the API maribavir does not present a risk to the environment when used according to SmPC and PL.

Table 3 Summary of main study results

| **Substance (INN/Invented Name): Maribavir** | | | |
|---|---|---|---|
| **CAS-number (if available): 176161-24-3** | | | |
| ***PBT screening*** | | **Result** | **Conclusion** |
| *Bioaccumulation potential-* log $K_{ow}$ | OECD 107 | pH 5: 2.0<br>pH 7: 3.0<br>pH 9: 1.2<br>at 20 °C | Potential PBT (N) |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Persistence | $DT50_{whole\ system}$ (12 °C) | DT50 = 271 d (I); 744.8 d (II) | vP<br>I = system 1;<br>II = system 2 |
| ***Phase I*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| $PEC_{surfacewater}$, refined (orphan designation) | 0.48 | µg/L | > 0.01 threshold (Y) |
| ***Phase II Physical-chemical properties and fate*** | | | |
| **Study type** | **Test protocol** | **Results** | **Remarks** |
| Adsorption-Desorption | OECD 106 | Soil:<br>Kd = 8 - 57 L/kg<br>Koc = 580 - 2714 L/kg<br>Sludge:<br>Kd = 74, 115 L/kg<br>Koc = 232, 338 L/kg. | List all values |
| Ready Biodegradability Test | OECD 301 | -1.43 % (28 d) | not readily biodegradable |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | $DT_{50,\ water}$ = 6.78 d (I); 22.2 d (II)<br>$DT_{50,\ sediment}$ = 157 d (I)<br>$DT_{50,\ whole\ system}$ = 127 d (I); 349 d (II)<br>% shifting to sediment = 59.3 (I); 42.4 (II)<br>% $CO_2$ = 0.13 (I); 0.07 (II)<br>% NER = 10.6 (I); 7.9 (II)<br><br>Transformation products > 10%:<br>Yes, TP1 = 27.1 % (I), day 101, whole system, continuously increasing | 20 °C<br>I = system 1;<br>II = system 2<br><br>at day 14<br><br>at test end<br>at test end<br><br>TP1 seems to be persistent; TP1 = 5,6-dichloro-2-(isopropylamino)-1H-benzimidazol-1yl riburonic acid |

| ***Phase IIa Effect studies*** | | | | | |
|---|---|---|---|---|---|
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/*Species* | OECD 201 | NOErC | 9100 | µg/L | *Raphidocelis subcapitata* |
| *Daphnia* sp. Reproduction Test | OECD 211 | NOEC | 4300 | µg/L | *Daphnia magna* |
| Fish, Early Life Stage Toxicity Test/*Species* | OECD 210 | NOEC | 10000 | µg/L | *Pimephales promelas* |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | NOEC | 90 | mg/L | |
| ***Phase IIb Effect studies*** | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Sediment dwelling organism *Chironomus riparius* | OECD 218 | NOEC | 765 | mg/kg dw | 2.4% o.c.<br>Not normalised to 10% o.c. since sorption is not OC dependent, *mean measured* |

## 2.5.6. Discussion on non-clinical aspects

Considering the above data, maribavir is not expected to pose a risk to the environment when used according to SmPC and PL.

Animal *in vivo* models for pharmacodynamic effects of maribavir are of limited relevance due to the species-specify of CMV and therefore not further discussed.

The secondary pharmacodynamic studies were conducted in 1996 and are therefore of older origin. Maribavir was investigated on its broad pharmacological effects on the CNS, CV, and GI systems, as well as on metabolic, inflammation and allergy, microbiological activity. The study reports are of low quality and a thorough assessment of the reports is not possible.

Maribavir showed anticholinergic and antihistaminergic activity *in vitro* at 10 µM (3.76 µg/mL) in guinea pig ileum. The concentration used is approximately 10-fold the unbound clinical Cmax level of 0.91 µM. Antihistaminergic and anticholinergic activity of maribavir are also proposed by the applicant for the effects seen in the safety pharmacology study in mice on CNS.

A core battery of *in vivo* and *in vitro* safety pharmacology studies was performed with maribavir. These included studies on effects on central nervous, cardiovascular (*in vivo* and *in vitro*) and respiratory systems. The *in vivo* safety pharmacology studies were conducted in 1996 and are therefore of older origin. Whereas the *in vitro* hERG assay was performed under GLP, the *in vivo* safety pharmacology studies have not been performed under GLP. As outlined in the ICH S7A guideline, the safety pharmacology core battery should ordinarily be conducted in compliance with GLP. The applicant justifies that except for the hERG study, the safety pharmacology studies were conducted prior to the introduction of ICH S7A guidance and were therefore not Good Laboratory Practice (GLP-)compliant. However, the studies were conducted in reputable laboratories, using suitable group sizes to allow

adequate statistical analysis of the results. Therefore, the applicant concludes that the overall safety pharmacology assessment is considered to be robust. Considering that the *in vivo* safety pharmacology studies have been performed prior to introduction of the ICH S7A guideline and in view of the available GLP-compliant single-and repeated dose toxicity studies and the clinical studies the lack of GLP compliance is acceptable.

Maribavir induced pronounced effects on the CNS (hypoactivity, hypothermia, blepharospasm, tremors, ataxia and variable changes in respiration rate) in a behavioral study in CD-1 male mice at oral doses ≥ 250 mg/kg. Clinical signs of CNS-related effects (hypoactivity, convulsion, tremors, respiration changes) were also seen in a range of single and repeat dose toxicity studies in mice, rats and monkeys at clinically relevant exposures. Penetration into CNS of maribavir cannot be excluded (see pharmacokinetics) and CNS-related adverse reactions like taste disorder have been very commonly seen in clinical studies.

Significant binding and retention of maribavir in melanin-containing tissue was further analysed for its *in vitro* phototoxic potential.

Maribavir showed a moderate binding to plasma proteins in animals and a high binding in humans. Since the very high extent could not only be attributed to the binding to HSA and AAG, a relevant binding to lipoproteins is expected and a relevant covalent binding to liver microsomes (human < animals) was shown. In the conducted repeat-dose toxicity studies no obvious liver toxicity was determined. The conclusion of a low clinical risk due to covalent binding to human liver microsomes is therefore followed. Maribavir was significantly distributed into the cellular fraction of the blood with higher blood-to-plasma-ratios.

CYP and UGT-related metabolism was adequately analysed in rats, monkeys, mice. However, limitations in the analysis of human metabolism are still present. Significant inter-species differences were identified *in vitro* in liver microsomes and hepatocytes. Due to a relevant enterohepatic deconjugation and recirculation these differences were not so distinct *in vivo*, with a relevant exposure of VP 44469, the main human metabolite in the repeat-dose, reproductive toxicity and in carcinogenicity studies. Thus, the metabolite is considered qualified in non-clinical studies.

A comprehensive quantitative comparison of the inter-species differences for relevant circulating and excreted metabolites was provided for the non-clinical species in comparison to humans. Maribavir showed species-dependent metabolism and excretion patterns. Most obviously, excretion of drug-related radioactivity into the urine was a major route of elimination in humans while being only a minor route of elimination in the analysed non-clinical species. However, due to missing respective clinical safety signals this gap of non-clinical information was concluded of minor overall clinical relevance.

It should also be noted that in humans after a single oral dose of $^{14}$C-maribavir, 75% of drug-related material is recovered, with 61% in urine and 14% in faeces. Thus 25% of the dose is thus unaccounted for and may potentially be unidentified metabolites. This is further discussed in section 3.3.3.

Maribavir was majorly eliminated by biliary and fecal excretion in animals. The renal route was a relevant route for some metabolites, with a low contribution to the total excretion.

Maribavir has a high potential for PK-related DDI through metabolising enzymes and transporters, *in vitro*.

In the section 3, Drug-drug interactions, the Applicant refers a wide therapeutic window of up to 1200 mg maribavir BID corresponding to $C_{max}$ and $AUC_{0-\tau}$ of approximately 36.7 µg/mL and 379 µg·h/mL, respectively. These $C_{max}$ and AUC exposures have not generally been reached in the non-clinical safety studies, and thus, the non-clinical study package provides no support for this wide therapeutic window.

However, this exposure is covered by both the 800 mg and 1200 mg phase 2 studies and may therefore be acceptable based on clinical safety data.

The **toxicology** programme was adequate in general. **Repeated-dose toxicity studies** were performed in rodents (mice and rats) and non-rodents (cynomolgus monkeys) for sufficiently long duration, up to 26 weeks in rats and up to 52 weeks in monkeys. Dose-range finding studies preceded all of the pivotal studies in the three animal species. Pivotal studies were performed according to GLP. Toxicokinetic data were obtained for maribavir and the main metabolite VP 44469 within most of these studies.

**Genotoxicity and Carcinogenicity studies** submitted are considered sufficient for characterisation of the genotoxic and carcinogenic potential of maribavir. In the rat carcinogenicity study, there were no neoplasms attributed to maribavir treatment. In the mouse carcinogenicity study, the incidence of combined haemangiomas/haemangiosarcomas in multiple organs in male animals only was 4/60 (6.7%), 1/60 (1.7%), 4/60 (6.7%), 5/78 (6.4%) and 14/77 (18%) at 0, 0, 25, 75 and 150 mg/kg/day, respectively, indicating an increased incidence at 150 mg/kg/day. The Applicant of the opinion that these findings are equivocal with one of the arguments put forward is the addition of satellite animals to Groups 4 and 5 after one year. The Applicant was asked to provide further arguments supporting this position (as example separate analysis of vascular neoplasms in the former satellite animals in comparison with the main study animals). Based on a separate analysis on the incidence of haemangiomas and haemangiosarcomas of the satellite animals moved into the main study, there is no strong support for the argument that moving of satellite animals to Groups 4 (75 mg/kg/day) and 5 (150 mg/kg/day) after one year have confounded the findings of haemangiomas and haemangiosarcomas in the study. The findings are considered adequately presented in section 5.3 of the SmPC.

Exposure margins obtained at the NOAEL for carcinogenicity are not existing or rather low with regard to the total concentrations or free concentrations of maribavir based on AUC. Considering the proposed indication and the limited treatment duration, the low exposure multiples should not be a concern.

**The reproductive toxicity studies** submitted are considered sufficient for characterisation of the reproductive potential of maribavir, despite the maximum tolerated dose was apparently not achieved in pregnant rabbits, as no maternal toxicity occurred. However, two DRF studies, one in non-pregnant and another in pregnant rabbits preceded the pivotal study and dosages for the pivotal study were selected on the results of these studies.

There were no apparent effects on male and female fertility, although a decreased straightline velocity of sperm was observed in all maribavir treatment groups. The reversibility of this effect is not known. Given the absence of findings in all other semen parameters (actual path velocity, total counts, % motility and sperm morphology), in male reproductive tract organ weights and histopathology, and in fertility parameters, the biological significance seems low. The observation is presented in the SmPC which is endorsed. Furthermore, the clinical relevance for the intended patient population is regarded as low. Most patients have been treated with ganciclovir, valganciclovir, cidofovir or foscarnet, all of which have clear genotoxic potential and ganciclovir, valganciclovir and cidofovir also have adverse effects on spermatogenesis in animals.

HanWistar rats, a strain generally used for toxicity studies at that time, were used for the combined FEED and EFD study as well as for the PPND study. According to the study report of the combined study, this strain is associated with a so-called “cleft palate syndrome”, a fact, that could have made the interpretation of the foetal findings more difficult. Foetuses with cleft palates were indeed found not only in the combined FEED and EFD study but also in the PPND study, with the highest incidence in each study in the respective control groups, which excludes a maribavir related effect.

Exposure margins obtained at the NOAEL/LOAEL in the reproductive toxicity studies are rather low especially with regard to comparison of the total concentrations. Comparison of the free and unbound concentrations at the NOAEL/LOAEL revealed somewhat higher margins. However, considering the proposed indication "Treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease who are resistant and/or refractory to one or more prior therapy, including ganciclovir, valganciclovir, cidofovir or foscarnet" as a "last line therapy", the low exposure multiples should not be a concern as the fact is indicated in the relevant sections of the SmPC.

The proposed labelling for the relevant SmPC sections 4.6 and 5.3 adequately reflects the results except the NOAEL for maternal toxicity in rats, and the wording for section 4.6 is in line with the relevant guideline. Indeed, the non-existent or low safety margins are clearly indicated in section 5.3 of the SmPC.

Two pivotal juvenile toxicity studies were submitted, too. However, at present there is no application for paediatric treatment.  A critical assessment of these studies will be done at a later stage.

Based on the results of an immunotoxicity study in female rats and the lack of specific immunomodulatory response in the repeat-dose toxicity studies, the potential for maribavir-mediated immunotoxicity is deemed low.

### 2.5.7. Conclusion on the non-clinical aspects

In general, the non-clinical programme sufficiently addressed the pharmacokinetics (ADME) in animals in vivo and human in vitro.

Overall, the non-clinical programme sufficiently characterises the toxicity of maribavir. The study results of the repeat-dose toxicity, genotoxicity studies as well as the low and / or non-existent safety margins at the respective NOAELs/LOAELs are adequately reflected in the relevant sections of the SmPC.

The proposed labelling for the relevant SmPC sections 4.6 and 5.3 adequately reflects the results except the NOAEL for maternal toxicity in rats, and the wording for section 4.6 is in line with the relevant guideline. Indeed, the non-existent or low safety margins are clearly indicated in section 5.3 of the SmPC.

ERA was completed and no risk to the environment when used according to SmPC and PL concluded for maribavir.

## *2.6. Clinical aspects*

### 2.6.1. Introduction

***GCP aspects***

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

A triggered GCP inspection for the clinical study SHP 620-303 was conducted. The final integrated inspection report of the sponsor inspection and two clinical sites in Belgium and Germany was provided on the 17$^{th}$ of March. At the sponsor site one critical, twelve major and three minor findings were identified. At the investigator site in Belgium, one major and six minor findings were issued, while at the investigator site in Germany, three major and six minor findings were identified. The findings of the GCP inspections are highlighted in the relevant sections.

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.

The clinical development of maribavir comprises 17 Phase I studies, 3 Phase II studies and 3 Phase III studies with five different oral immediate-release (IR) formulations (one capsule and four tablet formulations). Tablet IV formulation was used in the pivotal Phase III study (SHP620-303) and has the same composition as the to-be-marketed product. The applied dose is 400 mg twice daily.

Three initial safety, tolerability and intravitreal distribution studies were conducted in HIV patients when maribavir was evaluated as a potential treatment for CMV retinitis. All other Phase I studies, with the exception of the renal and hepatic impairment studies and a DDI study with tacrolimus, were conducted in healthy patients.

A summary of all clinical studies conducted with maribavir is shown in below.

- **Tabular overview of clinical studies**

| Study ID | Study objective(s) | Study design | Patients; Gender | Dosage regimen | Maribavir formulation | Total No. of patients entered/completed |
|---|---|---|---|---|---|---|
| **Phase I studies** | | | | | | |
| CMAB1001 | to assess safety, tolerability and PK of a single maribavir dose | single-centre, double-blind, randomised, placebo-controlled, 6-period, single ascending dose study | healthy male patients (fasted state) | 50 mg, 100 mg, 200 mg, 400 mg, 800 mg and 1600 mg maribavir / placebo, single dose | Capsule | 13 patients enrolled<br>12 patients completed |
| CMAB1002 | to determine safety, tolerability and PK of a single dose maribavir in HIV-infected patients | single-centre, double-blind, randomised, placebo-controlled, single dose escalating study | HIV-infected male patients<br>(fasted and fed state) | 100 mg, 400 mg, 800 mg and 1600 mg maribavir / placebo, single dose | Capsule | 17 patients enrolled<br>14 patients completed |
| CMAA1003 | to assess tolerability, anti-CMV activity and PK of multiple maribavir doses | single-centre, randomised, parallel-group, dose-ranging study | HIV-infected male patients with asymptomatic CMV shedding | 100 mg, 200 mg, 400 mg maribavir / placebo TID for 28 days<br>600 mg, 900 mg, 1200 mg maribavir / placebo BID for 28 days | Capsule | 78 patients enrolled<br>69 patients completed |
| CMAA1004 | to determine ocular penetration of maribavir | single-centre, open-label, parallel group, multiple dose study | HIV-infected male patients with CMV retinitis | 800 mg maribavir TID for 7 days, followed by a single 800 mg maribavir dose at Day 8<br>1200 mg maribavir BID for 7 days, followed by a single 1200 mg maribavir dose at Day 8 | Capsule | 8 patients enrolled<br>7 patients completed |
| 1263-104 | to determine the relative BA of two maribavir formulations and food effect | single-centre, randomised, 3-way, cross-over study | healthy male and female patients<br>(fasted and fed state) | 400 mg maribavir | Tablet I<br>Tablet II | 30 patients enrolled<br>28 patients completed |
| 1263-109 | to determine the relative BA of crushed maribavir vs whole maribavir tablet<br><br>to determine the effect of antacids on whole maribavir tablet | single-centre, open-label, randomised, 3-way, cross-over study | healthy male and female patients<br>(fasted state) | 100 mg maribavir tablet (whole), single-dose<br>100 mg maribavir tablet (crushed in solution), single dose<br>100 mg maribavir tablet (whole) + MAG-AL liquid antacid, single dose | Tablet III | 15 patients enrolled<br>15 patients completed |

| | | | | | | |
|---|---|---|---|---|---|---|
| TAK-620-1019 | Part 1<br>to assess relative BA of 2 candidate paediatric formulations compared to adult tablet formulation<br><br>Part 2<br>to investigate dose proportionality and food effect of paediatric formulations | single-centre, open-label, randomised, cross-over study<br><br>Part 1<br>3-period cross-over<br><br>Part 2<br>4-period cross-over | healthy male and female patients<br>(Part 1: fasted state) | Part 1<br>200 mg maribavir, single-dose<br><br>Part 2<br>50 mg, 100 mg and 200 mg maribavir | Tablet IV<br>2 candidate paediatric formulations (not part of this submission) | Part 1:<br>20 patients enrolled<br>18 patients completed<br><br>Part 2:<br>Not conducted |
| 1263-106 | to assess mass balance recovery and metabolite profiling of maribavir | single-centre, open-label mass balance and metabolite profiling study | healthy male and female patients<br>(fasted state) | 400 mg [$^{14}$C]-maribavir, single dose | Oral solution | 6 patients enrolled<br>6 patients completed |
| 1263-101 | to evaluate the effect of renal impairment on the PK of maribavir | multi-centre, open-label, parallel group, single-dose study | male and female patients who are healthy or who have mild, moderate or severe renal disease<br>(fasted state) | 400 mg maribavir, single dose | Tablet I | 31 patients enrolled<br>31 patients completed |
| 1263-103 | to assess the effect of hepatic impairment on the PK of maribavir | single-centre, open-label, parallel group, single-dose study | male and female patients who are healthy or who have moderate hepatic impairment<br>(fasted state) | 200 mg maribavir, single-dose | Tablet I | 20 patients enrolled<br>20 patients completed |
| 1263-100 | to determine the effect of repeat maribavir doses on CYP450 enzyme activity | single-centre, double-blind, randomised, placebo-controlled DDI study | healthy adult male and female patients | 400 mg maribavir / placebo BID<br>0.075 mg/kg midazolam<br>2 mg/kg caffeine<br>10 mg warfarin + 10 mg vitamin K<br>40 mg omeprazole<br>30 mg dextromethorphan | Tablet I | 20 patients enrolled<br>20 patients completed |
| 1263-102 | to determine the effect of ketoconazole on maribavir PK | single-centre, open-label, randomised, 2-way, cross-over DDI study | healthy adult male and female patients | 400 mg maribavir<br>400 mg ketoconazole | Tablet I | 20 patients enrolled<br>19 patients completed |
| 1263-105 | to determine the effect of repeat | multi-centre, double-blind, randomised, | stable renal transplant recipients | 400 mg maribavir / placebo BID | Table I | 25 patients enrolled<br>24 patients completed |

| | | | | | | |
|---|---|---|---|---|---|---|
| | doses of maribavir on tacrolimus PK | placebo-controlled DDI study | | tacrolimus BID | | |
| 1263-107 | to determine the effect of repeat doses of maribavir on PK of voriconazole | single-centre, double-blind, randomised, placebo-controlled DDI study | healthy adult male and female patients | 400 mg maribavir / placebo BID<br>400 mg voriconazole BID (first day), then 200 mg BID | Tablet II | 23 patients enrolled<br>23 patients completed |
| 1263-110 | to determine the effect of rifampicin on PK of maribavir | single-centre, open-label, 3-period, fixed sequence DDI study | healthy male and adult patients | 400 mg maribavir BID<br>600 mg rifampicin | Tablet II | 15 patients enrolled<br>15 patients completed |
| SHP620-115 | to determine the effect of repeat doses of maribavir on PK of digoxin and dextromethorphan | single-centre, open-label, 3-period, fixed sequence DDI study | healthy male and female adult patients | 400 mg maribavir BID<br>0.5 mg digoxin<br>30 mg dextromethorphan | Tablet IV | 18 patients enrolled<br>17 patients completed |
| 1263-108 | to determine the effect of maribavir on ECG parameters | single-centre, double-blind, randomised, placebo- and active-controlled, 4-period study | healthy adult male and female patients | 100 mg and 1200 mg maribavir<br>400 mg moxifloxacin / placebo | Tablet II<br>Tablet III | 52 patients enrolled<br>50 patients completed |
| **Phase II studies** | | | | | | |
| 1263-200 | to assess safety, tolerability, and prophylactic anti-CMV activity (efficacy) of maribavir | multi-centre, double-blind, randomised, placebo-controlled, dose-ranging study | adult male and female patients with allographic SCT | 100 mg maribavir BID<br>400 mg maribavir QD<br>400 mg maribavir BID<br>placebo<br>for 12 weeks | Tablet I | 111 patients enrolled<br>34 patients completed |
| SHP620-202 | to assess safety and anti-CMV activity of maribavir | multi-centre, randomised, parallel group, dose-ranging study | adult transplant recipients with documented CMV infection | 400 mg, 800 mg and 1200 mg maribavir BID<br>up to 24 weeks | Tablet II | 120 patients enrolled<br>27 patients completed |
| SHP620-203 | to assess safety and anti-CMV activity of maribavir | multi-centre, randomised, parallel group, active-controlled study | adult transplant recipients without CMV organ disease | 400 mg, 800 mg and 1200 mg BID<br>900 mg valganciclovir BID for 1-3 weeks, then 900 mg QD up to 12 weeks | Tablet II | 161 patients enrolled<br>47 patients completed |
| **Phase III studies** | | | | | | |
| 1263-300 | to assess efficacy and safety of maribavir for CMV disease prophylaxis | multi-centre, double-blind, randomised, placebo-controlled study | adult allogenic SCT recipients | 100 mg maribavir / placebo BID for 12 weeks | Tablet III | 681 patients enrolled<br>328 patients completed |
| 1263-301 | to assess efficacy and safety of maribavir for CMV disease prophylaxis | multi-centre, double-blind, randomised, active-controlled study | adult liver transplant recipients | 100 mg maribavir / placebo BID<br>1000 mg ganciclovir TID for 14 weeks | Tablet III | 307 patients enrolled<br>163 patients completed |

| | | | | | | |
|---|---|---|---|---|---|---|
| SHP620-303 | to assess the efficacy and safety of maribavir for treatment of CMV infection | multi-centre, open-label, randomised, active-controlled study | adult transplant recipients who were refractory or resistant to prior anti-CMV treatment | 400 mg maribavir BID<br>ganciclovir<br>valganciclovir<br>foscarnet<br>cidofovir<br>for 8 weeks | Tablet IV | 352 patients enrolled<br>257 patients completed |

## 2.6.2. Clinical pharmacology

### *2.6.2.1. Pharmacokinetics*

***Absorption***

- **Bioavailability**

An intravenous formulation of maribavir was not developed due to the low aqueous solubility of the active substance. Thus, absolute bioavailability has not been determined.

Orally administered maribavir is rapidly absorbed with mean peak plasma concentrations of 1 to 3 h post-dose.

Following the applied dose of 400 mg BID, the terminal half-life ($t_{1/2}$) of maribavir was 3.87 h in healthy patients (studies 1263-100, 1263-110 and SHP620-115) and 4.32 h in transplant patients (study SHP620-202).

PK parameters of maribavir following a single dose of tablet formulations II, III and IV are shown in table below,(studies 1263-104, 1263-109, TAK-620-1019).

Table 4 Descriptive statistics for pharmacokinetic parameters of maribavir following a single oral dose of maribavir via formulations Tablet II, Tablet III and Tablet IV in healthy patients (studies 1263-104, 1263-109, TAK-620-1019)

| Formulation Strength | Dose (mg) | N | $AUC_{0-\infty}$ (µg*h/mL) | DN $AUC_{0-\infty}$ [a] (µg*h/mL) | $C_{max}$ (µg/mL) | $DNC_{max}$ [a] (µg/mL) | $T_{max}$ (h) | $t_{1/2}$ (h) | CL/F (L/h) | Vz/F (L) |
|---|---|---|---|---|---|---|---|---|---|---|
| Tablet II 200 mg [b] | 400 | 29 | 106.1 (39.6) | 106.1 (39.6) | 16.7 (32.2) | 16.7 (32.2) | 1.5 (1.0, 4.0) | 5.04 (28.1) | 4.30 (34.1) | 29.3 (25.7) |
| Tablet III 100 mg [c] | 100 | 15 | 26.0 (41.0) | 104.0 (41.0) | 5.83 (33.1) | 23.3 (33.0) | 1.0 (0.5, 2.0) | 3.86 (35.0) | 4.36 (34.6) | 22.6 (29.0) |
| Tablet IV 200 mg [d] | 200 | 18 | 58.6 (52.1) | 117.1 (52.1) | 11.2 (31.4) | 22.4 (31.4) | 1.0 (0.5, 2.0) | 4.27 (44.2) | 4.21 (47.3) | NC |

$AUC_{0-\infty}$=area under the plasma concentration-versus-time curve from time 0 to infinity; CL/F=oral clearance; $C_{max}$=maximum measured plasma concentration; DN=dose normalized; NC=not calculated; $t_{1/2}$=terminal half-life; $T_{max}$=time to $C_{max}$; Vz/F=oral terminal-phase distribution volume

[a] Dose normalized to maribavir 400 mg.

[b] Study 1263-104, Treatment B, drug product lot PD123M-001.
[c] Study 1263-109, Treatment B, drug product lot PD198M-001.
[d] Study TAK-620-1019, Treatment A, Treatment A, drug product lot XXVG.
Note: All values presented as arithmetic mean (%CV) except $T_{max}$, which is presented as median (minimum-maximum).
Source: Module 2.7.1 Table 17.

In study 1263-109 the relative bioavailability of crushed and whole maribavir tablets (Tablet III formulation) was determined to evaluate if maribavir can also administered crushed, e.g. via nasogastric tube (NG) in case patients are not able to swallow the tablets during recovery from transplant surgery. AUC and $C_{max}$ of crushed and whole tablets administered under fasting conditions were comparable and the 90% CIs were within the bioequivalence interval of 0.8 to 1.25.

- **Bioequivalence**

<u>Study 1263-104</u>

During clinical development five different oral IR formulations of maribavir were used. However, bioequivalence was only investigated for Tablet I and Tablet II under fasting conditions in study 1263-104. The systemic exposures in terms of AUC and $C_{max}$ following administration of a single oral dose of 400 mg maribavir (Tablet I and Tablet II) were comparable and the 90% CIs were within the

bioequivalence acceptance range of 80-125%. Median $T_{max}$ occurred after 1.5 h for both formulations (Table 5).

Table 5 Statistical analysis of the pharmacokinetic parameters of maribavir following a single oral dose of 400 mg tablet I or tablet II under fasted conditions (study 1263-104)

| Parameter | Tablet II (N=29) | Tablet I (N=28) | Tablet II/Tablet I[a] (90% CI) (N=28) |
|---|---|---|---|
| $AUC_{0-t}$ (µg*h/mL)[b] | 95.0 | 91.8 | 1.038 (0.968, 1.114) |
| $AUC_{0-\infty}$ (µg*h/mL)[b] | 99.0 | 95.6 | 1.040 (0.968, 1.118) |
| $C_{max}$ (µg/mL)[b] | 15.9 | 16.5 | 0.964 (0.887, 1.059) |
| $T_{max}$ (h)[c] | 1.5 (1.0, 4.0) | 1.5 (0.5, 4.0) | N/A[d] |

ANOVA=analysis of variance; AUC=area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration ($AUC_{0-t}$) and from time 0 to infinity ($AUC_{0-\infty}$); CI=confidence interval; $C_{max}$=maximum measured plasma concentration; N/A=not applicable; $T_{max}$=time to $C_{max}$

[a] Least squares geometric mean ratio.

[b] Geometric mean.

[c] Median (minimum, maximum).

[d] The p-value for the ranked values of $T_{max}$ from the ANOVA model was 0.858.

Source: Study 1263-104 CSR, Table 10.2.3.1, Table 10.2.3.2, and Table 10.2.3.4

For bridging between different formulations used during clinical development, the applicant performed a post-hoc analysis comparing the pharmacokinetic parameters after a 400 mg maribavir dose under fasting conditions (Table 6).

According to this analysis the geometric mean ratios for $AUC_{0-\infty}$ after a single dose are all close to 1 (0.98 to 1.08), however, the 90% CI are not in the bioequivalence range of 0.8 to 1.25.

The $C_{max}$ values were equivalent between Tablet III and Tablet IV; however, Tablet III and Tablet IV had 40% and 35%, higher $C_{max}$, respectively, compared to Tablet II, along with slightly shorter $T_{max}$.

Table 6 Post-hoc statistical analysis of the pharmacokinetic parameters of maribavir following a single oral dose of 400 mg maribavir via different formulations (under fasting conditions)

| Parameter (Unit) | N | Tablet I GLSM | N | Capsule GLSM | Geometric Mean Ratio (Tablet I/Capsule) | 90% CI for GLSM Ratio |
|---|---|---|---|---|---|---|
| $AUC_{0-t}$ (µg*h/mL)[a] | 25 | 87.85 | 10 | 92.42 | 0.95 | (0.774, 1.167) |
| $AUC_{0-\infty}$ (µg*h/mL)[a] | 25 | 92.17 | 10 | 94.34 | 0.98 | (0.784, 1.218) |
| $C_{max}$ (µg/mL)[a] | 25 | 16.00 | 10 | 15.86 | 1.01 | (0.852, 1.195) |
| $T_{max}$ (h)[a,b] | 25 | 1.50 (1.00, 4.00) | 10 | 1.75 (1.00, 3.00) | NA | NA |
| | N | Tablet III GLSM | N | Tablet II GLSM | Geometric Mean Ratio (Tablet III/Tablet II) | 90% CI for GLSM Ratio |
| DN $AUC_{0-t}$ (µg*h/mL)[c] | 15 | 88.32 | 29 | 94.96 | 0.93 | (0.756, 1.144) |
| DN $AUC_{0-\infty}$ (µg*h/mL)[c] | 15 | 97.32 | 29 | 99.05 | 0.98 | (0.794, 1.216) |
| DN $C_{max}$ (µg/mL)[c] | 15 | 22.18 | 29 | 15.88 | 1.40 | (1.181, 1.651) |
| $T_{max}$ (h)[c,d] | 15 | 1.00 (0.50, 2.00) | 29 | 1.50 (1.00, 4.00) | NA | NA |
| | N | Tablet IV GLSM | N | Tablet II GLSM | Geometric Mean Ratio (Tablet IV/Tablet II) | 90% CI for GLSM Ratio |
| DN $AUC_{0-t}$ (µg*h/mL)[e] | 18 | 100.23 | 29 | 94.96 | 1.06 | (0.869, 1.283) |
| DN $AUC_{0-\infty}$ (µg*h/mL)[e] | 18 | 105.08 | 29 | 99.05 | 1.06 | (0.868, 1.297) |
| DN $C_{max}$ (µg/mL)[e] | 18 | 21.39 | 29 | 15.88 | 1.35 | (1.150, 1.578) |
| $T_{max}$ (h)[e,f] | 18 | 1.00 (0.50, 2.00) | 29 | 1.50 (1.00, 4.00) | NA | NA |
| | N | Tablet IV GLSM | N | Tablet III GLSM | Geometric Mean Ratio (Tablet IV/Tablet III) | 90% CI for GLSM Ratio |
| DN $AUC_{0-t}$ (µg*h/mL)[g] | 18 | 100.23 | 15 | 88.32 | 1.13 | (0.904, 1.424) |
| DN $AUC_{0-\infty}$ (µg*h/mL)[g] | 18 | 105.08 | 15 | 97.32 | 1.08 | (0.854, 1.365) |
| DN $C_{max}$ (µg/mL)[g] | 18 | 21.39 | 15 | 22.18 | 0.96 | (0.802, 1.160) |
| $T_{max}$ (h)[g,h] | 18 | 1.00 (0.50, 2.00) | 15 | 1.00 (0.50, 2.00) | NA | NA |

$AUC_{0-t}$=area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$=area under the plasma concentration-versus-time curve from time 0 to infinity; CI=confidence interval; $C_{max}$=maximum measured plasma concentration; DN=dose-normalized; GLSM=geometric least square mean; $T_{max}$=time to $C_{max}$

[a] $AUC_{0-t}$, $AUC_{0-\infty}$, $C_{max}$ and $T_{max}$ for capsule were from Study CMAB1001 400 mg dose group, and $AUC_{0-t}$, $AUC_{0-\infty}$, $C_{max}$, and $T_{max}$ for Tablet I were calculated based on Study 1263-102, treatment with maribavir alone, male subjects only and Study 1263-104, Treatment B, male subjects only.

[b] The p-value from Wilcoxon rank sum test was 0.158.

[c] $AUC_{0-t}$, $AUC_{0-\infty}$, $C_{max}$, and $T_{max}$ for Tablet II were from Study 1263-104 Treatment B and $T_{max}$ and dose-normalized $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ for Tablet III were calculated based on Study 1263-109 Treatment B.

[d] The p-value from Wilcoxon rank sum test was 0.006.

[e] $AUC_{0-t}$, $AUC_{0-\infty}$, $C_{max}$, and $T_{max}$ for Tablet II were from Study 1263-104 Treatment B and $T_{max}$ and dose-normalized $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ for Tablet IV were calculated based on Study TAK-620-1019 Treatment B.

[f] The p-value from Wilcoxon rank sum test was 0.096.

[g] Dose-normalized $AUC_{0-t}$, $AUC_{0-\infty}$, $C_{max}$, and $T_{max}$ for Tablet III were calculated based on Study 1263-109 Treatment B, and $T_{max}$ and dose-normalized $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ for Tablet IV were calculated based on TAK-620-1019 Treatment B.

[h] The p-value from Wilcoxon rank sum test was 0.029.

Note: An analysis of variance with treatment as fixed effect was used to fit to ln-transformed pharmacokinetic parameters and estimate all treatment differences and corresponding two-sided 90% CIs. The difference and 90% CI of the difference were back-transformed and expressed as geometric least square mean ratios and 90% CI of the ratios.

Source: Maribavir PK Post Hoc Analysis, Table 2.2, Table 1.3, Table 1.4, and Table 1.5

- **Influence of food**

The effect of food on the PK of maribavir was investigated for the capsule and Tablet II formulation.

Study CMAB1002

Administration of maribavir capsule with a high fat, high caloric meal (fat: 67 g, carbohydrate: 58 g, protein: 33 g) decreased $C_{max}$ and AUC and delayed the time of maximum maribavir concentration ($T_{max}$) by about 2 h. The ratio of geometric mean (fed/fasted) were 0.715 (90% CI: 0.61, 0.84) for $C_{max}$ and 0.729 (90% CI: 0.58, 0.91) for $AUC_{0-\infty}$ (Table 7).

Table 7 Statistical analysis of the pharmacokinetic parameters of maribavir following a single oral dose of 400 mg maribavir (capsule) under fed and fasted conditions (study CMAB1002)

| Parameter | Maribavir 400 mg Fed (N=10) | Maribavir 400 mg Fasted (N=13) | Maribavir 400 mg Fed/Fasted[a] (90% CI) (N=13) |
|---|---|---|---|
| $AUC_{0-t}$ (µg*h/mL)[b] | 52.01 | 69.99 | 0.734 (0.588, 0.917) |
| $AUC_{0-\infty}$ (µg*h/mL)[b] | 53.09 | 71.85 | 0.729 (0.579, 0.918) |
| $C_{max}$ (µg/mL)[b] | 11.41 | 16.11 | 0.715, (0.609, 0.840) |
| $T_{max}$ (h)[c] | 3.5 (1.5, 5.0) | 1.5 (1.0, 2.0) | N/A[d] |

ANOVA=analysis of variance; AUC=area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration ($AUC_{0-t}$) and from time 0 to infinity ($AUC_{0-\infty}$); CI=confidence interval; $C_{max}$=maximum measured plasma concentration; N/A=not applicable; $T_{max}$=time to $C_{max}$
[a] Least squares geometric mean ratio.
[b] Geometric mean.
[c] Median (minimum, maximum).
[d] The p-value for the ranked values of $T_{max}$ from the ANOVA model was 0.0015.
Note: The maribavir 100 mg capsule formulation was used in this study.
Source: Study CMAB1002 CSR, Table 10.2.11.2, Table 10.2.11.5, Table 10.2.11.6, and Table 10.2.11.7

Study 1263-104

Results from the statistical analysis of the maribavir PK parameters following a single-dose of 400 mg (Tablet II) under moderate-fat and fasted conditions are presented in table below. Based on the ratio of geometric means of the two treatments, $C_{max}$ was 28% lower when maribavir was administered with food. AUC values, although 14% lower when maribavir was administered under moderate-fat conditions, can still be considered as bioequivalent with 90% CI of 0.8-0.93. $T_{max}$ was prolonged from 1.5 h to 2 h (Table 8).

Table 8 Statistical analysis of the pharmacokinetic parameters of maribavir following a single oral dose of 400 mg maribavir Tablet II under fed (moderate-fat) and fasted conditions (study 1263-104)

| Parameter | Tablet II Fed (N=29) | Tablet II Fasted (N=29) | Tablet II Fed / Tablet II Fasted[a] (90% CI) (N=28) |
|---|---|---|---|
| $AUC_{0-t}$ (µg*h/mL)[b] | 81.6 | 95.0 | 0.860 (0.802, 0.922) |
| $AUC_{0-\infty}$ (µg*h/mL)[b] | 85.6 | 99.0 | 0.864 (0.804, 0.929) |
| $C_{max}$ (µg/mL)[b] | 11.4 | 15.9 | 0.722 (0.656, 0.793) |
| $T_{max}$ (h)[c] | 2.0 (1.0, 4.0) | 1.5 (1.0, 4.0) | N/A[d] |

ANOVA=analysis of variance; AUC=area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration ($AUC_{0-t}$) and from time 0 to infinity ($AUC_{0-\infty}$); CI=confidence interval; $C_{max}$=maximum measured plasma concentration; N/A=not applicable; $T_{max}$=time to $C_{max}$
[a] Least squares geometric mean ratio.
[b] Geometric mean.
[c] Median (minimum, maximum).
[d] The p-value for the ranked values of $T_{max}$ from the ANOVA model was <0.001.
Source: Study 1263-104 CSR, Table 10.2.3.2, Table 10.2.3.3, and Table 10.2.3.4

The results of studies CMAB1002 and 1263-104 indicate that the systemic exposure of maribavir depends on the fat content of the meal. However, $C_{trough}$ (most relevant PK parameter for antiviral

activity) seems not to be impacted by food based on available data and thus administration of maribavir without regard to food is considered acceptable.

***Distribution***

Maribavir is highly bound to plasma proteins. Ex vivo protein binding of maribavir (98.5-99.0%) was consistent with in vitro binding (98.0%), with no apparent difference observed between different study populations, i.e. healthy patients, patients with hepatic (moderate) or renal (mild/moderate or severe) impairment, HIV patients, or CMV-seropositive transplant patients.

Plasma protein binding for the maribavir main metabolite VP44469 was 89.7 to 92.4% ex vivo.

***Elimination***

Following administration of a [$^{14}$C]-maribavir solution, unchanged maribavir was the principal drug-related species circulating in plasma, and maribavir's despropyl metabolite (M4, VP 44469) accounts for the remainder of the circulating systemic radioactivity for the first 24 hours after drug administration.

75% (ranging from 59% to 88%) of the drug-related material was recovered, the majority within 24 to 48 h after drug administration. The main metabolite identified in urine and faeces was VP 44469, accounting for 34.0% and 7.2% of the dose, respectively. The unchanged drug accounted for 1.8% and 5.7% of the dose in urine and faeces, respectively. M1, M2, M3, M5 and M6 (Figure 2) were identified as minor metabolites in urine, and no other metabolites than VP 44469 was identified in faeces.

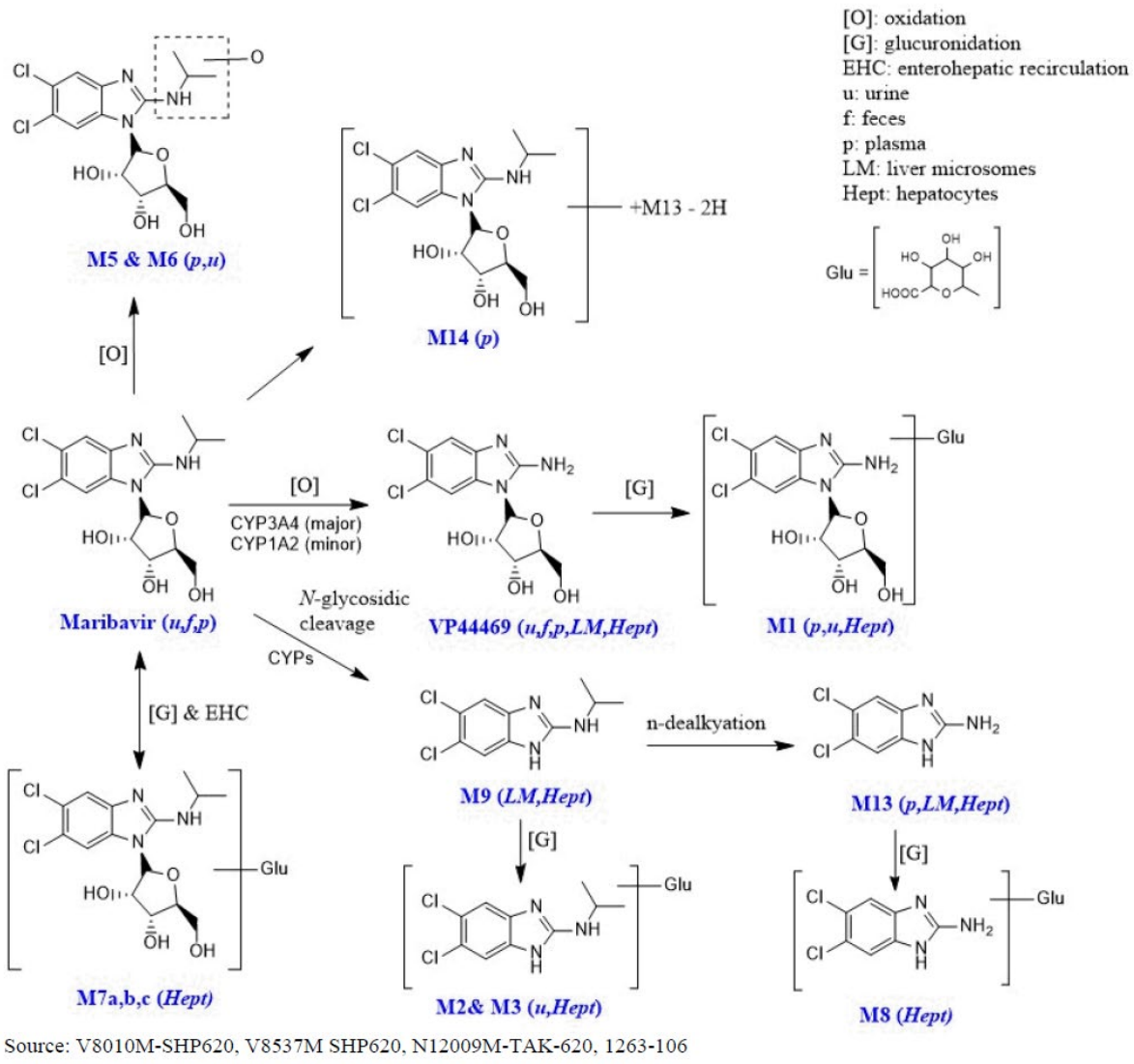
***Metabolism***

Following oral administration, maribavir is primarily eliminated by hepatic metabolism followed by urinary and faecal excretion of the metabolites.

The proposed metabolic scheme for maribavir in humans is shown in Figure 22. Metabolic pathways include N-dealkylation of the isopropyl moiety to form VP 44469 (M4) followed by glucuronide conjugation to yield M1, hydrolysis to lose ribose and subsequent formation of glucuronides M2 and M3 and oxidation of the isopropyl amine moiety to form metabolites M5 and M6.

Formation of VP 44469 is mainly mediated by CYP3A4 with some contribution from CYP1A2.

Multiple UGT enzymes, namely UGT1A1, UGT1A3, UGT2B7, and possibly UGT1A9, are involved in the glucuronidation of maribavir in humans.




Source: V8010M-SHP620, V8537M SHP620, N12009M-TAK-620, 1263-106

Figure 2 Pathways for maribavir metabolism in humans

**Population PK Analysis for Phases 1 through 3 Studies, including 303 (Final PopPK Analysis)**

A PopPK model was developed to describe the time course of maribavir concentrations in plasma in healthy volunteers, subjects with hepatic impairment, subjects with renal impairment, stable renal transplant patients, and haematopoietic SCT or SOT patients with CMV infections using NONMEM (version 7.4.3). The following covariates were evaluated for their impact on the PK of maribavir: age, body weight, body mass index (BMI), age category, gender, race, health status, study, diarrhoea, vomiting, dose, disease characteristics (transplant type, baseline plasma CMV DNA category, CMV category [asymptomatic CMV infection, CMV organ disease and symptomatic CMV infection], hepatic impairment, presence of CMV mutations, baseline use of antilymphocyte antibody, episode of qualifying infection, prior use of CMV prophylaxis, GI GVHD), concurrent medications of strong CYP3A inhibitors, concurrent medications of strong CYP3A inducers, concurrent medications of acid-reducing agents such as H2 blockers (H2B), proton pump inhibitors (PPI) and antacids. Although various solid formulations were used in clinical trials, formulation was not evaluated as a covariate in the PopPK analysis.

The final PK model was a two-compartment disposition model with first-order absorption and elimination, and an absorption lag-time. The model included CYP3A inhibitor and inducer effects on

CL/F, dose effect on absorption rate constant (Ka) and patients with CMV effect on CL/F. In addition, CL/F, Vc/F, apparent volume of peripheral compartment (Vp/F) and inter compartment clearance between central and peripheral compartments (Q/F) all increased with weight fixed to allometric scalars. The parameters from the final population PK model are defined below and the parameter estimates are presented in Table 9.

$CL/F = 3.77 \times (WT/70)^{0.75} \times 0.700^{\text{CYP3A inhibitors}} \times 2.24^{\text{CYP3A inducers}} \times 0.756^{\text{patients with CMV}}$

$Q/F = 0.908 \times (WT/70)^{0.75}$

$Vc/F = 18.6 \times (WT/70)^{1}$

$Vp/F = 8.66 \times (WT/70)^{1}$

$Ka = 0.336 \times (DOSE/800)^{-1.94}$

Lag-time = 0.271

Table 9 Parameter Estimates of Final PopPK Model

| | | **NONMEM Estimates** | | | | **MCMC BAYES Estimates[a]** |
|---|---|---|---|---|---|---|
| **Parameter** | **Units** | **Estimate[a]** | **%RSE[b]** | **95% CI[a]** | **IIV CV%[c] (%RSE)** | **Median [95% CI]** |
| **CL/F** | L/h | 3.77 | 3.79 | 3.50 to 4.06 | 52.5 (6.43) | 3.79 [3.54 to 4.10] |
| **Vc/F** | L | 18.6 | 3.45 | 17.3 to 19.8 | 34.0 (14.4) | 17.7 [16.5 to 19.1] |
| **Q/F** | L/h | 0.908 | 12.9 | 0.705 to 1.17 | 90.7 (24.5) | 0.841 [0.692 to 1.04] |
| **Vp/F** | L | 8.66 | 10.4 | 7.05 to 10.6 | 103 (20.7) | 7.26 [6.08 to 8.85] |
| **$K_a$** | $h^{-1}$ | 0.336 | 10.9 | 0.271 to 0.415 | 152 (14.2) | 0.396 [0.299 to 0.521] |
| **Lag-time** | h | 0.271 | 5.91 | 0.241 to 0.304 | 44.1 (28.8) | 0.253 [0.218 to 0.284] |
| **CL/F~weight** | unitless | 0.75 fixed | - | - | - | 0.75 fixed |
| **Vc/F~weight** | unitless | 1 fixed | - | - | - | 1 fixed |
| **Q/F~weight** | unitless | 0.75 fixed | - | - | - | 0.75 fixed |
| **Vp/F~weight** | unitless | 1 fixed | - | - | - | 1 fixed |
| **CL/F~strong CYP3A inhibitors** | unitless | 0.700 | 1.98 | 0.673 to 0.727 | | 0.704 [0.678 to 0.733] |

Table 9 Parameter Estimates of Final PopPK Model

| | | NONMEM Estimates | | | | MCMC BAYES Estimates[a] |
|---|---|---|---|---|---|---|
| **Parameter** | **Units** | **Estimate[a]** | **%RSE[b]** | **95% CI[a]** | **IIV CV%[c] (%RSE)** | **Median [95% CI]** |
| **CL/F~strong CYP3A inducers** | unitless | 2.24 | 2.95 | 2.11 to 2.37 | | 2.23 [2.13 to 2.34] |
| **$K_a$~dose** | unitless | -1.94 | 6.49 | -2.19 to -1.70 | | -1.78 [-2.08 to -1.49] |
| **CL/F~ transplant patients** | unitless | 0.756 | 4.63 | 0.690 to 0.827 | | 0.747 [0.684 to 0.817] |
| **$\sigma^2_{prop\ Phase\ 1}$** | unitless | 0.0673 | 2.86 | 0.0635-0.0710 | 25.9[d] | 0.0682 [0.0645 to 0.0723] |
| **$\sigma^2_{prop\ Phase\ 2}$** | unitless | 0.137 | 3.67 | 0.127-0.147 | 37.0[d] | 0.136 [0.127 to 0.147] |

CI=confidence interval; CL/F=apparent total clearance; CV=coefficient of variation; IV=inter-subject variability; $K_a$=first-order absorption, Q/F=inter compartment clearance between central and peripheral compartments, RSE=relative standard error, $\sigma^2_{prop}$=proportional residual error; Vc/F=apparent volume of central compartment, Vp/F=apparent volume of peripheral compartment

[a] Back-transformed from natural log scale (except for $s^2$, CL/F~ weight, Vc/F~weight, Q/F~weight, Vp/F~weight, CL/F~strong CYP3A inhibitors, CL/F~strong CYP3A inducers, Ka~dose)

[b] RSE=SE.100 (except for $s^2$, CL/F~ weight, Vc/F~weight, Q/F~weight, Vp/F~weight, CL/F~strong CYP3A inhibitors, CL/F~strong CYP3A inducers, Ka~dose). RSE for $s^2$, CL/F~ weight, Vc/F~weight, Q/F~weight, Vp/F~weight, CL/F~strong CYP3A inhibitors, CL/F~strong CYP3A inducers, Ka~dose =SE(q)/q.100

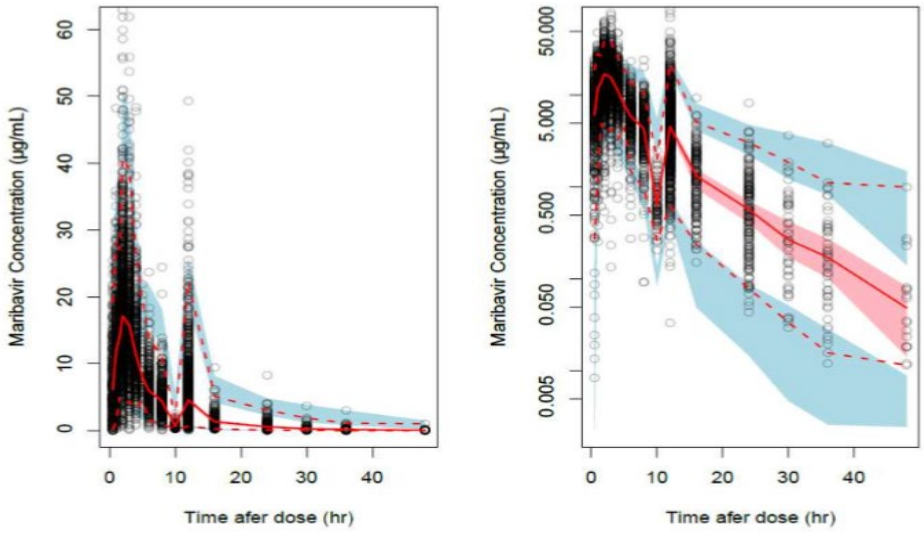
[c] CV for IIV calculated as $CV_{TVP}= \sqrt{e^{\omega_p^2}}*100$ if $\omega_p^2 \leq 0.15$, else $CV_{TVP} = \sqrt{e^{\omega_p^2} - 1}*100$

[d] Proportional residual error expressed as CV.

The reference population is a 70-kg subject without CMV administered 800 mg maribavir in the absence of strong CYP3A inhibitors or inducers.

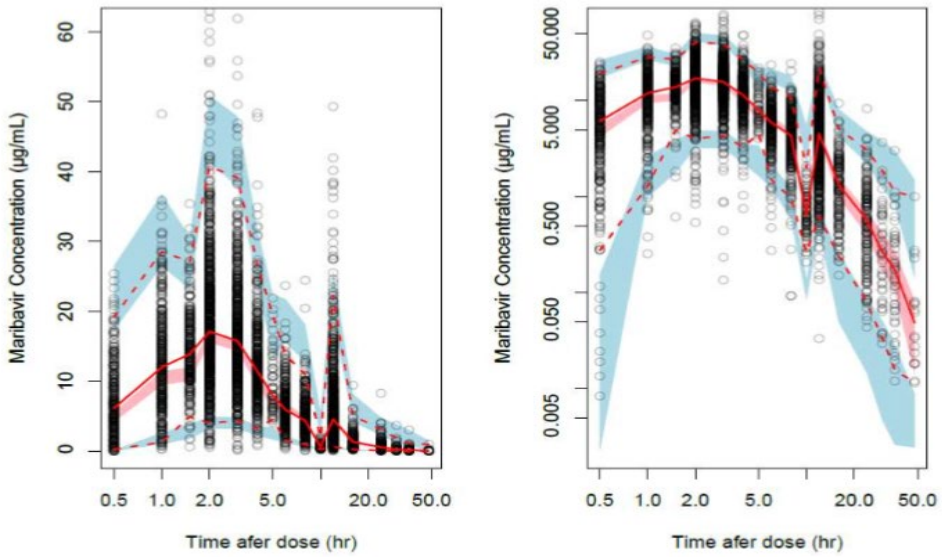
Source: Final Population PK report.

Figure 3 Prediction-Corrected Visual Predictive Check for the final PK Model (Run 171)




Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th Percentile of Observed Concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th Percentiles of Predicted Concentrations
Source:171VPC.tab

**Figure 5-6 Prediction-Corrected Visual Predictive Check for the Final PK Model (Run 171)**




Time after dose on logarithmic scale
Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th Percentile of Observed Concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th Percentiles of Predicted Concentrations
Source: 171VPC.tab

CL/F was estimated to be 30% lower in the presence of strong CYP3A inhibitors and 2.24-fold higher in the presence of strong CYP3A inducers, consistent with the findings from Studies 1263-102 and 1263-110, respectively

CL/F was estimated to be 24% lower for transplant patients with CMV compared to all other subjects, 3.77 L/hr and 2.85 L/hr for healthy volunteers and transplant patients with CMV, respectively. The estimates of IIV were small to moderate (CV ranged from 34% to 53%) for all parameters apart from Q/F, Vp/F and Ka (91% to 152%). The shrinkages of individual random effects were estimated as 6% for CL/F, 21% for Vc/F, 39%for Q/F, 46% for Vp/F, 35% for Ka and 47% for lag-time.

**Intra- and inter-individual variability**

Intra- and inter-subject variability in $AUC_{0-\infty}$ and $C_{max}$ were determined in studies 1263-104 (Tablet I and Tablet II formulation) and 1263-109 (Tablet III formulation).

The inter-subject variability of maribavir was moderate for $C_{max}$ and $AUC_{0-\infty}$, with %CV ranging from 18.3% to 34.0% and from 36.0% to 36.2%, respectively. The intra-subject variability for $C_{max}$ and $AUC_{0-\infty}$ was lower, ranging from 18.5% to 21.1% and from 11.8% to 16.1%, respectively.

**Pharmacokinetics in target population**

Some serial PK samples were taken in the Phase II studies 1263-200, SHP620-202 and SHP620-203, in which maribavir doses up to 1200 mg BID (Tablet I and II formulation) were investigated in adult transplant recipients.

Table 10 Definition of lower and upper no effect boundaries for dose adjustment considerations

| | | Lower No Effect Boundary | Upper No Effect Boundary | |
|---|---|---|---|---|
| Parameter | 400 mg BID [a] | (80% of 400 mg BID Exposure) | Exposure [b] | Exposure Ratio [c] |
| $C_{max}$ (µg/mL) | 17.2 | NA | 36.7 | 2.1 |
| $AUC_{0-\tau}$ (µg*h/mL) | 128 | 102 | 379 | 3.0 |
| $C_{trough}$ (µg/mL) | 4.90 | 3.92 | NA | NA |

$AUC_{0-\tau}$=area under the plasma concentration-time curve over the dosing interval; $C_{max}$=maximum observed plasma concentration; $C_{trough}$=plasma concentration at the end of a dosing interval; NA=not applicable

[a] Based on the post hoc geometric mean estimates for all transplant patients with CMV infections (n=485) at 400 mg BID from final popPK analysis.

[b] Based on the post hoc geometric mean estimates for transplant patients with CMV infections in Phase 2 studies (n=232) at 1200 mg BID from final popPK analysis.

[c] Ratio of steady-state exposure at 1200 mg BID to steady-state exposure at 400 mg BID in transplant patients with CMV infections.

Source: Final Population PK report, Table 5-9, Table 5-10

**Special population**

- **Impaired renal function**

Study 1263-101

Study 1263-101 was an open-label, parallel group, single-dose study to evaluate the effect of renal impairment on the PK of maribavir. Thirty-one (31) adult patients with either normal renal function (CLcr >80 ml/min) or varying degrees of renal impairment (mild: CLcr 50-80 ml/min, moderate: CLcr 30 - <50 ml/min, severe: CLcr <30 ml/min) were enrolled. A single 400 mg maribavir dose (Tablet I) was administered under fasting conditions on Day 1.

Groups with mild and moderate renal impairment were merged due to small sample size per group. The PK results for the three renal function groups are shown in Table 11 and the statistical analysis for maribavir AUC and Cmax in Table 12.

Table 11 Summary of mean (SD) maribavir (a) and VP 44469 (b) pharmacokinetic parameters for patients with mild/moderate or severe renal impairment versus healthy control patients (study 1263-101)

**a**)

| Total Maribavir | Unit | Normal Renal Function (N=12) | | Mild/Moderate Renal Impairment (N=10) | | Severe Renal Impairment (N=8) | |
|---|---|---|---|---|---|---|---|
| $T_{max}$ | (h) | 1.8 | (0.7) | 2.2 | (1.1) | 1.8 | (0.8) |
| $C_{max}$ | (µg/mL) | 22.56 | (5.98) | 21.97 | (6.89) | 21.5 | (7.7) |
| Kel | (1/h) | 0.132 | (0.03) | 0.125 | (0.015) | 0.136 | (0.029) |
| $T_{1/2}$ | (h) | 5.51 | (1.16) | 5.61 | (0.65) | 5.28 | (1.05) |
| $AUC_{0-t}$ | (µg*h/mL) | 136.6 | (59.5) | 143.6 | (44.5) | 133.8 | (70.6) |
| $AUC_{0-\infty}$ | (µg*h/mL) | 138.6 | (61.9) | 145.3 | (45.4) | 135.7 | (72.6) |
| % Extrap. | (%) | 1.04 | (0.98) | 1.09 | (0.57) | 1.16 | (0.99) |
| $V_z/F$ | (L) | 25.5 | (8.7) | 24.7 | (9.8) | 26.8 | (11.1) |
| CL/F | (L/h) | 3.38 | (1.29) | 3.05 | (1.12) | 3.56 | (1.53) |
| $V_z/F/kg$ | (L/kg) | 0.327 | (0.131) | 0.297 | (0.096) | 0.336 | (0.116) |
| CL/F/kg | (L/h/kg) | 0.0434 | (0.0185) | 0.037 | (0.0114) | 0.0445 | (0.0132) |

**b)**

| Total VP 44469 | Unit | Normal Renal Function (N=12) | | Mild/Moderate Renal Impairment (N=10) | | Severe Renal Impairment (N=8) | |
|---|---|---|---|---|---|---|---|
| $T_{max}$ | (h) | 3.2 | (1.4) | 4.7 | (1.2) | 4.6 | (2.0) |
| $C_{max}$ | (µg/mL) | 1.85 | (0.62) | 2.45 | (0.59) | 2.44 | (0.66) |
| Kel | (1/h) | 0.105 | (0.03) | 0.090 | (0.019) | 0.084 | (0.029) |
| $T_{1/2}$ | (h) | 7.28 | (2.66) | 8.08 | (1.92) | 9.74 | (5.68) |
| $AUC_{0-t}$ | (µg*h/mL) | 21.8 | (7.40) | 39.4 | (10.2) | 41.7 | (10.3) |
| $AUC_{0-\infty}$ | (µg*h/mL) | 23.0 | (8.2) | 42.5 | (11.4) | 46.9 | (13.1) |
| % Extrap. | (%) | 4.3 | (4.61) | 6.95 | (3.85) | 10.01 | (8.80) |
| $V_z/F$ | (L) | 194.1 | (69.0) | 114.2 | (27.6) | 120.5 | (52.1) |
| CL/F | (L/h) | 19.24 | (5.81) | 10.14 | (3.09) | 9.08 | (2.31) |
| $V_z/F/kg$ | (L/kg) | 2.437 | (0.813) | 1.399 | (0.338) | 1.563 | (0.728) |
| CL/F/kg | (L/h/kg) | 0.2425 | (0.0712) | 0.1255 | (0.0421) | 0.1193 | (0.0408) |

Table 12 Statistical analysis of the pharmacokinetic parameters of maribavir for patients with mild/moderate or severe renal impairment versus healthy control patients (study 1263-101)

| **Maribavir** | | |
|---|---|---|
| | **Mild/Moderate Renal Impairment/ Healthy Control[b]**<br><br>**(90% CI), N=10** | **Severe Renal Impairment/Healthy Control[b]**<br><br>**(90% CI), N=8** |
| $AUC_{0-\infty}$ (µg*h/ml) | 1.084 (0.806, 1.458) | 0.961 (0.701, 1.318) |
| $AUC_{0-\infty,u}$ (µg*h/ml) | 1.111 (0.817, 1.510) | 1.197 (0.872, 1.643) |
| $C_{max}$ (µg/ml) | 0.959 (0.767, 1.200) | 0.930 (0.732, 1.180) |
| $C_{max,u}$ (µg/ml) | 1.043 (0.764, 1.425) | 1.226 (0.888, 1.691) |

[b] Least square geometric mean ratio

No clinically significant effect of mild/moderate (CLcr between 30 and 80 ml/min) or severe (CLcr ≤30 ml/min) renal impairment was observed on maribavir total PK parameters following a single dose of 400 mg maribavir. No dose adjustment is proposed.

For VP 44469, AUC values for mild/moderate renal impairment and severe renal impairment groups were about 2 times higher while clearance values were about 2 times lower compared to the respective values for the normal renal function group. These increases in VP 44469 exposure are not considered clinically significant.

PK data in patients with ESRD including patients on haemo- or peritoneal dialysis are not available. However, based on protein binding data it is unlikely that maribavir will be significantly removed by dialysis and a dose adjustment is not considered necessary.

- **Impaired hepatic function**

Study 1263-103

Study 1263-103 was a single-centre, open-label, parallel group, single-dose study to evaluate the PK of maribavir in adult patients with moderate hepatic impairment compared to patients with normal hepatic function. A single 200 mg dose of maribavir (Tablet I) was administered under fasting conditions on Day 1.

A summary of mean (SD) maribavir pharmacokinetic parameters for patients with normal hepatic function and patients with moderate hepatic impairment is presented in Table 13. Except for Cmax, statistical analysis did not reveal significant differences between the hepatic function groups. Mean Cmax values were 35% higher in patients with moderate hepatic impairment compared to patients with normal hepatic function. Mean Cmax,u values were 10% higher in patients with moderate hepatic impairment compared to patients with normal hepatic function. Based on total plasma maribavir concentrations, patients with moderately impaired hepatic function tended to show higher AUC values (about 25%) and lower clearance values (about 20%) compared to patients with normal hepatic function. AUC and clearance values, based on unbound maribavir plasma concentrations, for patients with normal hepatic function and moderately impaired hepatic function were comparable.

Statistical analysis of VP 44469 pharmacokinetic parameters did not reveal significant differences between the two hepatic function groups. Compared to patients with normal hepatic function, patients with moderately impaired hepatic function tended to show slightly longer half-life and lower clearance values (i.e. higher AUC values).

Table 13 Summary of mean (SD) maribavir (a) and VP 44469 (b) pharmacokinetic parameters for patients with moderate hepatic impairment versus healthy control patients

**a)**

| Mean (SD) Maribavir Pharmacokinetic Parameters, P-Values, and Ratios of Geometric Means (90% CI) | | | | | |
|---|---|---|---|---|---|
| **Maribavir Parameter** | **Unit** | **Normal Hepatic Function (N=10)** | **Moderate Hepatic Impairment (N=10)** | **P-Value** | **Ratio of Geometric Means (90% CI)** |
| $T_{max}$ | (h) | 1.95 (1.5) | 1 .25 (0.42) | 0.1725 | NC |
| $C_{max}$ | (µg/mL) | 9.59 (1.72) | 13.45 (5.21) | 0.0243 | 1.346 (1.091, 1.660) |
| Kel | (1/h) | 0.1085 (0.0274) | 0.1090 (0.0560) | NC | NC |
| $T_{1/2}$ | (h) | 6.91 (2.47) | 8.05 (3.89) | 0.4470 | NC |
| $AUC_{0-t}$ | (µg•h/mL) | 64.3 (18.4) | 88.1 (51.8) | 0.2799 | 1.240 (0.887, 1.733) |
| $AUC_{0-\infty}$ | (µg•h/mL) | 64.7 (18.6) | 91.6 (57.6) | 0.2646 | 1.261 (0.889, 1.787) |
| $V_z/F$ | (L) | 32.6 (14.2) | 27.2 (7.0) | 0.2824 | 0.860 (0.678, 1.089) |
| CL/F | (L/h) | 3.33 (0.97) | 2.89 (1.40) | 0.2651 | 0.793 (0.560, 1.125) |
| CL/F/kg | (mL/h/kg) | 48.1 (16.4) | 39.6 (17.9) | 0.2110 | 0.770 (0.542, 1.092) |
| $f_u$ | (%) | 1.5 (0.4) | 1.3 (0.4) | 0.1015 | 0.817 (0.667, 1.001) |
| $C_{max,\,u}$ | (µg/mL) | 0.143 (0.036) | 0.160 (0.049) | 0.4381 | 1.101 (0.892, 1.360) |
| $AUC_{0-\infty,\,u}$ | (µg*h/mL) | 0.949 (0.266) | 1.093 (0.599) | 0.8839 | 1.030 (0.727, 1.460 |
| $V_z/F_{,\,u}$ | (L) | 2167 (704) | 2313 (817) | 0.7342 | 1.052 (0.816, 1.356) |
| $CL/F_{,\,u}$ | (L/h) | 225 (58) | 245 (139) | 0.8842 | 0.971 (0.685, 1.376) |
| $CL/F/kg_{,\,u}$ | (mL/h/kg) | 3203 (868) | 3269 (1570) | 0.7430 | 0.942 (0.690, 1.287) |
| NC=not calculated | | | | | |

**b)**

| Mean (SD) VP 44469 Pharmacokinetic Parameters, P-Values, and Ratios of Geometric Means (90% CI) | | | | | |
|---|---|---|---|---|---|
| **VP 44469 Parameter** | **Unit** | **Normal Hepatic Function (N=10)** | **Moderate Hepatic Impairment (N=10)** | **P-Value** | **Ratio of Geometric Means (90% CI)** |
| $T_{max}$ | (h) | 2.7 (1.62) | 2.8 (0.89) | 0.8660 | NC |
| $C_{max}$ | (µg/mL) | 0.884 (0.254) | 1.16 (0.596) | 0.4041 | 1.190 (0.836, 1.693) |
| Kel | (1/h) | 0.1101 (0.0371) | 0.0957 (0.0476) | NC | NC |
| $T_{1/2}$ | (h) | 6.98 (2.46) | 8.65 (3.55) | 0.2368 | NC |
| $AUC_{0-t}$ | (µg•h/mL) | 9.73 (2.45) | 12.97 (5.12) | 0.1119 | 1.284 (0.991, 1.665) |
| $AUC_{0-\infty}$ | (µg•h/mL) | 9.84 (2.50) | 13.4 (5.36) | 0.0921 | 1.309 (1.007, 1.702) |
| $V_z/F$ | (L) | 212 (73.0) | 220 (127) | 0.7257 | 0.919 (0.607, 1.389) |
| CL/F | (L/h) | 21.7 (6.45) | 17.16 (6.67) | 0.0921 | 0.764 (0.588, 0.993) |
| CL/F/kg | (mL/h/kg) | 306 (72.0) | 243 (123) | 0.0677 | 0.742 (0.568, 0.968) |
| NC=not calculated | | | | | |

Maribavir has not been studied in patients with severe hepatic impairment. However, it is expected that severe hepatic impairment might not lead to a significant increase of maribavir exposure.

**Drug-Drug-Interactions**

The Applicant has conducted several in vitro experiments to investigate the interaction potential of maribavir via relevant enzymes and transporters. Maribavir appeared to be in vitro inhibitor of CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzymes, as well as an inducer of CYP3A4 and CYP1A2. In addition, positive inhibitory in vitro signals were observed for P-gp (IC50= 33.8 µM), BCRP (IC50= 7.05 µM), OAT3 (IC50= 33.3 µM) and MATE1 (IC50= 20.4 µM) transporters when compared to corresponding EMA DDI concentration cut-off value for the systemic exposure of maribavir (50 x Cmax,u = 45.7 µM). In vitro experiments have also revealed that maribavir is a susbtrate of P-gp, BCRP and OCT1 transporters.

UGT inhibition was shown for UGT1A1 with an $IC_{50}$ of 32.3 µM, while UGT1A3, UGT1A9 and UGT1B7 inhibition occurred at higher $IC_{50}$, 184 µM, 123 µM and 153 µM, respectively. The EMA cut-off value was exceeded for all 4 UGT. No significant changes in the serum bilirubin concentration in the Phase 1

study occurred, in addition to a lack of drug-induced hyperbilirubinemia in Phase 2 and 3 studies, which suggested there was no clinically significant UGT1A1 inhibition with co-administration of maribavir. Considering the uncertainties in the intestinal expression of individual UGT enzymes as well as the lack of sufficiently specific probe drugs for individual UGTs, the probability of a clinically relevant interaction is assumed to be negligible

BSEP inhibition by maribavir occurred with an $IC_{50}$ of 46.5 µM *in vitro*.

Seven clinical DDI studies were conducted to further evaluate the interaction potential of maribavir, i.e., the effect of other compounds on the PK of maribavir ("victim" studies) as well as the effect of maribavir on the PK of other compounds ("perpetrator" studies).

Effect of other drugs on the PK of maribavir – "victim" studies

Maribavir is primarily metabolised by CYP3A4 and hence products that induce or inhibit CYP3A4 are expected to affect the clearance of maribavir. In a clinical DDI study, concomitant administration with rifampicin (a strong inducer of CYP3A4 and moderate inducer of CYP1A2) resulted in a significant decrease in the systemic exposure of maribavir (AUC, $C_{max}$ and $C_{trough}$ decreased to about 40%, 60%, and 20% of its initial values, respectively), and increased its apparent clearance. Thus, co-administration with strong CYP3A4 inducers may decrease the efficacy of maribavir and should be avoided.

In another clinical DDI study, co-administration of maribavir with 400 mg ketoconazole (strong CYP3A4 and P-gp inhibitor) led to an increase in maribavir AUC about 53% and $C_{max}$ about 10%. However, no dose adjustment is needed when maribavir is co-administered with CYP3A4 inhibitors due to lack of dose-limiting toxicity up to 1200 mg maribavir BID and a wide therapeutic window. For efficacy consideration of higher maribavir doses please refer to the efficacy section.

The effect of CYP1A2 inducer/inhibitors on maribavir exposure was not studied *in vivo* although CYP1A2 is involved in maribavir metabolism with an estimated fm of no more than 25%. Based on the finding that strong CYP3A4 inhibitors did not increase the plasma exposure of maribavir to a clinically significant extent, the impacts from CYP1A2 inhibitors on the PK of maribavir are expected to be low (i.e. below the upper no effect boundary) and no dose adjustment is needed when maribavir is co-administered with CYP1A2 inhibitors.

Effect of maribavir on the PK of other drugs – "perpetrator" studies

Based on the available *in vivo* DDI results maribavir does not change the activity of CYP1A2 (caffeine), CYP2C9 (S-warfarin), CYP2C19 (voriconazole), CYP2D6 (dextromethorphan/dextrorphan) and CYP3A (midazolam), and therefore dose adjustments for the substrates of these CYP enzymes are not required.

In a clinical DDI study with digoxin (P-gp substrate), maribavir caused an increase in digoxin AUC and $C_{max}$ by 21 and 25%, respectively. Since digoxin has a relatively high bioavailability (60-80%) and it is not regarded as a sufficiently sensitive probe substrate for P-gp inhibition in the intestine, these data are indicative of P-gp inhibition, and could be even more pronounced for P-gp substrates with lower oral bioavailablity. Indeed, in another clinical DDI study with tacrolimus, a CYP3A4 and P-gp substrate with a narrow therapeutic window, co-administration with maribavir 400 mg BID resulted in a clinically relevant increase in $C_{max}$ and AUC of tacrolimus by 38% and 51%, respectively. Thus, appropriate monitoring is recommended when using tacrolimus or other immunosuppressants (cyclosporine, everolimus, sirolimus) concomitantly with maribavir especially following initiation of maribavir (when immunosuppressant concentrations may increase) and after discontinuation of maribavir therapy (when immunosuppressant concentrations may decrease). In addition, clinically relevant interactions

between maribavir and other sensitive P-gp substrates cannot be excluded based on the currently available clinical data.

Table 14 Summary of effects of maribavir (400 mg BID) on the pharmacokinetics of co- administered drugs – "perpetrator" studies.

| Coadministered Drug | | | | | Geometric Mean Ratio (90% CI) of coadministered drug with/without Maribavir | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Therapeutic Class | DDI mechanism | Drug Name | Dose and Frequency | N | AUC | $C_{max}$ | $C_{trough}$ | Others | Data Source | Dose Recommendation |
| CNS Stimulants | CYP1A2 substrate | Caffeine | 2 mg/kg SD | 15 | NA | NA | NA | 0.86 (0.80, 0.92) [a] | 1263-100 Appendix 12.1.9.1.2 | No dose adjustment |
| Oral Anticoagulants | CYP2C9 substrate | Warfarin | 10 mg SD | 16 | 1.01 (0.95, 1.07) [b] | NA | NA | NA | 1263-100 Appendix 12.1.9.2.2 | No dose adjustment |
| Proton Pump Inhibitors | CPY2C19 substrate | Omeprazole | 40 mg SD | 16 | NA | NA | NA | 1.71 (1.51, 1.92) [c] | 1263-100 Appendix 12.1.9.3.2 | No dose adjustment |
| Antifungals | CPY2C19 substrate | Voriconazole | 200 mg BID | 19 | 0.93 (0.83, 1.05) | 1.00 (0.87, 1.15) | NA | 1.12 (1.02, 1.23) [d] | 1263-107 Table 10.2.5.4, Table 10.2.7.3 | No dose adjustment |
| Antitussives | CYP2D6 substrate | Dextromethorphan | 30 mg SD | 18 | 0.97 (0.94, 1.00) [e] | 0.94 (0.88, 1.01) [f] | NA | NA | SHP620-115 Section 14 Table 2.3.2 | No dose adjustment |
| Sedatives | CYP3A substrate | Midazolam | 0.025 mg/kg IV SD | 16 | NA | NA | NA | 1.13 (1.01, 1.24) [g] | 1263-100 Appendix 12.1.9.5.2 | No dose adjustment |
| Immunosuppressants | CYP3A/P-gp substrate | Tacrolimus | stable dose, BID (total daily dose range: 0.5-16 mg) | 20 | 1.51 (1.39, 1.65) | 1.38 (1.20, 1.57) | 1.57 (1.41, 1.74) | NA | 1263-105 Table 10.2.8.1 and Table 10.2.11.2 | Frequently monitor tacrolimus whole blood concentrations during treatment and after discontinuation of maribavir |
| Antiarrhythmics | P-gp substrate | Digoxin | 0.5 mg SD | 18 | 1.21 (1.10, 1.32) | 1.25 (1.13, 1.38) | NA | NA | SHP620-115 Section 14 Table 2.3.1 | No dose adjustment |

Pharmacodynamic interactions

Maribavir is contraindicated with valganciclovir/ganciclovir as it may antagonise ganciclovir's antiviral effects due to maribavir's inhibitory effect on UL97 Ser/Thr kinase, which is required for activation/phosphorylation of ganciclovir.

### *2.6.2.2. Pharmacodynamics*

*Primary pharmacology*

MBV antiviral activity is based on inhibition of the HCMV protein kinase UL97, thereby interfering with viral DNA replication, encapsidation, and nuclear egress. The applicant has shown that virus yield is reduced under MBV with viral DNA synthesis being inhibited by MBV, whereas concatamer processing was not affected. Formation of replication centres is blocked by MBV, while no effect on their function was observed. A variety of studies have shown resistance mutations mapping MBV antiviral activity to the ATP-binding, phosphotransfer and substrate binding domains of UL97.

In general, MBV showed efficacy in antiviral assays with a mean EC50 of 0,1 µM against laboratory strain AD169 and a limited panel of 10 clinical isolates originating from different locations in the United States, the majority from immunocompromised patients. These assays, which were primarily based on DNA hybridisation using MRC-5 cells, showed that the EC50 of MBV is around 4- to 5-fold lower

compared to GCV. Investigations for MBV activity included ten baseline clinical isolates with glycoprotein B genotypes and did not reveal an impact of these genotypes on MBV antiviral activity.

In general, selectivity of MBV is well addressed by investigation of the antiviral effect by MBV on several human/animal RNA/DNA viruses (HIV, HBV, VZV, SV-40, SARS-CoV, HSV-1, RSV, vaccinia virus, tacaribe virus, rotavirus, LCMV and BVDV). No effect by MBV was observed at the highest concentration tested, showing that MBV is specific for HCMV. However, there is one exception, as literature data show antiviral activity of MBV against EBV (gamma herpesvirus) by affecting the viral DNA replication and virus transcription. No information is available on combination antiviral activity of MBV and HCV-antivirals.

Adequate information has been provided on the anti-HCMV activity of MBV in combination with other HCMV inhibitors and sirolimus. Absolute antagonism was found for the combination of MBV with GCV and strong synergy for MBV combined with sirolimus. Additive effects for were seen for GW275175X, LTV, CDV, and FOS. The data obtained from studies in 2018 rectify earlier study results (from 1996) which indicated additive effect of MBV and GCV.

The MBV anti-HCMV activity when combined with several anti-HIV agents has been analysed. No antagonistic effect on MBV activity was detected while there were slight additive (AZT, indinavir, amprenavir) and synergistic interactions (abacavir). Further, the anti-HIV activity of MBV was analysed, alone or in combination with anti-HIV compounds (amprenavir, indinavir, AZT, ddI, ddC, abacavir). MBV alone did not inhibit HIV-1 replication and in combination did not alter the anti-HIV activity of the respective compounds. The data support the combined use of MBV with these anti-HIV compounds.

In vitro, resistance mutations in UL97 gene to MBV developed fast (passage 10) at low concentrations (0.3 µM MBV) and conferred a mid/high grade of resistance (12 to 80 FC). This demonstrates that MBV has a low genetic barrier to resistance development. During further exposure, several resistance mutations were found, mapping to the vicinity of the ATP-binding site, the phosphotransfer domain and the substrate-recognition site of UL97: L337M, F342S/Y, V356G, V353A, L397R, T409M, H411L/N/Y, D456N, V466G, C480R, P521L and Y617del. The FC conferred by these mutations are wide-ranging (3.5 to >200). Continued exposure to MBV also selected for double and triple mutations. Double mutants conferred high levels of resistance (FC >150).

A diversity of singular resistance mutations emerge at UL27 under MBV treatment. Most of these confer only mild resistance to MBV (FC <5).. Combination of mutations in UL27 and UL97 (R233S + L337M or V353A) result in ~2 FC increases in MBV EC50. The effect of UL27 mutations on MBV antiviral activity is not quite clear but seems to be a compensatory function for loss of function mutations in UL97.

Generally, MBV has been shown to be active against HCMV strains resistant to acyclovir, cidofovir, letermovir, and BDCRB. As regards GCV/vGCV, most common clinical GCV resistance mutations do not impact MBV antiviral activity. Nevertheless, various GCV resistance mutations in UL97 have been identified which confer high grade cross-resistance to MBV (FC of 18 to 428): K335del, F342Y, F342S, V356G, D456N, V466G, C480R, C480F, P521L, and Y617del. The clinical relevance of these mutations remains unclear, as some mutant strains showed viral growth defects.

*Secondary pharmacology*

To determine the effects of maribavir on ECG parameters (with a focus on QTc interval prolongation) a single-dose, randomised, Phase 1, placebo- and positive-controlled four-period cross-over study (study 1263-108) was performed.

The therapeutic maribavir dose used for this study was a single 100 mg dose. This dose was selected because a regimen of 100 mg BID was initially evaluated for prevention of CMV disease. The supratherapeutic maribavir dose was a single 1200 mg dose. In order to address the maribavir dose of 400 mg BID applied for treatment of CMV disease, the Applicant provided an addendum to the CSR of study 1263-108 dated August 2020. In this addendum results of an exploratory exposure-response (ER) statistical analysis based on study data 1263-108 are presented which assessed the potential relationship between maribavir and VP 44469 concentrations at maribavir doses of 100 mg and 1200 mg and time-matched, baseline-adjusted mean differences in the QTc interval (QT interval corrected using Fridericia's formula [QTcF] and QT rate-corrected individually with placebo QT-RR data [QTcIb]) prolongation. In addition, QTc interval prolongation was predicted for Cmax at maribavir 400 mg BID using the final maribavir plasma concentration-QTc model.

The time-matched analysis of study 1263-108 demonstrated that for both the 100 mg and 1200 mg maribavir doses, which provided approximately twice the steady-state Cmax following 400 mg BID doses of maribavir in transplant patients, at all-time points the upper bound of the two-sided 90% CI of the difference in the means of dQTcIb from placebo (ddQTcIb) was below the 10 msec regulatory threshold which indicates no significant effect on cardiac repolarisation. Similar results were observed for QT interval corrected using Fridericia's and Bazett's formula. Study sensitivity was confirmed by an increase of ddQTcIb for moxifloxacin with a lower confidence bound exceeding 5 msec at multiple time points during the expected period of peak plasma concentration. Furthermore, no extreme outliers (i.e., QTc >480 msec or QTc change >60 msec) were observed during study 1263-108.

Results from the linear model to evaluate the relationship between ddQTc and plasma maribavir concentration indicated that there was no increase in the QTc interval with increasing concentration of maribavir. At the estimated mean plasma maribavir Cmax of 16.5 µg/mL at the proposed therapeutic dose of 400 mg BID, the model-based estimates of ddQTcIb and ddQTcF were 1.1255 msec (90% CI, 0.1612 to 2.4122 msec) and 0.9308 msec (90% CI, 0.4889 to 2.3504 msec), respectively. The upper bound of the 90% CI of the model-based estimates of ddQTcIb and ddQTcF for Cmax of 16.5 µg/mL at the proposed therapeutic dose of 400 mg BID was below the 10 msec regulatory threshold.

## 2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of maribavir and its main metabolite VP 44469 have been well characterised in 17 Phase I studies with 5 different oral IR formulations (capsule, Tablet I, Tablet II, Tablet III, Tablet IV) following administration up to 2400 mg daily. Bridging between formulations is considered essential to demonstrate that results of the Phase I studies are applicable to the Tablet IV formulation which was used in the pivotal Phase III study SHP620-303 and which has the same composition as the to-be-marketed formulation. Bioequivalence has only be investigated between Tablet I and Tablet II. Thus, the applicant performed a post-hoc analysis comparing the PK parameters following

400 mg maribavir (which corresponds to the applied dose) under fasting conditions. According to this analysis the geometric mean ratios for AUC0-∞ after a single dose are all close to 1 (0.98 to 1.08), however, the 90% CI are not in the bioequivalence range of 0.8 to 1.25. The Cmax values were equivalent between Tablet III and Tablet IV; however, Tablet III and Tablet IV had 40% and 35%, higher Cmax, respectively, compared to Tablet II, along with slightly shorter Tmax.

The food effect was investigated for maribavir capsule and Tablet II formulation with a dose of 400 mg (studies CMAB1002 and 1263-104). In both studies food decreased the systemic exposure of maribavir. Under high-fat and high-caloric conditions both AUC and Cmax were decreased whereas

under medium-fat conditions, the 90% CI for AUC was still inside the bioequivalence acceptance range (but at the very low end). Moreover, Ctrough seems not to be impacted by food.

Generally, the PK parameters AUC and Cmax were comparable between healthy patients and transplant patients following 400 mg maribavir BID across studies. Interestingly, Ctrough seems to be higher in patients than in healthy patients which may be associated with a lower clearance. Unfortunately, serial blood samples for PK analysis were not collected in the pivotal Phase III study and thus PK data from Tablet IV formulation in transplant patients are not available.

After a single oral dose of 14C-maribavir, 75% (ranging from 59% to 88%) of drug related material is recovered, with 61% (ranging from 52% to 70%) in urine and 14% (range 6% to 23%) in feces. A mean of ~79% of the recovered radioactivity from urine and feces was identified. In conclusion only 60% of the administered dose has been identified. Analysis of both clinical and human biomaterial data estimates the unknown or unidentified clearance pathway to be ~28%. Given the therapeutic window, allowing for a 3-fold increase in exposure, inhibition of this unknown pathway is not a clinical concern. Remaining is a potential concern if there could be other medical products which could induce metabolism of maribavir to the extent that dose adjustments are needed. There is some reassurance in the fact that many of the known important inducers of CYPs and UGTs also are inducers of CYP3A4 thus already covered in the proposed SmPC-wordings. Further it is considered unlikely that the unknown pathway would consist of a single inducible pathway or of multiple pathways induced by the same substance thus leading to the need for dose adjustments upon co-administration.

Maribavir is eliminated from the body almost exclusively by non-renal processes. Enzymes involved in formation of VP 44469 are CYP3A4 and to a lower extent CYP1A2. Dose adjustment for patients with renal impairment including ESRD patients on haemo- or peritoneal dialysis and hepatic impairment is not required.

*Interactions*

*In vitro* CYP induction experiment V7676M-SHP620 indicated more than 100% increase in mRNA levels for all three tested enzymes CYP1A2 (up to 3-fold), CYP2B6 (up to 23-fold) and CYP3A4 (up to 18-fold) relative to vehicle control. However, it is difficult to say whether the observed effect was concentration dependent, because the experiment included three maribavir concentrations which were not optimally selected, i.e., only the lowest maribavir concentration of 36 µM was close to the EMA DDI systemic concentration cut-off (45.7 µM), while other maribavir concentrations were well-above the clinically relevant exposures (144, 200 or 480 µM). Moreover, there were also signs of cell toxicity observed at some of these high maribavir concentrations, which makes data inconclusive. Therefore, a new *in vitro* experiment was conducted for CYP2B6 and CYP1A2 enzymes with a more appropriate selection of maribavir concentrations (1 -100 µM) to further investigate induction risks for these two enzymes. This study revealed an up to 14-fold increase in CYP1A2 mRNA while no relevant risk of CYP2B6 induction was concluded.

*In vitro* transporter substrate experiments have indicated that maribavir is a substrate of P-gp, BCRP and OCT1 transporters. This information was requested to be included in the SmPC. However, it is also worth noting that based on the overall available data (including a relatively high upper boundary of the therapeutic window for maribavir) it was agreed that potential DDIs with P-gp, BCRP and/or OCT1 inhibitors are unlikely to result in a clinically relevant interaction with maribavir.

The Applicant has used the PBPK modelling to predict DDI scenarios with different strong/moderate CYP3A4 inducers, as well as to provide different dose recommendations for maribavir based on the PBPK analyses. These were however considered as a high regulatory impact analyses according to the EMA PBPK guideline, which would require a much more thorough qualification of the PBPK platform for

the intended purpose, i.e., the prediction of different CYP3A4 induction scenarios. Importantly, there was no sufficient amount of clinically observed data provided for the different inducers to consider the PBPK platform qualified, and no clinical data for maribavir (apart from a rifampicin DDI study) were available to verify the model predictive performance with different classes of inducers (i.e., different levels of CYP3A4 induction). On the other hand, when considering the upper boundaries of the therapeutic window of maribavir (i.e. up to 3-fold increase in AUC and 2.1-fold increase in $C_{max}$), a common dose adjustment apporoach with 1200 mg BID was suggested for most of the concomitantly administered strong/moderate CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital and efavirenz). Moreover, it was also agreed that for strong CYP3A4 inducers such as rifampicin (for which clinical DDI data are available), same dose adjustment approach might be insufficient in terms of $C_{trough}$ parameter, which might still be under the lower boundary of the therapeutic window (i.e. lower than 80% of exposure with the proposed standard therapeutic dose for maribavir). Therefore, use of rifampicin (as well as rifabutin and St. John's wort) together with maribavir is not recommended.

In a clinical DDI study (SHP620-115) conducted with digoxin as a P-gp substrate (victim drug), maribavir (perpetrator drug) has caused an increase in digoxin AUC and $C_{max}$ by 21% and 25%, respectively. Importantly, digoxin has a relatively high bioavailability (60-80%) and it is not regarded as a sufficiently sensitive probe substrate to investigate P-gp inhibition effects in the intestine but rather effects of the systemic P-gp inhibition. Therefore, the currently observed increase in digoxin exposure is indicative of P-gp inhibition, which could be even more pronounced for other P-gp substrates with lower oral bioavailability. Indeed, this might be clinically relevant as already seen in a clinical DDI study (1263-105) with tacrolimus as a CYP3A4/P-gp substrate, in which a clinically relevant increase in tacrolimus exposure was observed for AUC (1.5-fold), $C_{max}$ (1.4-fold) and $C_{trough}$ (1.6-fold) when co-administered with maribavir.

Therefore, appropriate SmPC information concerning the co-administration of sensitive P-gp substrates with maribavir was requested and implemented.

Besides the P-gp inhibition by maribavir, *in vitro* transporter inhibition experiments have also indicated positive DDI signals for BCRP ($IC_{50}$= 7.05 µM), OAT3 ($IC_{50}$= 33.3 µM) and MATE1 ($IC_{50}$= 20.4 µM) transporters when compared to corresponding EMA DDI concentration cut-off value for the systemic exposure (50 x $C_{max,u}$ = 45.7 µM). Importantly, only $IC_{50}$ values were estimated without corresponding Ki values (i.e., if competitive inhibition can be assumed as well as Ki=$IC_{50/2}$, this would imply even higher interaction risk). No clinical DDI data are available regarding the potential inhibition of BCRP, OAT3 and MATE1 transporters. Therefore, appropriate SmPC restrictions/information concerning the concomitant use of maribavir with sensitive substrates of the above-mentioned transporters were also requested and implemented.

Regarding the CYP2C19 inhibition, the Applicant has conducted a cocktail study (1263-100) in which parent to metabolite (omeprazole/5-hydroxyomeprazole) ratio was determined at a single time point (i.e., no complete PK profiles measured) 2 hours post-dose in the presence and absence of maribavir. These parent to metabolite ratios implied an interaction risk (1.7-fold increase). However, this study approach was not considered adequate and not according to the EMA DDI guideline requirements: "*Full characterisation of the plasma concentration-time curves of the probe drug is recommended, estimating the effect on (oral) clearance or AUC*". In another clinical DDI study (1263-107) with voriconazole as a less sensitive CYP2C19 substrate (drug not listed in the current EMA DDI guideline as a probe substrate for CYP2C19) the Applicant has concluded no risk for CYP2C19 inhibition. Based on the overall available clinical data it can be concluded that maribavir can act as a weak CYP2C19 inhibitor.

*PPK modelling*

A PPK model was developed to describe the time course of maribavir concentrations in plasma in healthy volunteers and patients using NONMEM.

A difference in PK between HV and transplant patients was observed: 24% lower clearance for patients (3.77 vs 2.85 L/h), AUC was 27% higher, and $C_{min}$ was 2.89 µg/mL in HV vs. 4.90 µg/mL in patients. pcVPCs revealed that these differences were only partly described through the model leading to an underestimation of plasma concentrations in CMV patients.

The pcVPCs indicate slight model misspecification mainly for the first 2 hours but overall look reasonable. RSEs are low. For the GoF plots, where the Loess may indicate a trend there is very little data. The shrinkage for CL was low, but higher for other parameters such as Ka and lag-time. The pcVPCs stratified on study show that the model satisfactory predicts 2 of the 3 studies in CMV patient. For Study 202 a slight over-prediction is seen. The Phase 2 transplant patients with CMV study (Study 203) and the Phase 3 transplant patients with CMV study (Study 303) were both adequately predicted by the model. Overall, the model is considered satisfactory to support the text in section 5.2 of the SmPC.

The preliminary PPK model showed high unexplained variability and had no covariates included, except of body weight in the allometric functions on clearance and volume terms. In the final model, body weight was not found to be a significant predictor of maribavir PK, but it was retained in the model (with fixed allometric coefficients of 0.75 for CL/F and Q/F and 1 for Vc/F and Vp/F). The Applicant explained that the PPK model will be used to simulate the concentration-time profiles in a paediatric population to support future paediatric development, this is endorsed.

Different formulations were not evaluated as a covariate, even though various formulations were used. This could be a reason for unexplained variability.

The PopPK analysis is considered only supportive with regards to investigation of CYP3A4 inhibitors/With respect to potential interactions investigated with the PPK model, the Applicant clarified that for strong CYP3A inducers data was mainly derived from the Phase 1 DDI study with ketoconazole (1263-102), whereas 65% of data regarding strong CYP3A inhibitors was derived also from the Phase 2 and 3 studies.

The first exploratory exposure-response analyses based on studies SHP620-202 and -203 showed a treatment effect but no significant effects for the predefined objectives. Only for Study 202 a significant negative effect of exposure on recurrence was investigated. All results derived from these exploratory exposure-response analyses should be interpreted with caution because maribavir treatment discontinuation led to low patient numbers from week 8 onwards. At Week 24 for the 400 mg and 800 mg group only n=7 and 6 patients, respectively, were still under treatment. This is considered not appropriate for time to recurrence and time to undetectable viral DNA analyses until day 180 (25 weeks). Furthermore, the preliminary PPK model, which was used to calculate $AUC_{0\text{-}12}$ $C_{max}$ and $C_{min,}$ is considered not robust enough as a base for exposure response modelling. The negative relationship between exposure parameters and probability of recurrence for Study 202 could be caused by methodical difficulties. However, similar results were observed in the final exposure response with a different data base from phase 3 (which is reported in the following under exposure-response analyses based on study 620-303).

*Exposure-safety (202 and 203)*

The exposure-safety analysis indicates potential increased safety concern at the exposure levels associated with the 1200 mg BID dosing regimen. If the conclusion that safety of the 800 and 1200 mg BID dose are acceptable and comparable to the 400 mg BID regimen based on the phase 2 data, is mainly based on clinical safety data.

For the second exposure-response analyses based on study 620-303, logistic regression models were developed to link maribavir exposure to the probability of viraemia clearance and adverse events. The exposure metric resulting in the best fitting model according to AIC was selected to perform the covariate analysis. In addition to the proposed covariates in the analysis plan, presence of strong CYP3A inhibitors was formally evaluated as a potential risk factor to explain variability in exposure-safety relationships but was not significant.

Exposure-response analyses regarding efficacy revealed that of the 231 patients, a total of 131 patients presented a confirmed CMV viraemia clearance at Study Week 8. This response was not maintained in all patients through Study Week 16: At this later time point, only for 44 patients confirmed viraemia clearance was shown. Treatment emergent CMV mutation and CD4CD69+ cell count at baseline were significant covariates for the probability of viraemia clearance, suggesting a highly significant link between mutations and resistance to maribavir in non-responders.

Exposure-response analyses regarding safety revealed that fatigue and serious adverse events showed a significant positive relationship with exposure parameters, which is considered plausible. It might be linked with the finding that the quartile with the highest exposures has included many non-responders resistant to maribavir. The Covariate analysis revealed that North American patients had a higher probability for fatigue compared to Asian or European patients. SAE were more probable in patients with high CMV DNA level at baseline, which seems plausible. Furthermore, only data from study SHP620-303 was used for the final exposure-response modelling was used**.**

The phase 2 data indicate that a higher dose than 400 BID may have been preferred. Also, regarding resistance, maybe a 3 times daily dosing could have been preferred over twice daily dosing. However, the applicant made the decision to go forward with the 400 mg BID dose in the pivotal trial. Exposure-response analysis on the pivotal trial (one dose level) has limited value and issues regarding this analysis are not further pursued.

*Therapeutic index*

Note that lower doses than 400 mg BID has not been adequately evaluated and provided. If the efficacy MOs are solved, then the exposure from the 400 mg BID regimen should be considered the lower level of the therapeutic index. Any exposure reduction (i.e. due to DDIs) warrants an increased dose to avoid potential lack of efficacy.

The upper level of the therapeutic index is based on the phase 2 clinical safety data for the higher doses studied in phase 2. Since the 400 mg BID dosing was studied in the pivotal trial, that is the main dose to evaluate the B/R for, however a higher exposure with regards to DDI (i.e., co-administration of CYP3A4 inducers and there for an increased dose maribavir) may be appropriate

*Primary Pharmacology*

The data provided on MBV antiviral activity (DNA hybridisation assay in MRC-5 cells) have been generated using lab strain AD169 and ten clinical isolates from the United States. As requested these *in vitro* derived $EC_{50}$ values were substantiated by submission of further data. The applicant has provided summarised $EC_{50}$ values published in literature on additional clinical isolates mainly from the USA.

The determination of the antiviral activity of MBV is highly variable as the $EC_{50}$ for the same HCMV strain can vary up to 100-fold), depending on the assay system, cell type and culture conditions used. Nevertheless, this has been addressed by standardizing the assay system (SEAP yield reduction assay) during further analysis (resistance phenotyping), but changes have been made in the cells employed (change from HEL to ARPEp). As stated by Chou (2020), it remains still unclear what cell culture system best represents the *in vivo* activity of MBV.

As indicated by the applicant $EC_{50}$ assays were performed in the presence of 2-4% bovine serum, which the applicant presumes to be adequate for binding 98% of free MBV. Upon request for further information the applicant commits to perform an additional study to investigate the potential effects by human serum albumin binding. These data are envisaged by June 2023 and should be submitted once available.

Combination antiviral activity analysis of MBV with anti-HCMV compounds have been performed in 1998. Analysis of the anti-HIV activity of MBV was performed in 1996. The choice of HIV antivirals seems partly outdated, as new substances and even new classes of substances have been introduced in the meantime.

MBV has been demonstrated to exhibit potent anti-EBV activity *in vitro* ($EC_{50}$ 0.15 to 1.1 µM).

The triple mutations emerging under MBV pressure have not been phenotyped and the Applicant does not plan to further characterise phenotypic triple mutations. The Applicant considers that each multiple variant will at a minimum confer maribavir resistance of the highest fold change of the RAS included in the multiple RAS genotype and considers that RASs which confer a 15-fold or higher increase in $EC_{50}$ are extremely difficult to clear. Following this argumentation, the Applicant was asked to include all identified treatment-emergent multiple RAS genotypes should be listed in section 5.1 of the SmPC to indicate that maribavir is no longer susceptible to the multiple RAS F342Y+T409M+H411N (78-fold), C480F+H411L+H411Y (224-fold), F342Y+H411Y (56-fold, as determined experimentally by Chou et al., 2019), T409M+C480F (224-fold) and H411Y+C480F (224-fold).

Various cross-resistance mutations have been found for MBV and GCV. As the indication for MBV includes patients refractory and/or resistant to GCV/vGCV, the potential impact of these mutations on MBV efficacy should be taken into account. Therefore, for treatment of HCMV-infected patients pre-treated with GCV/vGCV or CPV, screening for these resistance mutations should be performed at baseline. Diagnostic genotyping of UL97 should best cover the whole UL97 gene, but at least the relevant regions and domains correlated with resistance mutations, starting at ATP-binding region (P-loop) residue 335 and spanning also the substrate binding domain (up to residue 707) should be included.

***Secondary pharmacology***

To determine the effects of maribavir on ECG parameters (with a focus on QTc interval prolongation) a single-dose, randomised, Phase 1, placebo- and positive-controlled four-period crossover study (study 1263-108) was performed. The used therapeutic maribavir dose (100 mg) was selected because a regimen of 100 mg BID was initially evaluated for prevention of CMV disease. The supratherapeutic maribavir dose was a single 1200 mg dose. In order to address the maribavir dose of 400 mg BID applied for treatment of CMV disease, an exploratory exposure-response (ER) statistical analysis was investigated to assess the potential relationships between plasma concentrations of maribavir and its metabolite, VP 44469, and change in corrected QT (QTc) interval to evaluate the potential of maribavir and VP 44469 to prolong QTc interval. In addition, QTc interval prolongation was predicted for $C_{max}$ at maribavir 400 mg BID using the final maribavir plasma concentration-QTc model. Results demonstrated no clinically significant repolarisation effect of maribavir administered orally at a single dose of 100 mg or a supratherapeutic dose of 1200 mg, which provided approximately twice the steady-state $C_{max}$ following 400 mg BID doses of maribavir in transplant patients. Furthermore, no correlations between time-matched, baseline-adjusted QTc intervals and plasma concentrations of maribavir were observed. The upper bound of the 90% CI of the model-based estimates of ddQTcIb and ddQTcF for $C_{max}$ of 16.5 µg/mL at the proposed therapeutic dose of 400 mg BID was below the 10 msec regulatory threshold.

## 2.6.4. Conclusions on clinical pharmacology

***Pharmacokinetics***

Study results (*in vitro* data of CYP2B6 and CYP1A2 induction and interference assessment of maribavir and tacrolimus) have been submitted by the applicant. The data showed an up to 14-fold increase in CYP1A2 mRNA while no relevant risk of CYP2B6 induction was concluded.

***PPK modelling***

The popPK model is considered adequate for descriptive purposes (support text in section 5.2 of the SmPC).

***Primary pharmacology***

Generally, the data provided are generally considered adequate to demonstrate the antiviral activity of MBV against HCMV ($EC_{50}$ ~ 0.1 µM). As requested, these data were substantiated by provision of additional $EC_{50}$ data from literature for further clinical isolates. As regards the impact of serum binding on MBV activity the applicant commits to perform an additional study to investigate the potential effects by human serum albumin binding. For selectivity of MBV data on further Herpesviruses and HCV are outstanding. Information on the selectivity of MBV for other viruses and on the combination studies of MBV with other antivirals are partly outdated or relevant viruses/antiviral are missing. Updates are requested for these studies. The resistance analysis performed are generally adequate. MBV demonstrated a low genetic barrier of resistance development. Several resistance mutations (also in double/triple) have been identified in UL97. The relevance of mutations in UL27 remains unclear. Cross-resistances for GCV and MBV have been found, conferring very high FCs. For patients pre-treated with GCV/vGCV, screening for these resistance mutations should be performed at baseline.

## 2.6.5. Clinical efficacy

The clinical development programme of maribavir consists of a single pivotal Phase 3 study (Study SHP620-303, Study 303) in adult transplant recipients with cytomegalovirus (CMV) infections that are refractory or resistant to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir. In addition, there are two supportive phase 2 studies, Study SHP620-202 in adult transplant recipients with CMV infections that are refractory or resistant to treatment with ganciclovir, valganciclovir or foscarnet (study 202) and Study SHP620-203 in adult transplant recipients with CMV infections without CMV organ disease and resistance to any CMV treatment (study 203) (Table 15).

Table 15 Clinical studies supporting the efficacy of maribavir

| Study No. | Study Design | Treatments Administered | Study Population | No. of Subjects Enrolled/treated |
|---|---|---|---|---|
| **Pivotal Phase 3 Study** | | | | |
| SHP620-303 | Phase 3, multicenter, randomized, open-label, active-controlled<br>CMV infection must have been refractory and possibly resistant to at least 1 of available anti-CMV agents (ganciclovir, valganciclovir, foscarnet or cidofovir)[a]<br>Randomization: 2:1 ratio to maribavir or active control<br>Randomization was stratified by transplant type (HSCT or SOT) and screening whole blood or plasma CMV DNA concentration (viral load high, intermediate, low)<br>Treatment duration was 8 weeks<br>Post-treatment follow-up was 12 weeks | Maribavir 400 mg BID or investigator-assigned anti-CMV treatment | Subjects ≥12 years of age who had received either HSCT or SOT.<br>Had documented CMV infection that was refractory and possibly resistant to ganciclovir, valganciclovir, foscarnet, or cidofovir (Table 3) | Total enrolled: 352<br>Maribavir 400 mg: 234<br>IAT: 116 |
| **Supportive Phase 2 Studies** | | | | |
| SHP620-202 | Phase 2, multicenter, randomized, dose-ranging, parallel-group<br>Subjects were randomized in a 1:1:1 ratio<br>Randomization was stratified by transplant type (SCT or SOT)<br>Treatment duration was up to 24 weeks<br>Post-treatment follow-up duration was 12 weeks<br>At Weeks 3 and 6, minimum virologic responses were required for treatment to continue[b] | Maribavir 400 mg BID, 800 mg BID, 1200 mg BID | Subjects ≥12 years of age who had received either SCT or SOT.<br>Had documented CMV infection that was refractory and possibly resistant to prior CMV treatment (Table 3) | Total enro1led: 120<br>Maribavir 400 mg: 40<br>Maribavir 800 mg: 40<br>Maribavir 1200 mg: 40 |

| Study No. | Study Design | Treatments Administered | Study Population | No. of Subjects Enrolled/treated |
|---|---|---|---|---|
| SHP620-203 | Phase 2, multicenter, randomized, dose-ranging, parallel-group<br>Subjects were randomized in a 1:1:1:1 ratio<br>Randomization was stratified by transplant type (SCT or SOT)<br>Treatment duration was up to 12 weeks<br>Post-treatment follow-up duration was 12 weeks<br>At Weeks 3 and 6, minimum virologic responses were required for treatment to continue[b] | Maribavir 400 mg BID, 800 mg BID, 1200 mg BID<br>or<br>Valganciclovir | Subjects ≥18 years of age who had received either SCT or SOT.<br>Had a CMV infection that was not known to be resistant to ganciclovir/valganciclovir, foscarnet, or cidofovir based on genotypic evidence (Table 3) | Total enrolled:161<br>Maribavir 400 mg: 40<br>Maribavir 800 mg: 40<br>Maribavir 1200 mg: 39<br>Valganciclovir: 40 |

BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; HSCT=hematopoietic stem cell transplant; IAT=investigator-assigned anti-CMV treatment; SCT=stem cell transplant; SOT=solid organ transplant

[a] While subjects had to be refractory per protocol to at least 1 of these anti-CMV agents to be eligible for the study, the investigator could elect to treat subjects randomized to the IAT group with an anti-CMV agent to which the subject was not refractory or resistant. Thus, the IAT group consisted of a heterogeneous population of subjects, ie, some subjects were refractory (with or without resistance) to their study medication while others were not.

[b] Using the baseline (pre-dose Day 1) CMV DNA value as the comparator, subjects who had Week 2 results demonstrating any decrease in CMV DNA were permitted to continue study drug at the discretion of the investigator. Using the baseline (pre-dose Day 1) CMV DNA value as the comparator, subjects who had Week 5 results demonstrating a ≥2 log decrease from baseline or undetectable CMV DNA were permitted to continue study drug at the discretion of the investigator.

#### *2.6.5.1. Dose response study(ies)*

N/A

#### *2.6.5.2. Main study(ies)*

## (SHP620-303)

***Methods***

A Phase 3, multi-centre, randomised, open-label, active-controlled study to assess the efficacy and safety of Maribavir (MBV) treatment compared to Investigator-assigned treatment (IAT) in transplant recipients with Cytomegalovirus (CMV) infections that are refractory or resistant to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir**.**

To be eligible for the study, patients had to have a documented CMV infection and had to have a current CMV infection that was refractory to the most recently administered of the four anti-CMV treatment agents.

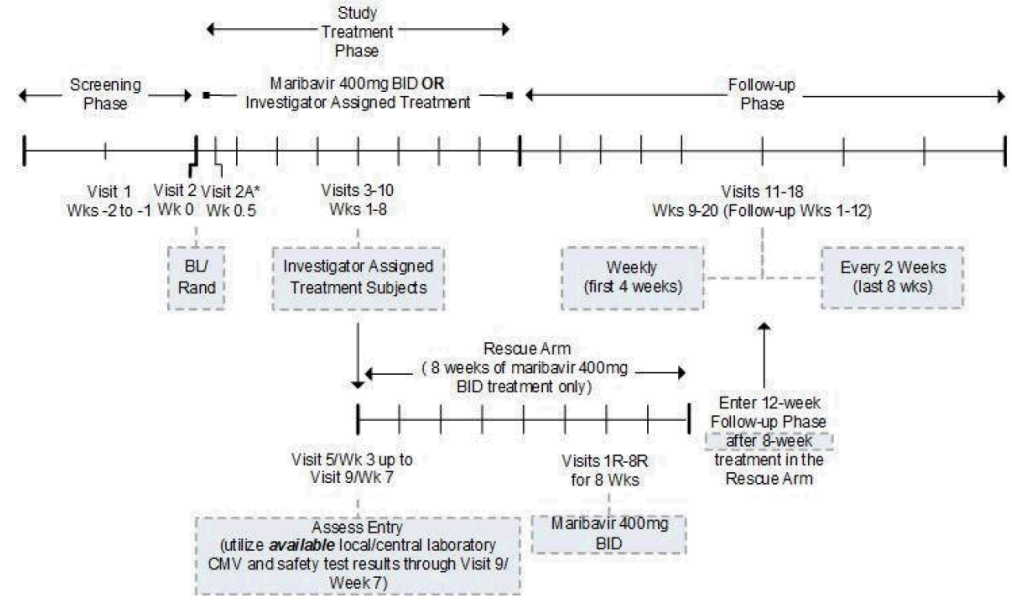
Study-qualifying refractory CMV infections were defined as documented failure to achieve >1 $\log_{10}$ (common logarithm to base 10) decrease in CMV DNA level in whole blood or plasma after a 14 day or longer treatment period with IV ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir. This definition applied to the current CMV infection and the most recently administered anti-CMV agent.

The definition of "refractory CMV-infection" used in study 303, differs relevantly from the currently accepted definition outlined in current treatment guidelines (please refer to clinical discussion for further details) for the intended target population.

Resistant CMV infection was defined as refractory CMV infection AND documentation of one or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir.

Consistent with the definitions above, all patients entering the study were refractory to treatment with at least 1 prior anti-CMV drug, and may, in addition, have had 1 or more resistance-associated amino acid substitutions (RASs) known to confer resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir at baseline.

The study included a maribavir rescue arm, which was an option for patients randomised to IAT and in whom despite a minimum of 3 weeks of therapy with IAT (Visit 5/Week 3) no CMV DNA decrease was seen. The patient had to meet stringent criteria for lack of improvement/worsening of CMV infection. The transition into the rescue arm was allowed after medical monitor review of the patient's eligibility for the rescue arm based on protocol-defined criteria.




BID=twice daily; BL=baseline; CMV=cytomegalovirus; R=rescue; RAND=randomized; wks=weeks

*Visit 2A/A(R) was only required for subjects who were taking tacrolimus, cyclosporine, everolimus, or sirolimus at Visit 2/2R.

Figure 4 Scheme of the study design of study 303

**Study Participants**

Study participants were male and female stem cell or solid organ transplantation recipients ⩾ 12 years of age with documented CMV infection in whole blood or plasma, with a screening value of ⩾2730 DNA IU/mL in whole blood • or ⩾910 IU/mL in plasma in two consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory qPCR or comparable quantitative CMV DNA results. Both samples should have been taken within 14 days prior to randomisation with second sample obtained within 5 days prior to randomisation. The same laboratory and same sample type (whole blood or plasma) must have been used for these assessments. Participants had to have a current CMV infection that was resistant or refractory to treatment to the most recently administered of the four anti-CMV treatment agents.

Resistant CMV was defined as documentation of one or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir and/or foscarnet documented failure to achieve >1 log10 (common logarithm to base 10) decrease in CMV DNA level in whole blood or plasma after a 14-day or longer treatment period with intravenous (IV) ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir.

Refractory CMV was defined as documented failure to achieve >1 log10 (common logarithm to base 10) decrease in CMV DNA level in whole blood or plasma after a 14-day or longer treatment period with intravenous (IV) ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir.

Patients with current CMV infection that was considered resistant or refractory due to inadequate adherence to prior oral anti-CMV treatment and had tissue-invasive disease with central nervous system involvement, including retina (eg CMV retinitis) were excluded from the study. Patients who received drugs with known anti-CMV activity must have been discontinued use at least 14 days before the first dose of study drug.

**Treatments**

**Maribavir:**

Two maribavir 200 mg tablets were orally administered at dose of 400 mg BID for 8 weeks. Maribavir was to be administered (preferably) every 12 hours (q12h). When q12h dosing was not feasible, the doses were to be separated by a minimum of 8 hours. If the timing of the first dose of maribavir on Visit 2/Day 0 did not allow for a minimum of 8 hours between doses, only 1 dose of maribavir was administered on Visit 2/Day 0.

The maribavir batch numbers were PR160108.001, PR170101.001, PR171020.001, PR171021.001, PR191107.001, and PR191108.001. The formulation used in study 303 (formulation IV) is not identical to the formulation used in dose-ranging studies 202 and 203 (formulation III).

**Investigator assigned treatment (IAT):**

IAT dose and dosing interval was selected by the investigator for a duration of 8 weeks.

Selection criteria for IAT:

- At the time of enrolment in the study, the investigator decided whether the patient should remain on the same anti-CMV therapy or change therapy at the time of randomisation/treatment initiation.
- One or a pre-specified combination of two of the available anti-CMV agents (GCV+FOS and CGV+FOS) from the following were utilised: IV ganciclovir, oral valganciclovir, IV foscarnet, or IV cidofovir.
- Dose and dose regimen of the IAT were at the discretion of the investigator following best clinical practice for each patient based on the specific situation.
- The investigators chose the IAT with knowledge of a patients' prior clinical course for treatment of the current CMV infection. Although refractoriness to at least one agent was required for entry into the study, patients in the IAT arm were not necessarily refractory or resistant to the study treatment that they received as IAT under the study protocol.
- If dual anti-CMV therapy was started for a patient randomised to IAT, withdrawal of one agent post-randomisation, while continuing the second agent, was permitted.
- Changes to the selected IAT(s) at randomisation could include change in dose (increase or decrease) and/or dosing regimen, but could not include an addition of, or switch to, another anti-CMV agent not selected at randomisation.
- Addition of, or switch to, another anti-CMV agent was declared a failure for the purpose of study analysis.
- Changes between IV ganciclovir and oral valganciclovir were allowed.
- Combination therapy with cidofovir and foscarnet was prohibited.

Investigator-assigned anti-CMV treatment was not considered an investigational product in the context of this study. The IAT (ganciclovir, valganciclovir, foscarnet or cidofovir) was prescribed by the investigator and either administered at the hospital or other facility used to administer IV products as per local site standard practice, or was prescribed by the investigator and typically purchased by the study patient at the commercial pharmacy.

Criteria for maribavir rescue treatment:

The transition into the rescue arm was allowed after medical monitor review of the patient's eligibility for the rescue arm based on meeting at least one of the following protocol-defined criteria:

a) Patient had increased whole blood or plasma CMV Viraemia levels of $\geq$1 $\log_{10}$ from baseline as measured by the local or central specialty laboratory qPCR assay (results from the same laboratory were to be compared). Local specialty laboratory results had to be documented.

b) Patient had tissue-invasive CMV disease after being on treatment for at least 3 weeks and met both of the following criteria:

- Patient's whole blood or plasma CMV DNA had decreased <1 $\log_{10}$ from baseline as measured by the local or specialty laboratory qPCR assay (results from the same laboratory were to be compared). Local specialty laboratory results had to be documented.
- The presenting tissue-invasive CMV disease for symptomatic patients did not improve, or worsened as assessed by the investigator OR patient who was asymptomatic at baseline developed tissue-invasive CMV disease.

2. Patient did not achieve CMV Viraemia clearance (results from the same laboratory were assessed) necessitating continued anti-CMV treatment AND the patient had demonstrated intolerance to the IAT, as evidenced by 1 of the following conditions:

- Acute increase in serum creatinine, at least 50% increase from the baseline value, attributed to treatment (cidofovir, foscarnet) toxicity.
- Development of haemorrhagic cystitis when on treatment with cidofovir or foscarnet.
- Development of neutropenia (absolute neutrophil count [ANC] <500/mm3 [0.5×109/L]) when on treatment with ganciclovir or valganciclovir.

**Objectives**

The primary objective of this study was to compare the efficacy of maribavir to IAT in CMV viraemia clearance at the end of study week 8 in transplant recipients who were refractory or resistant to prior anti-CMV treatment. The key secondary objective of this study was to compare the efficacy of the two study treatment arms on CMV viraemia clearance and tissue-invasive CMV disease and CMV syndrome improvement or resolution at the end of study week 8, and maintenance of this treatment effect through study week 16.

The secondary objectives for patients who completed 8 weeks of study treatment were to compare the efficacy of maribavir to IAT on CMV viraemia clearance at the end of Week 8 in transplant recipients who were refractory or resistant to prior anti-CMV treatment and to compare the efficacy of the 2 study treatment arms on CMV viraemia clearance and tissue-invasive CMV disease and CMV syndrome

improvement or resolution at the end of Week 8, and maintenance of this treatment effect through study weeks 12, 16, and 20.

Several other secondary objectives were related to maintenance of CMV viraemia clearance, the resolution or improvement of tissue-invasive CMV disease and CMV syndrome, incidence of recurrence of CMV viraemia, incidence of recurrence of CMV viraemia on and off treatment, to resistance analyses of mutations in the CMV genes conferring resistance to maribavir, all-cause mortality, safety and tolerability of maribavir, efficacy, maintenance of the treatment effect, and the safety of maribavir administered as the rescue treatment and to characterise the pharmacokinetics (PK) of maribavir.

**Outcomes/endpoints**

The primary efficacy endpoint was confirmed CMV viraemia clearance at the end of Study Week 8, defined as plasma CMV DNA concentration <LLOQ (i.e., <137 IU/mL) per central laboratory result in 2 consecutive postbaseline samples, separated by at least 5 days.

The key secondars endpoint was achievement of CMV viraemia clearance and symptom control at the end of study week 8, followed by maintenance of this treatment effect for an additional 8 weeks off treatment (i.e., Follow-up week 16). Symptom control was defined as resolution or improvement of tissue-invasive CMV disease or CMV syndrome for patients symptomatic at baseline or no new symptoms of tissue-invasive CMV disease or CMV syndrome for patients asymptomatic at baseline.

Both, the primary and key secondary endpoint were assessed regardless of whether patients completed the stipulated 8 weeks of study-assigned treatment. Patients who initiated alternative (non-study) anti-CMV therapy or rescue treatment before Week 8 were counted as non-responders.

For the following other secondary endpoints, subject who initiated alternative (non study) anti-CMV therapy before the time point of interest were counted as non-responders: the maintenance of the CMV viraemia clearance and CMV infection symptom control achieved at the end of Study Week 8 through Weeks 12 and 20, achievement of confirmed CMV viraemia clearance after 8 weeks of receiving study-assigned treatment, achievement of confirmed CMV viraemia clearance and CMV infection symptom control after 8 weeks of receiving study-assigned treatment.

Recurrence of CMV viraemia was an additional secondary endpoint and was defined as plasma CMV DNA concentrations ≥LLOQ, when assessed by central specialty laboratory, in 2 consecutive plasma samples separated by at least 5 days after achieving confirmed viraemia clearance. The following recurrence endpoints were assessed using all CMV DNA measurements after achieving confirmed CMV viraemia clearance regardless of rescue or alternative treatment: Recurrence of CMV viraemia by study period, recurrence of CMV viraemia on treatment and off treatment, recurrence by the laboratory definition (ie, based only on CMV DNA), particularly before week 8, may not be clinically meaningful due to usual viral load fluctuations. Therefore, recurrence was evaluated in patients with CMV viraemia clearance at Week 8 (i.e., who fulfilled the requirement for the primary efficacy endpoint) and who received alternative treatment after week 8.

All-cause mortality was analysed regardless of the use of rescue treatment or alternative anti-CMV treatment. The time to all-cause mortality by the end of study participation in days was calculated as stop date (event date of death due to any cause or censored at date of last contact) minus randomisation date plus 1. The analysis was repeated for all-cause mortality on study after receiving study-assigned treatments but censoring at time of alternative anti-CMV treatment or maribavir rescue therapy.

Patients who received maribavir as rescue therapy were evaluated for CMV viraemia clearance at week 8 of the rescue phase.

The maribavir resistance profile was evaluated using genotyping data from baseline and postbaseline CMV DNA samples. Results of this analysis are presented in a separate Resistance Report.

**Definitions:**

The baseline value for efficacy was based on the results from central laboratory, for tissue invasive disease symptoms evaluation, the adjudicated results by EAC were used for efficacy analysis.

The baseline value for efficacy variables is defined as the last available value before or on the first dose of study drug on Visit 2/Day 0. The strata based on the central laboratory baseline plasma CMV DNA concentrations for the efficacy analysis are defined as:

- high viral load with CMV DNA ≥91000 IU/mL
- intermediate viral load ≥9100 and <91000 IU/mL,
- low viral load CMV DNA <9100 IU/mL

**Confirmed CMV viraemia clearance:**

defined as plasma CMV DNA concentration below the lower limit of quantification (<LLOQ; ie, <137 IU/mL) when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test at a central specialty laboratory, in 2 consecutive post-baseline samples, separated by at least 5 days.

**Recurrence of CMV viraemia:**

defined as plasma CMV DNA concentration ≥LLOQ when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test in 2 consecutive plasma samples at least 5 days apart, after achieving confirmed viraemia clearance.

**Recurrence of symptomatic CMV infection:**

defined as the presence of signs or symptoms of the tissue invasive CMV disease or CMV syndrome (same or new symptomatology) confirmed as per Ljungman et al. (2017), after the period of resolution of the symptomatic infection in patients symptomatic at baseline.

Importantly, the primary and secondary objectives/endpoints and the respective analyses were changed with protocol amendment 3, 17 months after the start of the study to include patients who had discontinued study treatment early and met the criteria of confirmed CMV viraemia clearance at study week 8 as responders in the primary efficacy analysis.

**Original protocol**

| Scenario | Assessment/Visit Week | | | | | Responder | Comments |
|---|---|---|---|---|---|---|---|
| | 4 | 5 | 6 | 7 | 8 | | |
| 1 | +/- | +/- | +/- | - | - | YES | Confirmed based on Week 7/Week 8 |
| 2a | +/- | +/- | +/- | - | + | NO | Not confirmed : at least 1 of the Week 7/Week 8 results is positive |
| 2b | +/- | +/- | +/- | + | - | NO | |
| 2c | +/- | +/- | +/- | + | + | NO | |
| 3 | +/- | +/- | - | - | Miss. | YES* | Confirmed (2 consecutive unquantifiable results) at Week 6/Week 7 with "Missing" at Week 8* |
| 4 | +/- | - | - | Miss. | - | YES | Confirmed (2 consecutive unquantifiable results) at Week 5/Week 6 with "Missing" at Week 7 and 1 negative result at Week 8 |
| 5 | +/- | +/- | +/- | + | Miss. | NO | Not confirmed: at least 1 of the Week 7/Week 8 results is positive |
| 6 | +/- | +/- | +/- | Miss. | + | NO | Not confirmed: at least 1 of the Week 7/Week 8 results is positive |
| 7 | +/- | +/- | +/- | Miss. | Miss. | NO | Not confirmed if both Week 7 and Week 8 are missing |

Miss. = Missing

**Post amendment 3**

**Table 7: Assessments of Virological Responders at Study Week 8**

| Scenario | CMV DNA Weeks on Study | | | | | |
|---|---|---|---|---|---|---|
| | Up to Week 6 | Week 7 | Week 8 | Week 9* | Response | Rationale |
| 1 | + / - | - | - | +/-/NA | Yes | 2 consecutive "-" at Week 7 and Week 8 |
| 2 | + / - | - | + | +/-/NA | No | Not 2 consecutive "-" at Week 7 and Week 8 |
| 3 | + / - | + | - | +/-/NA | No | Not 2 consecutive "-" at Week 7 and Week 8 |
| 4 | + / - | - | NA | - | Yes | 2 consecutive "-" as shown by available data and both "-" at week 7 and week 9 for missing week 8, otherwise nonresponder |
| 5 | - | NA | - | +/-/NA | Yes | 2 consecutive "-" as shown by available data and both '-' at week 6 and week 8 for missing Week 7, otherwise nonresponder |
| 6 | - | NA | NA | - | Yes | 2 consecutive "-" as shown by available data at week 6 and week 9 and both "-", otherwise nonresponder |

NA = *not available for evaluation of study drug effect*; reason could be not assessable by lab, or starting

**Randomisation and Blinding (masking)**

All eligible patients were first stratified based on two factors:

1. By transplant type (HSCT or SOT)

2. By the most recent screening whole blood or plasma CMV DNA viral load categorised into 3 CMV DNA concentration-level groups based on local or central specialty laboratory qPCR results, as described above.

Following stratification, patients were randomised in a 2:1 allocation ratio to receive open-label maribavir 400 mg BID or IAT for 8 weeks using interactive response technology (IRT). Within the IAT group, the investigator selected the actual study treatment.

**Statistical methods**

Analysis of Primary Efficacy Endpoint compared the proportion of responder in maribavir treatment group who achieve confirmed viraemia clearance at end of study week 8, with proportion of responder in IAT group who achieve confirmed viraemia clearance at end of study week 8 using a composite estimand strategy counting patients switching to an alternative treatment, to the maribavir rescue treatment and missing CMV measurement at week 8 as non-responder in the primary analysis supplemented by several sensitivity analyses.

The difference in proportion of responders between treatment groups will be obtained using Cochran-Mantel-Haenszel (CMH) weighted average across all strata, and tested using CMH method, with transplant type and baseline plasma CMV DNA concentration as two stratification factors. The 95% confidence limits of the weighted average of difference across strata will be provided using the normal approximation. If the minimum number of patients in a response category in a treatment group, for example, in the high viral load group, is less than 5, the high and intermediate viral load groups will be collapsed into 1 stratum level.

The proportion of responders for the key secondary endpoint were compared in a similar way. The difference in proportion of responders between treatment groups will be obtained and tested using the same method as described for the primary efficacy endpoint. The EAC's adjudicated tissue-invasive disease or CMV syndrome symptoms and outcome will be used for the analysis.

The hypothesis-testing of the primary and key secondary endpoint will be adjusted for multiple comparisons using a fixed-sequence testing procedure to control the family-wise Type 1 error rate at 5% level.

If the proportion of responders for the primary efficacy endpoint is higher in the maribavir group and the test of adjusted difference in proportion of responders between treatment groups is statistically significant, and the proportion of response for the key secondary efficacy endpoint is higher in maribavir group and the test is significant at 0.05 level, it will be concluded that the treatment effect is more durable for maribavir as compared to the control group.

The analysis of the primary and key secondary efficacy endpoint were conducted using the Randomised Set as primary.

The primary version of the SAP was finalised on 30 May 2018, i.e. more than 17 months after the first patient was enrolled. Three amendments were generated after that date.

According to the Applicant, the SAP was finalised late on 30 May 2018 but prior to database lock (14 November 2020).

Estimand definition and missing data handling were specified for a composite estimand strategy regarding the intercurrent events "switch to MBV rescue", "alternative anti-CMV treatment", "study discontinuation" and "missing CMV measurement but remained in the study". However, this strategy is prone to bias in favour of maribavir due to the open-label nature of the study. Instead, a treatment policy estimand strategy should be pursued for the first two intercurrent events. It is noted that CMV DNA measurements at week 8 were available in most cases after treatment switch and can be used.

The use of the CMV viraemia clearance at the time of discontinuation in one of the sensitivity analyses refers to a LOCF analysis which may not be fully adequate (although acceptable as a sensitivity analysis) since recurrence had occurred in a number of patients.

Because this study was the only pivotal study, the treatment allocation unbalanced between regions and the potentially different medical care in the different countries, homogeneity between subgroups and countries or regions would be important to show. Even if the randomisation was not stratified by centre or country, homogeneity between countries and regions has to be justified. However, relevant differences in treatment assignments and treatment response between countries have been observed and questions the fulfilment of the requirements of the EMA Points to Consider on Application with 1. Meta-analyses; 2. One pivotal study.

***Results***

- **Participant flow**

As per protocol, the randomised set was the primary analysis set.

A total of 415 patients were screened for the study and 352 patients were enrolled and randomised (randomised set), with 235 patients randomised to maribavir and 117 patients randomised to IAT.

The main reasons for ineligibility in the screened but not randomised population were failure to demonstrate confirmed minimum CMV viral load (Inclusion Criterion 3; N=31) and failure to demonstrate that current CMV infection was refractory to the most recent CMV treatment (Inclusion

Criterion 4A, N=21). The requirement for central laboratory testing CMV DNA viral load ≥ 910 IU/mL was not mandatory for the screening visit and local laboratory testing results could be used to determine eligibility for study randomisation. Divergent results from the central and local laboratory have resulted in the randomisation of many of ineligible patients.

Two randomised patients (one in each treatment group) were not dosed; therefore, the modified randomised set and the safety set included 350 patients (maribavir: 234; IAT: 116). Most patients in the control group received monotherapy with either ganciclovir/valganciclovir (48.3%) or foscarnet (40.5%) as the IAT.

Differential drop out was observed in the IAT arm. Only half of the patients in the IAT group, who did not switch to the rescue arm, completed the study (49%) compared to 85% patients in the maribavir arm. Overall, 220 (62.5%) randomised patients completed 8 weeks of study-assigned treatment, 78% in the maribavir group and 32% in the IAT group. Treatment discontinuation due to AEs, was nearly 5-fold higher for the IAT group than for maribavir-treated patients (30.8% vs 6.4%, respectively). Treatment discontinuation for lack of efficacy (IAT: 13.7%; maribavir: 8.9%) and other reasons for discontinuation (IAT: 13.7%; maribavir: 1.7%) were also more frequent in the IAT group. Death led to treatment discontinuation for 3.0% of maribavir-treated patients compared with 0.9% for IAT.

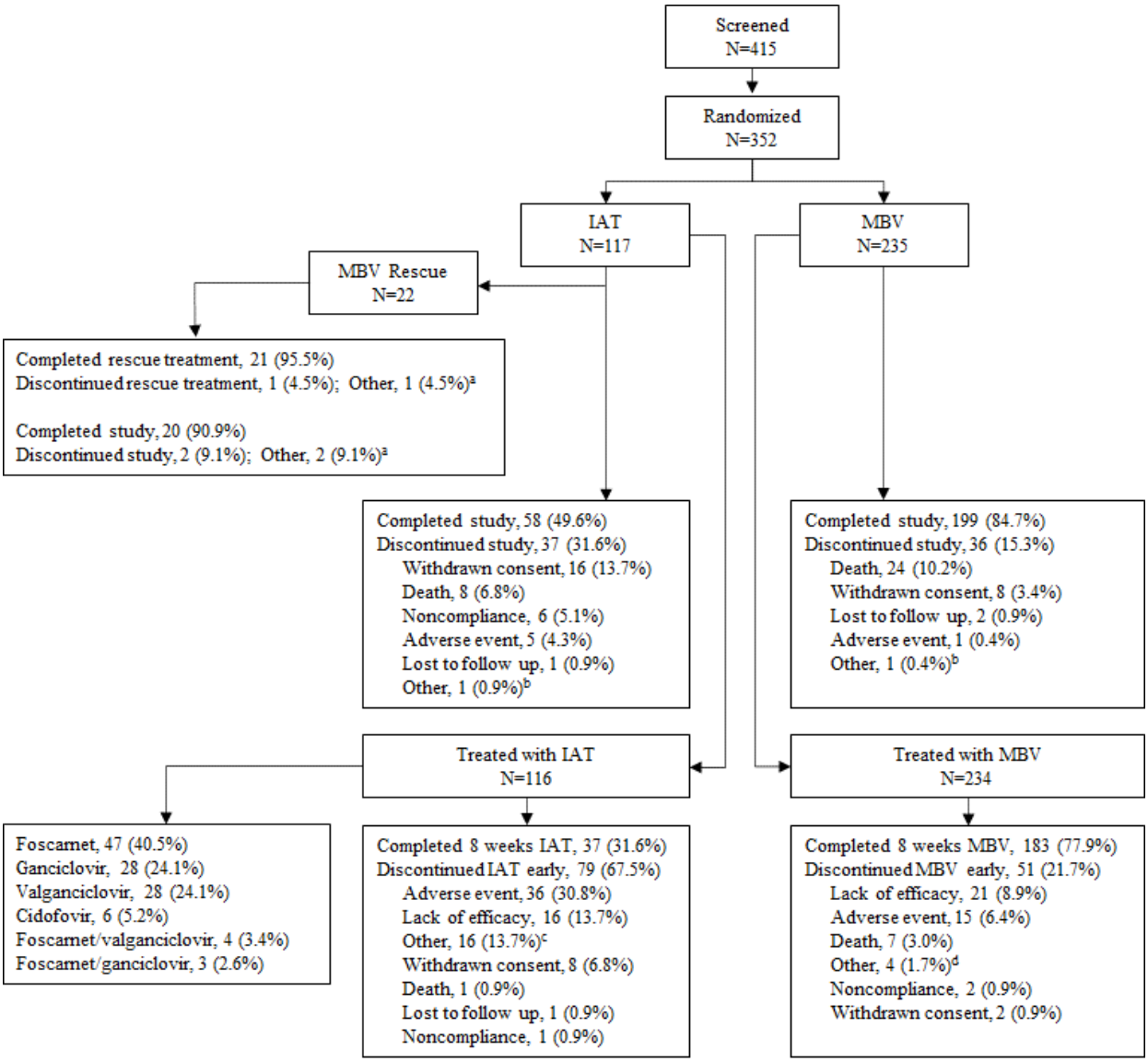


Figure 5 Flow diagram of patient disposition (Enrolled Set)

CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment; MBV=maribavir; PI=principal investigator

All percentages are based on the number of randomized patients.

[a] One patient discontinued rescue treatment and the study due to sponsor decision. One patient discontinued the study due to hospitalization in a different city (unable to complete follow-up visits).

[b] Other reasons for study discontinuation included PI discretion to discontinue 1 patient before dosing with maribavir and no efficacy with IAT for a patient who was not eligible for rescue therapy.

[c] Other reasons for treatment discontinuation in the IAT group fell into the general categories of low viral load/CMV clearance (with concern of toxicity with continued administration of IAT) (9 patients), patient safety (3 patients), patient/PI request (2 patients), no efficacy and patient ineligible for rescue therapy (1 patient), and peripherally inserted central catheter issues (1 patient).

[d] Other reasons for treatment discontinuation in the maribavir group included PI decision to switch to letermovir (1 patient), CMV detected in patient's cerebrospinal fluid (1 patient), nothing-by-mouth status with mental status change with risk for aspiration (1 patient), and disease progression (1 patient).

Source: Study 303 CSR, Table 14.1.1.1 and Section 16.2, Appendix 16.2.1, Listing 16.2.1.2

A total of 22 patients (19%) met the criteria for entry into the maribavir rescue arm. Reasons for inclusion in the rescue set were failure to achieve CMV viraemia clearance necessitating continued anti-CMV treatment and intolerance to the IAT (N=15), more than ⩾1 log10 increase from baseline in CMV DNA (N=4) less or failure to achieve at least <one $\log_{10}$ decrease from baseline in CMV DNA and persistent or new symptomatic CMV infection (N=3). The rescue set included patients who switched from all four of the protocol-defined IAT types: foscarnet (36.4%), ganciclovir (27.3%), valganciclovir (18.2%), and cidofovir (18.2%).

- **Conduct of the study**

The study protocol was amended 6 times during the conduct of study 303, including substantial changes in the primary and key secondary objectives, endpoints and analyses more than 17 months after study start to include patients who had discontinued study treatment early and met the criteria of confirmed CMV viraemia clearance at study week 8 as responders in the primary efficacy analysis and the change of definition of symptomatic CMV infection to include both tissue-invasive CMV disease and CMV syndrome.

A high number of protocol deviations/GCP deviation was noted in study 303. In total, 341 patients (97%) had at least one protocol deviation/GCP deviation during the conduct of study 303. Protocol deviation/GCP deviations classified as major were reported for 229 (65.1%) patients (MBV: 66.0% and IAT: 63.2%, respectively). A high number of GCP deviations, related to investigator related issues (qualifications/agreements, record keeping source docs, safety reporting (CRF), safety reporting (regulatory/sponsor) and patient medical care) was reported.

An "eDiary malfunction" was mentioned in the CSR of study 303 that seems to have affected PK related data (please refer to the pharmacokinetic section above). The impact of concentrations associated with missed dosing records in Study 620-303 was evaluated during development of PPK model. Missed dosing records were related to 14% of the concentrations in this study and were imputed from the PPK model. No substantial influence of the missing data was seen.

A high number of missing endpoint assessment were noted (11% in the IAT group and 9% in the maribavir group). Upon request, further information on the missing endpoint assessment were provided.

- **Baseline data**

Patient demographic characteristics were similar between the maribavir and IAT groups for race, ethnicity, height, weight, and BMI. The study population was predominantly white (75.6%) and not Hispanic or Latino (83.2%). The median age was similar between the maribavir and IAT groups (57 years [range: 19 to 79] and 54 [range: 19 to 77] years, respectively). The maribavir group had a higher proportion of patients ⩾65 years of age compared with IAT (23.0% and 13.7%, respectively),

as well as a higher proportion of male patients (63.0% and 55.6%, respectively).

Although adolescent patients ⩾12 years of age were permitted to enrol according to the protocol, no patients <18 years of age enrolled in the study. As no indication for adolescents is sought in this MAA, this is acceptable.

Sites in North America accounted for more than half of the randomised patients (58.2%), with a similar percentage of patients allocated to each treatment group. Sites in Europe randomised 38.6% of patients overall (maribavir: 41.3%; IAT: 33.3%) with some imbalances concerning the treatment allocation.

In total, 60% of the patient had a SOT, while slightly less patients had a HSC transplant (40%). Transplant type was used as stratification factor, hence the distribution of the two transplant types was similar across treatment arms. Among SOT recipients, the most common current transplant type was kidney (50.2%), followed by lung transplant (29.4%), and heart transplant (10.9%).

A higher percentage of maribavir-treated patients underwent a myeloablative preparative conditioning regimen prior to HSCT compared with patients in the IAT group (maribavir: 47 [51.5%] patients; IAT: 16 [33.3%] patients). The majority of the HSCTs performed were allogeneic.

The proportion of maribavir-treated patients with moderate renal impairment at baseline was higher than in the IAT group (26% vs 18%, respectively).

Table 16 General Baseline Characteristics and Transplant Status by Treatment Group study 303 (randomised set).

| Characteristic | IAT (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) | Total (N=352) n (%) |
|---|---|---|---|
| Current transplant type | | | |
| Solid organ transplant | 69 (59.0) | 142 (60.4) | 211 (59.9) |
| Heart | 9 (13.0) | 14 (9.9) | 23 (10.9) |
| Lung | 22 (31.9) | 40 (28.2) | 62 (29.4) |
| Liver | 1 (1.4) | 6 (4.2) | 7 (3.3) |
| Pancreas | 0 | 2 (1.4) | 2 (0.9) |
| Intestine | 0 | 1 (0.7) | 1 (0.5) |
| Kidney | 32 (46.4) | 74 (52.1) | 106 (50.2) |
| Multiple | 5 (7.2) | 5 (3.5) | 10 (4.7) |
| Hematopoietic stem cell transplant | 48 (41.0) | 93 (39.6) | 141 (40.1) |
| Autologous | 0 | 1 (1.1) | 1 (0.7) |
| Allogeneic | 48 (100.0) | 92 (98.9) | 140 (99.3) |
| Underlying disease | | | |
| Leukemia (acute myeloid) | 18 (37.5) | 36 (38.7) | 54 (38.3) |
| Leukemia (chronic myeloid) | 0 | 2 (2.2) | 2 (1.4) |
| Leukemia (acute lymphocytic) | 7 (14.6) | 12 (12.9) | 19 (13.5) |
| Lymphoma (non-Hodgkin's) | 4 (8.3) | 9 (9.7) | 13 (9.2) |
| Myelodysplastic syndrome | 8 (16.7) | 11 (11.8) | 19 (13.5) |
| Other myeloid malignancy | 1 (2.1) | 2 (2.2) | 3 (2.1) |
| Other | 10 (20.8) | 21 (22.6) | 31 (22.0) |
| Current graft status at baseline | | | |
| Solid organ transplant | | | |
| Functioning with complications | 8 (11.6) | 12 (8.5) | 20 (9.5) |
| Functioning | 61 (88.4) | 127 (89.4) | 188 (89.1) |
| Other[a] | 0 | 3 (2.1) | 3 (1.4) |
| Hematopoietic stem cell transplant | | | |
| Partially engrafted | 1 (2.1) | 4 (4.3) | 5 (3.5) |
| Functioning with complications | 5 (10.4) | 11 (11.8) | 16 (11.3) |
| Functioning | 42 (87.5) | 78 (83.9) | 120 (85.1) |
| Acute GVHD confirmed | | | |
| No | 109 (93.2) | 212 (90.2) | 321 (91.2) |

| Characteristic | IAT (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) | Total (N=352) n (%) |
|---|---|---|---|
| Yes | 8 (6.8) | 23 (9.8) | 31 (8.8) |
| Chronic GVHD confirmed | | | |
| No | 112 (95.7) | 229 (97.4) | 341 (96.9) |
| Yes | 5 (4.3) | 6 (2.6) | 11 (3.1) |
| Type of preparative conditioning regimen | | | |
| Myeloablative | 16 (33.3) | 47 (51.1) | 63 (45.0) |
| Non-myeloablative | 12 (25.0) | 17 (18.5) | 29 (20.7) |
| Reduced intensity conditioning regimen | 17 (35.4) | 28 (30.4) | 45 (32.1) |
| NA | 1 (2.1) | 0 | 1 (0.7) |
| Missing | 2 (4.2) | 0 | 2 (1.4) |
| Net immunosuppression use changed prior to the study | | | |
| No | 80 (68.4) | 181 (77.0) | 261 (74.1) |
| Yes | 36 (30.8) | 54 (23.0) | 90 (25.6) |
| Missing | 1 (0.9) | 0 | 1 (0.3) |
| Antilymphocyte use | | | |
| No | 68 (58.1) | 135 (57.4) | 203 (57.7) |
| Yes | 49 (41.9) | 100 (42.6) | 149 (42.3) |
| Renal impairment | | | |
| No impairment | 39 (33.3) | 81 (34.5) | 120 (34.1) |
| Mild | 42 (35.9) | 71 (30.2) | 113 (32.1) |
| Moderate | 22 (18.8) | 60 (25.5) | 82 (23.3) |
| Severe | 3 (2.6) | 8 (3.4) | 11 (3.1) |
| Missing | 11 (9.4) | 15 (6.4) | 26 (7.4) |
| Hepatic impairment | | | |
| No impairment | 107 (91.5) | 218 (92.8) | 325 (92.3) |
| Grade 1 | 3 (2.6) | 9 (3.8) | 12 (3.4) |
| Grade 2 | 3 (2.6) | 4 (1.7) | 7 (2.0) |
| Grade 3 or 4 | 0 | 0 | 0 |
| Missing | 4 (3.4) | 4 (1.7) | 8 (2.3) |
| Karnofsky Scale Performance Status, n | 108 | 213 | 321 |
| 100 | 22 (18.8) | 37 (15.7) | 59 (16.8) |
| 90 | 20 (17.1) | 65 (27.7) | 85 (24.1) |
| 80 | 29 (24.8) | 39 (16.6) | 68 (19.3) |
| 70 | 26 (22.2) | 43 (18.3) | 69 (19.6) |
| 60 | 5 (4.3) | 15 (6.4) | 20 (5.7) |
| 50 | 1 (0.9) | 5 (2.1) | 6 (1.7) |
| 40 | 3 (2.6) | 6 (2.6) | 9 (2.6) |
| 30 | 2 (1.7) | 1 (0.4) | 3 (0.9) |
| 20 | 0 | 2 (0.9) | 2 (0.6) |
| 10 | 0 | 0 | 0 |
| 0 | 0 | 0 | 0 |

| Characteristic | IAT (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) | Total (N=352) n (%) |
|---|---|---|---|
| Missing | 9 (7.7) | 22 (9.4) | 31 (8.8) |

BID=twice daily; CMV=cytomegalovirus; GVHD=graft-versus-host-disease; IAT=investigator-assigned anti-CMV treatment; NA=not applicable

[a] Includes grafts that failed (5 subjects) and 1 subject with stable renal function.

Source: Section 14, Table 14.1.4.2.1

Current CMV infection

The majority of patients meeting virologic inclusion criteria, as determined by the central laboratory, fell into the category of low CMV DNA viral load (<9100 IU/mL) (>65%), while only 6% had viral load categorised as high (≥91000 IU/mL) and most did not have EAC-confirmed CMV tissue-invasive disease or CMV syndrome at baseline.

Although baseline CMV DNA was used as stratification factor, imbalance in the distribution of viral load categories based on central lab results were noted. This imbalance is based on the use of local instead of central laboratory assays results for randomisation.

Only 29 patients had EAC confirmed symptomatic CMV infection. Imbalances concerning the distribution of patients with EAC confirmed symptomatic infection across treatment arms (IAT: 8 patients (6.8%); maribavir: 21 (8.9 %)) were noted.

Table 17 Status of Current CMV Infection at Baseline by Treatment Group study 303 (randomised set)

| Characteristic[a] | IAT (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) | Total (N=352) n (%) |
|---|---|---|---|
| Baseline CMV DNA levels from plasma by central laboratory (IU/mL)[b] | | | |
| n | 117 | 235 | 352 |
| Mean (SD) | 88171.8 (595022.17) | 52921.6 (335894.69) | 64638.3 (438750.25) |
| Median | 2869.0 | 3377.0 | 3237.5 |
| Q1, Q3 | 927.0, 11636.0 | 1036.0, 12544.0 | 1019.5, 12340.0 |
| Min, max | 69, 6191784 | 69, 4730375 | 69, 6191784 |
| CMV DNA levels category as reported by central laboratory | | | |
| Low | 85 (72.6) | 153 (65.1) | 238 (67.6) |
| Intermediate | 25 (21.4) | 68 (28.9) | 93 (26.4) |
| High | 7 (6.0) | 14 (6.0) | 21 (6.0) |
| CMV DNA levels category at randomization | | | |
| Low | 54 (46.2) | 108 (46.0) | 162 (46.0) |
| Intermediate | 49 (41.9) | 99 (42.1) | 148 (42.0) |
| High | 14 (12.0) | 28 (11.9) | 42 (11.9) |
| Category of current CMV infection based on investigator assessment | | | |
| CMV syndrome (SOT only) | 10 (8.5) | 16 (6.8) | 26 (7.4) |
| CMV tissue-invasive disease | 4 (3.4) | 18 (7.7) | 22 (6.3) |
| Asymptomatic CMV infection | 103 (88.0) | 201 (85.5) | 304 (86.4) |
| Baseline symptomatic CMV infection by EAC | | | |
| No | 109 (93.2) | 214 (91.1) | 323 (91.8) |
| Yes[c,d] | 8 (6.8) | 21 (8.9) | 29 (8.2) |
| CMV syndrome in SOT subjects | 7 (87.5) | 10 (47.6) | 17 (58.6) |
| Tissue-invasive disease | 1 (12.5) | 12 (57.1) | 13 (44.8) |
| CMV serostatus for SOT[c] | | | |
| Donor +/Recipient + | 8 (11.6) | 11 (7.7) | 19 (9.0) |
| Donor -/Recipient + | 1 (1.4) | 3 (2.1) | 4 (1.9) |
| Donor +/Recipient - | 56 (81.2) | 120 (84.5) | 176 (83.4) |
| Donor -/Recipient - | 3 (4.3) | 7 (4.9) | 10 (4.7) |
| Missing | 1 (1.4) | 1 (0.7) | 2 (0.9) |
| CMV serostatus for HSCT[c] | | | |
| Donor +/Recipient + | 17 (35.4) | 42 (45.2) | 59 (41.8) |
| Donor -/Recipient + | 26 (54.2) | 39 (41.9) | 65 (46.1) |
| Donor +/Recipient - | 3 (6.3) | 6 (6.5) | 9 (6.4) |
| Donor -/Recipient - | 1 (2.1) | 5 (5.4) | 6 (4.3) |
| Missing | 1 (2.1) | 1 (1.1) | 2 (1.4) |
| Prior use of CMV prophylaxis | | | |
| No | 72 (61.5) | 135 (57.4) | 207 (58.8) |
| Yes | 45 (38.5) | 100 (42.6) | 145 (41.2) |

| Characteristic[a] | IAT (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) | Total (N=352) n (%) |
|---|---|---|---|
| The current CMV infection is the first episode post-transplant | | | |
| No | 39 (33.3) | 73 (31.1) | 112 (31.8) |
| Yes | 78 (66.7) | 162 (68.9) | 240 (68.2) |
| Days from onset of current CMV infection based on virologic testing to first dose of study-assigned treatment | | | |
| n | 117 | 235 | 352 |
| Mean (SD) | 63.4 (58.16) | 70.5 (85.53) | 68.2 (77.50) |
| Median | 40.0 | 38.0 | 39.0 |
| Q1, Q3 | 25.0, 79.0 | 23.0, 93.0 | 24.0, 88.0 |
| Min, max | 3, 312 | 3, 716 | 3, 716 |

BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; EAC=endpoint adjudication committee; GVHD=graft-versus-host-disease; HSCT=hematopoietic stem cell transplant; IAT=investigator-assigned anti-CMV treatment; LLOQ=lower limit of quantification; max=maximum; min=minimum; Q1=first quartile; Q3=third quartile; SD=standard deviation; SOT=solid organ transplant

[a] Baseline was defined as the last value on or before the first dose date of study-assigned treatment, or date of randomization for subjects who did not receive study-assigned treatment.

[b] Half of the LLOQ value (ie, 137/2=68.5) was imputed for those who had <LLOQ.

[c] Percentages are based on the number of subjects within the category.

[d] Subjects could have multiple reasons.

Source: Section 14, Table 14.1.4.2.1

Baseline Resistance Profile:

Genotyping of baseline plasma samples by the central laboratory for the presence of at least one CMV RAS known to confer resistance to ganciclovir, foscarnet, and/or cidofovir is shown in Table 18.

Patients with CMV harbouring RAS known to confer resistance to ganciclovir, foscarnet, and/or cidofovir constituted the primary resistance set (PRS). The 130 patients with genotyping data and for whom no baseline IAT RASs were identified constituted the non-primary resistance set (non-PRS).

More than half of the patients (54%) harboured virus with at least one resistance-associated amino acid substitution (RAS) known to confer resistance to one or more of the following: ganciclovir, foscarnet, and/or cidofovir. Baseline Imbalances between the treatment arms were noted, with more patients in the IAT group having CMV harbouring RAS conferring resistance to at least one IAT (59%) compared to maribavir (52%).

Four patients, who had not been previously exposed to maribavir had baseline RAS known to confer resistance to maribavir.

Table 18 Baseline Resistance Profile study 303 (Modified Randomised Set)

| Characteristic[a] | IAT (N=116) n (%) | Maribavir 400 mg BID (N=234) n (%) | Total (N=350) n (%) |
|---|---|---|---|
| Presence of CMV RASs known to confer resistance to ganciclovir, foscarnet, and/or cidofovir per central laboratory results | | | |
| No | 34 (29.3) | 96 (41.0) | 130 (37.1) |
| Yes | 69 (59.5) | 121 (51.7) | 190 (54.3) |
| Unable to genotype[a] | 13 (11.2) | 17 (7.3) | 30 (8.6) |
| Presence of CMV RASs known to confer resistance to maribavir per central laboratory results | | | |
| No | 97 (83.6) | 213 (91.0) | 310 (88.6) |
| Yes | 3 (2.6) | 1 (0.4) | 4 (1.1) |
| Unable to genotype[b] | 16 (13.8) | 20 (8.5) | 36 (10.3) |

BID=twice daily; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment; PCR=polymerase chain reaction; RAS=resistance-associated amino acid substitution

[a] Resistance results could not be provided for UL97/UL54 for 13 subjects in the IAT group and 17 subjects in the maribavir group.

[b] Resistance could not be provided for UL97/UL27 for 16 subjects in the IAT group and 20 subjects in the maribavir group.
Note: Analysis of the gene target(s) was not possible due to possible polymorphism(s) within 1 of the primer binding sites, an insufficient viral load, or PCR inhibitors in the sample.
Source: Resistance Report, Appendix 5, Table 1.1.1 and Table 2.1.1

More than half of the patients (57%) identified as having one or more baseline RASs known to confer resistance to ganciclovir/valganciclovir received ganciclovir/valganciclovir as the IAT (Table 19). Hence, they received a treatment their virus were already resistant to at baseline. Not all patients resistant to ganciclovir/valganciclovir were treated according to the "management algorithm for patients with suspected resistant CMV infection" recommended in current CMV treatment guidelines. Also, there was no requirement for documentation of host factors and the clinical rational for changing the treatment. This is a clear limitation of the study as it may have negatively impacted the failure rate in the IAT arm and hampers the assessment of treatment response in the target population, as well as factors that might have an impact on the treatment response.

Table 19 Summary of Baseline Genotyping Results by Anti-CMV Drug and IAT Type selected study 303 (modified randomised set).

| Resistant to: | IAT Randomized (N=116) | Maribavir Randomized (N=234) | IAT Type | | | | |
|---|---|---|---|---|---|---|---|
| | | | GCV/VGCV (N=56) | Foscarnet (N=47) | Cidofovir (N=6) | GCV/ Foscarnet (N=3) | VGCV/ Foscarnet (N=4) |
| GCV/VGCV | 69 (59.5) | 121 (51.7) | 32 (57.1) | 30 (63.8) | 4 (66.7) | 2 (66.7) | 1 (25.0) |
| Foscarnet | 7 (6.0) | 10 (4.3) | 5 (8.9) | 0 | 1 (16.7) | 1 (33.3) | 0 |
| Cidofovir | 14 (12.1) | 33 (14.1) | 11 (19.6) | 1 (2.1) | 1 (16.7) | 1 (33.3) | 0 |

CMV=cytomegalovirus; GCV=ganciclovir; IAT=investigator-assigned anti-CMV treatment; VGCV=valganciclovir

Source: Resistance Report, Appendix 5, Table 1.1.4

- **Numbers analysed**

The randomised set was used for primary efficacy analyses and included 117 patients in the IAT group and 235 patients in the maribavir group. The randomised set was supported by the modified randomised set that excluded two patients, one in each treatment group, who were randomised but not treated.

The PP set excluded 21 patients with major protocol deviations, i.e. patients who discontinued treatment early (i.e. 72 hours; MBV group (N=2), IAT group (N =1)), who received prohibited concomitant medications (MBV group (N=5), IAT group (N =5)) and without violation of inclusion and/or exclusion criteria (MBV group (N=6), IAT group (N =4)). As no adolescent patients were enrolled in study 303, no adolescent PK set is available.

- **Outcomes and estimation**

**Primary Efficacy Endpoint:**

The proportion of patients achieving confirmed CMV viraemia clearance at the end of Week 8 in transplant recipients with refractory CMV infection (with or without resistance) is shown in Table 20 below. Patients with confirmed CMV viraemia clearance at the end of Week 8 were considered as responders regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy.

The proportion of maribavir-treated subjects who achieved confirmed CMV viraemia clearance at Week 8 was higher in the maribavir goup compared to the IAT group in the randomised set (maribavir: 56%; IAT: 24%). After adjusting for the stratification factors (transplant type of SOT vs HSCT and baseline plasma CMV DNA viral load group of low vs pooled intermediate/high), using the CMH test, the difference in proportion of responders between treatment groups was highly statistically significant in favour of maribavir (32.8%; 95% CI: 22.80, 42.74, p<0.001).

Table 20 Primary Efficacy Endpoint Analysis: Confirmed CMV Viraemia Clearance at week 8

| CMV Viremia Clearance Response | IAT (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| Overall | | |
| Responders | 28 (23.9) | 131 (55.7) |
| Nonresponders | 89 (76.1) | 104 (44.3) |
| Unadjusted difference in proportion of responders (95% CI)[a] | | 31.8 (21.81, 41.82) |
| Adjusted difference in proportion of responders (95% CI)[b] | | 32.8 (22.80, 42.74) |
| p-value: adjusted[b] | | <0.001 |
| p-value: Homogeneity across strata[c] | | 0.598 |

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment; N=number of subjects

[a] Unadjusted difference in proportion (maribavir – IAT) and the corresponding 95% CI were computed by the normal approximation method.

[b] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration if homogeneity was met. The minimum risk weight method was used if the homogeneity was not met. Only those with both stratification factors were included in the computation.

[c] Breslow-Day test was used for testing the homogeneity across strata. The stratum-specific difference in proportion was reported only if the p-value for homogeneity across strata was significant.

Percentages were based on the number of subjects in the randomized set.

Subjects with confirmed CMV viremia clearance at the end of Week 8 were considered as responders regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. Plasma CMV DNA assessments after starting alternative anti-CMV treatment or rescue treatment were not evaluable for the assessment of study-assigned treatment effect.

Randomized subjects with no efficacy data were treated as nonresponders.

Source: Section 14, Table 14.2.1.1.1

Categorisation of the reasons for failure for the 104 (44.3%) patients in the maribavir group and 89 (76.1%) patients in the IAT group who failed to achieve the primary endpoint at the end of week 8 is shown in Table 21.

Table 21 Reasons for failure of achieving primary endpoint at study week 8 by treatment group (Randomised Set)

| | Investigator Assigned Treatment (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| Subjects who failed to achieve primary endpoint | 89 | 104 |
| Reasons for failing to achieve primary endpoint | | |
| CMV measurements through study week 8 but did not meet response criteria [a] | 18 (20.2) | 60 (57.7) |
| Randomized but not dosed and withdrew from the study [a] | 1 (1.1) | 1 (1.0) |
| Maribavir rescue therapy | 22 (24.7) | 0 |
| Alternative anti-CMV treatment | 24 (27.0) | 26 (25.0) |
| Missing CMV measurement | 24 (27.0) | 17 (16.3) |
| Due to early discontinuation | 21 (23.6) | 16 (15.4) |
| Reason for early discontinuation [b] | | |
| Death | 3 (3.4) | 10 (9.6) |
| Adverse event | 3 (3.4) | 2 (1.9) |
| Non-compliance with study procedures/visits or study drug | 4 (4.5) | 0 |
| Lack of efficacy | 0 | 1 (1.0) |
| Withdrawal of consent by the subject/parent guardian | 10 (11.2) | 3 (2.9) |
| Study terminated by sponsor | 0 | 0 |
| Lost to follow-up | 1 (1.1) | 0 |
| Pregnancy | 0 | 0 |
| Other | 0 | 0 |
| Due to other reason but remained on the study | 3 (3.4) | 1 (1.0) |

CMV = Cytomegalovirus.
Percentages are based on the number of subjects who failed to achieve primary endpoint at study week 8.
[a] Time to failure for achieving primary endpoint at study week 8 cannot be computed.
[b] From the 'Study Completion' CRF page or from the 'End of Treatment' CRF page if no reason was given in the 'Study Completion' CRF page.
Cross-reference: Listing 16.2.6.11

The median time to failure to achieve the primary endpoint at week 8 was evaluated for patients who failed due to early discontinuation or initiation of alternative anti-CMV treatment or maribavir rescue treatment. In this analysis, the median time to failure was longer for patients in the maribavir group (35 days [range: 2 to 57 days]) than for patients in the IAT group (26 days [range: 2 to 59 days]).

The subgroup analysis of the primary efficacy endpoint confirmed CMV viraemia clearance in patients who received 8 weeks of study assigned treatment was no longer statistically significant (Table 22).

Table 22 Analysis of the primary efficacy endpoint: confirmed CMV viraemia clearance in patients who received 8 weeks of study-assigned treatment (randomised set)

| CMV Viremia Clearance Response | IAT (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| Subjects who received 8 weeks of study-assigned treatment, n | 37 | 183 |
| Responders | 22 (59.5) | 129 (70.5) |
| Nonresponders | 15 (40.5) | 54 (29.5) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 10.2 (-7.01, 27.41) |
| p-value: adjusted[a] | | 0.245 |

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment; N=number of subjects
[a] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration, as homogeneity was met.
Percentages were based on the number of subjects who received 8 weeks of study- assigned treatment in the randomized set.
Subjects who received 8 weeks of exclusive study-assigned treatment and achieved a confirmed CMV viremia clearance at the end of Week 8 were considered as a responder. Plasma CMV DNA assessments after starting alternative anti-CMV treatment or rescue treatment were not evaluable for the assessment of study-assigned treatment effect.
Randomized subjects with no efficacy data were treated as nonresponders.
Source: Section 14, Table 14.2.1.8

**Sensitivity Analyses of the Primary Endpoint**

Sensitivity and supplemental analyses to assess the robustness of the primary efficacy results are shown in the table below. According to the Applicant these analyses were considered "pre-specified". However, as the SAP was generated during this open-label study, the analyses cannot be regarded as fully pre-specified.

Table 23 Sensitivity analyses of the primary efficacy endpoint based on alternate definitions of response (randomised set)

| Description of Sensitivity Analysis<br>CMV Viremia Clearance Response | IAT (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| Analysis that includes subjects who met the criteria of confirmed CMV viremia clearance at the time of study discontinuation as a responder | | |
| Responders | 39 (33.3) | 137 (58.3) |
| Nonresponders | 78 (66.7) | 98 (41.7) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 26.1 (15.61, 36.67) |
| p-value: adjusted[a] | | <0.001 |
| Analysis including subjects with confirmed CMV viremia clearance at any time during the treatment phase as a responder | | |
| Responders | 61 (52.1) | 174 (74.0) |
| Nonresponders | 56 (47.9) | 61 (26.0) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 23.6 (13.18, 33.93) |
| p-value: adjusted[a] | | <0.001 |
| Analysis including CMV DNA levels obtained after start of alternative anti-CMV treatment in the IAT group, but not in the maribavir group | | |
| Responders | 41 (35.0) | 131 (55.7) |
| Nonresponders | 76 (65.0) | 104 (44.3) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 21.7 (11.02, 32.48) |
| p-value: adjusted[a] | | <0.001 |

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment; N=number of subjects
[a] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration, as homogeneity was met.
Percentages were based on the number of subjects in the randomized set.
Subjects with confirmed CMV viremia clearance at the end of Week 8 were considered as responders regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. Plasma CMV DNA assessments after starting alternative anti-CMV treatment or rescue treatment were not evaluable for the assessment of study-assigned treatment effect, unless specified otherwise in the analysis.
Randomized subjects with no efficacy data were treated as nonresponders.
Source: Section 14, Table 14.2.1.3, Table 14.2.1.7, Table 14.2.1.9

Sensitivity analyses to assess the impact of the higher rate of treatment discontinuation in the IAT group compared with maribavir-treated patients are shown below.

Table 24 Sensitivity analyses of the primary efficacy endpoint: confirmed CMV viraemia clearance excluding early treatment discontinuations occurring within 72 hours or 7, 14, 21, and 28 days of initiating treatment (randomised set)

| Subjects Included in Analysis<br>CMV Viremia Clearance Response | IAT<br>(N=117)<br>n (%) | Maribavir<br>400 mg BID<br>(N=235)<br>n (%) |
|---|---|---|
| Subjects on treatment 72 hours after treatment initiation, n | 116 | 233 |
| Responders | 28 (24.1) | 131 (56.2) |
| Nonresponders | 88 (75.9) | 102 (43.8) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 33.1 (23.08, 43.12) |
| p-value: adjusted[a] | | <0.001 |
| Subjects on treatment 7 days after treatment initiation, n | 113 | 232 |
| Responders | 28 (24.8) | 131 (56.5) |
| Nonresponders | 85 (75.2) | 101 (43.5) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 32.6 (22.47, 42.79) |
| p-value: adjusted[a] | | <0.001 |
| Subjects on treatment 14 days after treatment initiation, n | 98 | 224 |
| Responders | 28 (28.6) | 131 (58.5) |
| Nonresponders | 70 (71.4) | 93 (41.5) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 30.8 (19.87, 41.81) |
| p-value: adjusted[a] | | <0.001 |
| Subjects on treatment 21 days after treatment initiation, n | 80 | 217 |
| Responders | 27 (33.8) | 131 (60.4) |
| Nonresponders | 53 (66.3) | 86 (39.6) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 27.5 (15.34, 39.75) |
| p-value: adjusted[a] | | <0.001 |
| Subjects on treatment 28 days after treatment initiation, n | 65 | 214 |
| Responders | 25 (38.5) | 131 (61.2) |
| Nonresponders | 40 (61.5) | 83 (38.8) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 23.4 (9.90, 36.94) |
| p-value: adjusted[a] | | <0.001 |

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment; N=number of subjects

[a] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration, as homogeneity was met.

Percentages were based on the number of randomized subjects who remained on treatment after the designated time period of starting the study-assigned treatment in the randomized set. Subjects with confirmed CMV viremia clearance at the end of Week 8 were considered as responders regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. Plasma CMV DNA assessments after starting alternative anti-CMV treatment or rescue treatment were not evaluable for the assessment of study-assigned treatment effect.

Randomized subjects with no efficacy data were treated as nonresponders.

Source: Section 14, Table 14.2.1.6.1, Table 14.2.1.6.2, Table 14.2.1.6.3, Table 14.2.1.6.4, and Table 14.2.1.6.5

The robustness of the primary efficacy endpoint result was assessed further by repeating the analysis using the stratification factors assigned at randomisation (see table below).

Table 25 Sensitivity analysis of the primary efficacy endpoint based on stratification used at randomisation (randomised set)

| CMV Viremia Clearance Response | IAT (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| Responders | 28 (23.9) | 131 (55.7) |
| Nonresponders | 89 (76.1) | 104 (44.3) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 31.8 (21.86, 41.76) |
| p-value: adjusted[a] | | <0.001 |

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment; N=number of subjects
[a] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration (used for randomization), as homogeneity was met.
Percentages were based on the number of subjects in the randomized set.
Subjects with confirmed CMV viremia clearance at the end of Week 8 were considered as a responder regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. Plasma CMV DNA assessments after starting alternative anti-CMV treatment or rescue treatment were not evaluable for the assessment of study-assigned treatment effect.
Randomized subjects with no efficacy data were treated as nonresponders.
Source: Section 14, Table 14.2.1.5

The sensitivity analysis for the primary efficacy endpoint of confirmed CMV viraemia clearance in patients with baseline central laboratory CMV DNA above the Lower Limit of Quantification or at least 910 IU/mL (Randomised Set) is provided below.

Table 26 Sensitivity analyses of the primary efficacy endpoint: confirmed CMV viraemia clearance in patients with baseline central laboratory CMV DNA above the lower limit of quantification or at least 910 IU/ml (randomised set)

| Baseline Central Laboratory CMV DNA<br>CMV Viremia Clearance Response | IAT (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| CMV DNA >LLOQ | | |
| Randomized subjects with baseline CMV DNA from the central laboratory >LLOQ, n | 109 | 225 |
| Responders | 27 (24.8) | 124 (55.1) |
| Nonresponders | 82 (75.2) | 101 (44.9) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 31.2 (20.85, 41.54) |
| p-value: adjusted[a] | | <0.001 |
| CMV DNA ≥910 IU/mL | | |
| Randomized subjects with baseline CMV DNA from the central laboratory ≥910 IU/mL, n | 88 | 182 |
| Responders | 22 (25.0) | 94 (51.6) |
| Nonresponders | 66 (75.0) | 88 (48.4) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 27.4 (15.86, 38.98) |
| p-value: adjusted[a] | | <0.001 |

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment; LLOQ=lower limit of quantification; N=number of subjects
[a] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration, as homogeneity was met.
Percentages were based on the number of randomized subjects who had baseline CMV DNA from the central laboratory as defined for the analysis (ie, either >LLOQ or ≥910 IU/mL). Subjects with confirmed CMV viremia clearance at the end of Week 8 were considered as responders regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. Plasma CMV DNA assessments after starting alternative anti-CMV treatment or rescue treatment were not evaluable for the assessment of study-assigned treatment effect.
Randomized subjects with no efficacy data were treated as nonresponders.
Source: Section 14, Table 14.2.1.11 and Table 14.2.1.12

Multivariable regression analysis

Table 27 Multivariable logistic regression of confirmed CMV viraemia clearance response at study week 8 by treatment group (randomised set)

| Final Model [a] | Adjusted OR (95% CI) [b] | p-value [b] |
|---|---|---|
| Treatment | | |
| Maribavir vs. IAT at Resistance=N | 1.72 (0.745, 3.986) | 0.204 |
| Maribavir vs. IAT at Resistance=Y | 7.97 (3.850, 16.493) | <0.001 |
| Transplant Type | | |
| HSCT vs. SOT at Region=Europe/Asia | 0.60 (0.278, 1.316) | 0.204 |
| HSCT vs. SOT at Region=North America | 1.82 (0.832, 3.980) | 0.134 |
| CMV DNA Viral Load | | |
| Intermediate/High vs. Low | 0.47 (0.274, 0.791) | 0.005 |
| Resistance Status | | |
| Yes vs. No at Treatment=IAT | 0.63 (0.233, 1.689) | 0.357 |
| Yes vs. No at Treatment=Maribavir | 2.90 (1.509, 5.588) | 0.001 |
| Enrolling Region | | |
| North America vs. Europe/Asia at Transplant type=SOT | 0.49 (0.255, 0.958) | 0.037 |
| North America vs. Europe/Asia at Transplant type=HSCT | 1.49 (0.679, 3.265) | 0.320 |

IAT = Investigator Assigned Treatment. CMV = Cytomegalovirus. SOT = Solid Organ Transplant. HSCT = Hematopoietic Stem Cell Transplant.
Subject with confirmed CMV viremia clearance at the end of Study Week 8 is considered as a responder regardless of whether the study assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy.
Randomized subjects with no efficacy data are treated as non-responders.
[a] The final model after backward selection method includes the following parameters (p-value from Wald test of the type 3 analysis of effect of the model): treatment (p=<0.001), transplant type (p=0.874), CMV DNA level (p=0.005), resistance (p=0.351), region (p=0.560), transplant type and region interaction (p=0.035), treatment and resistance interaction (p=0.007).
[b] Odds ratio, confidence interval, and the corresponding p-value are based on the Wald test from the final model.
Cross-reference: Listing 16.2.4.1, Listing 16.2.4.3, Listing 16.2.4.4.1, Listing 14.2.4.4.2, Listing 16.2.6.1, and Listing 16.2.6.2.

Sensitivity analysis to assess the impact of COVID-19 on the primary efficacy endpoint

Table 28 Analysis of confirmed cmv viraemia clearance response at study week 8 by the impact of COVID-19 using worst case scenario by treatment group (randomised set)

| CMV Viremia Clearance Response | Investigator Assigned Treatment (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| Overall | | |
| Responders | 30 (25.6) | 131 (55.7) |
| Non-responders | 87 (74.4) | 104 (44.3) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 30.1 (19.96, 40.25) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 31.1 (21.03, 41.20) |
| p-value: Adjusted [b] | | <0.001 |
| p-value: Homogeneity across strata [c] | | 0.706 |

CMV = Cytomegalovirus.
Percentages are based on the number of subjects in the Randomized Set.
The confirmed CMV viremia clearance for those without the impact of COVID-19 are defined the same as the primary endpoint analysis. For those with the impact of COVID-19, the consecutive samples from Week 5 and Week 10 are used to access the CMV viremia clearance if there are sufficient evaluable visits. IAT subjects impacted by COVID-19 but without sufficient evaluable visits are treated as responders, Maribavir subjects are treated as non-responders.
Randomized subjects with no efficacy data are treated as non-responders.
[a] Unadjusted difference in proportion (Maribavir - IAT) and the corresponding 95% CI is computed by the normal approximation method.
[b] Cochran-Mantel-Haenszel (CMH) weighted average approach is used for the adjusted difference in proportion (Maribavir - IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration if homogeneity is met. The minimum risk weight method is used if the homogeneity is not met. Only those with both stratification factors are included in the computation.
[c] Breslow-Day test is used for testing the homogeneity across strata. The stratum-specific difference in proportion is reported only if the p-value for homogeneity across strata is significant.
Cross-reference: Listing 16.2.6.1 and Listing 16.2.6.2.

**Key secondary endpoint**

Efficacy results of the composite key secondary endpoint of confirmed CMV viraemia clearance and CMV infection symptom control at week 8 and maintenance through week 16 by treatment group is shown in the table below.

Table 29 Analysis of key secondary endpoint of achieving confirmed CMV viraemia clearance and CMV infection symptom control followed by maintenance through week 16 by treatment group (randomised set)

| CMV Viremia Clearance and CMV Infection Symptom Control Response | IAT (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| Overall | | |
| Responders | 12 (10.3) | 44 (18.7) |
| Nonresponders | 105 (89.7) | 191 (81.3) |
| Unadjusted difference in proportion of responders (95% CI)[a] | | 8.5 (1.04, 15.89) |
| Adjusted difference in proportion of responders (95% CI)[b] | | 9.5 (2.02, 16.88) |
| p-value: Adjusted[b] | | 0.013 |
| p-value: Homogeneity across strata[c] | | 0.312 |

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment; N=number of subjects

[a] Unadjusted difference in proportion (maribavir – IAT) and the corresponding 95% CI were computed by the normal approximation method.

[b] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration if homogeneity was met. The minimum risk weight method was used if the homogeneity was not met. Only those with both stratification factors were included in the computation.

[c] Breslow-Day test was used for testing the homogeneity across strata. The stratum-specific difference in proportion was reported only if the p-value for homogeneity across strata was significant.

Percentages were based on the number of subjects in the randomized set.

Cytomegalovirus infection symptom control data is adjudicated by the Endpoint Adjudication Committee.

Subject with response (both CMV viremia clearance and CMV infection symptom control) at Week 8 regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy, and maintenance of this treatment effect through Week 16 was considered as a responder.

Randomized subjects with no efficacy data were treated as nonresponders.

Source: Section 14, Table 14.2.2.1.1

The subgroup analysis of the specified key secondary efficacy endpoint, confirmed CMV Viraemia clearance and CMV symptom control at week eight followed by maintenance through week 16 in patients who received 8 weeks of study-assigned treatment is shown in the table below.

Table 30 Analysis of achieving confirmed CMV viraemia clearance and CMV infection symptom control response followed by maintenance through study week 16 restricted to those who received 8-week study treatment by treatment group (randomised set)

| CMV Viremia Clearance and CMV Infection Symptom Control Response | Investigator Assigned Treatment (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| Number of subjects who had received 8-week study treatment | 37 | 183 |
| Overall | | |
| Responders | 6 (16.2) | 44 (24.0) |
| Non-responders | 31 (83.8) | 139 (76.0) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 7.8 (-5.57, 21.22) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 6.2 (-7.54, 19.84) |
| p-value: Adjusted [b] | | 0.379 |
| p-value: Homogeneity across strata [c] | | 0.091 |

CMV = Cytomegalovirus.
CMV infection symptom control data is adjudicated by the Endpoint Adjudication Committee.
Percentages are based on the number of subjects that received 8-week study treatment in the Randomized Set.
Subject who received 8-week of exclusive study assigned treatment and achieved the response (both virological response and symptomatic CMV infection control) at study week 8 and maintenance of this treatment effect through study week 16 is considered as a responder.
Randomized subjects with no efficacy data are treated as non-responders.
[a] Unadjusted difference in proportion (Maribavir - IAT) and the corresponding 95% CI is computed by the normal approximation method.
[b] Cochran-Mantel-Haenszel (CMH) weighted average approach is used for the adjusted difference in proportion (Maribavir - IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration if homogeneity is met. The minimum risk weight method is used if the homogeneity is not met. Only those with both stratification factors are included in the computation.
[c] Breslow-Day test is used for testing the homogeneity across strata. The stratum-specific difference in proportion is reported only if the p-value for homogeneity across strata is significant.
Cross-reference: Listing 16.2.6.3 and Listing 16.2.6.4.

**Sensitivity analyses of the key secondary endpoint**

Table 31 Sensitivity analyses of the key secondary efficacy endpoint based on alternate definitions of response (randomised set)

| Description of Sensitivity Analysis<br>CMV Viremia Clearance Response | IAT<br>(N=117)<br>n (%) | Maribavir<br>400 mg BID<br>(N=235)<br>n (%) |
|---|---|---|
| Analysis that includes subjects who met the criteria of confirmed CMV viremia clearance at the time of study discontinuation as a responder | | |
| Responders | 13 (11.1) | 45 (19.1) |
| Nonresponders | 104 (88.9) | 190 (80.9) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 9.0 (1.43, 16.57) |
| p-value: adjusted[a] | | 0.020 |
| Analysis including data after start of alternative anti-CMV treatment in the IAT group | | |
| Responders | 15 (12.8) | 44 (18.7) |
| Nonresponders | 102 (87.2) | 191 (81.3) |
| Adjusted difference in proportion of responders (95% CI)[a] | | 6.9 (-0.96, 14.67) |
| p-value: adjusted[a] | | 0.085 |

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment; N=number of subjects

[a] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration, as homogeneity was met.

Percentages were based on the number of subjects in the randomized set.

Response was assessed regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. Plasma CMV DNA assessments after starting alternative anti-CMV treatment or rescue treatment were not evaluable for the assessment of study-assigned treatment effect, unless specified otherwise in the analysis.

Randomized subjects with no efficacy data were treated as nonresponders.

Source: Section 14, Table 14.2.2.3 and Table 14.2.2.7

**Status of EAC confirmed CMV symptoms over time**

At week 8, the EAC confirmed status of symptomatic CMV was:

Resolution or improvement: MBV: 16/21 patients (76.2%)

IAT: 5/8 patients (62.5%)

No change: MBV: 5/21 patients (23.8%)

IAT: 1/8 patients (12.5%)

Worsening: MBV: 0 patients

IAT: 2/8 patients (25.0%)

Postbaseline new onset of symptomatic CMV infection

Table 32 Summary of post-baseline new onset of symptomatic CMV infection (randomised set)

| | IAT<br>(N=117)<br>n (%) | Maribavir<br>400 mg BID<br>(N=235)<br>n (%) |
|---|---|---|
| EAC-confirmed new onset CMV disease postbaseline | 7 (6.0%)[a] | 14 (6.0%) |
| Week 8 | 5 (4.3%) | 7 (3.0%) |
| Week 12 | 1 (0.9%) | 5 (2.1%) |
| Week 16 | 2 (1.7%) | 1 (0.4%) |
| Week 20 | 0 (0.0%) | 1 (0.4%) |

BID=twice daily; CMV=cytomegalovirus; EAC=Endpoint Adjudication Committee; IAT=investigator-assigned anti-CMV treatment

[a] One subject in the IAT group had new onset of symptomatic CMV infection at both Week 12 and Week 16.

Source: Section 14, Auxiliary Table 14.4.1.2a

**Recurrence of CMV**

Recurrence of CMV viraemia was assessed during the first 8 weeks of the study, during follow up and at any time of the study.

Table 33 CMV Viraemia recurrence in study 303

| | Investigator Assigned Treatment (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| Number of Subjects who had CMV Viremia Clearance after study assigned treatment at any time on study [a] | 65 (55.6) | 184 (78.3) |
| Subject with CMV Viremia Recurrence [b] | | |
| During the First 8 Weeks [c] | 8 (12.3) | 33 (17.9) |
| During the Follow-up Weeks [d] | 14 (21.5) | 71 (38.6) |
| Any Time on Study | 22 (33.8) | 104 (56.5) |

CMV = Cytomegalovirus.
Subjects who met the criteria for recurrence during the first 8 weeks of the study, in the follow-up period, and at any time during the study, regardless of whether the study assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy was provided. All CMV viral load results after achieving the viremia clearance were included in the assessment regardless of the use of alternative anti-cmv or rescue treatment.
[a] Percentages are based on the number of subjects in the Randomized Set.
[b] Percentages are based on the number of subjects in the Randomized Set who had CMV viremia clearance at any time on study.
[c] During first 8 weeks regardless of whether the study assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy.
[d] From week 9 through end of study, including rescue visits if applicable.
Cross-reference: Listing 16.2.6.5.

**All-cause mortality**

No effect of maribavir was seen on all-cause mortality. A similar percentage of patients in each treatment group died during the study (maribavir: 27 [11.5%] patients; IAT: 13 [11.1%] patients). Median time to death was shorter in the maribavir compared to the IAT group.

**Maintenance of CMV Viraemia clearance and CMV infection symptom control achieved at the end of week 8 through Weeks 12 and 20**

Patients who achieved confirmed CMV viraemia clearance and CMV infection symptom control at Week 8, and maintained the response through the designated time point (ie, Week 12 or Week 20), were classified as responders for the respective time point. Results of the analysis are shown below.

| CMV Viremia Clearance and CMV Infection Symptom Control Response | Investigator Assigned Treatment (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| At Study Week 8 | | |
| Responders | 28 (23.9) | 131 (55.7) |
| Non-responders | 89 (76.1) | 104 (44.3) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 31.8 (21.81, 41.82) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 32.8 (22.80, 42.74) |
| p-value: Adjusted [b] | | <0.001 |
| p-value: Homogeneity across strata [c] | | 0.598 |
| Maintenance through Study Week 12 | | |
| Responders | 12 (10.3) | 53 (22.6) |
| Non-responders | 105 (89.7) | 182 (77.4) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 12.3 (4.63, 19.96) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 13.5 (5.84, 21.17) |
| p-value: Adjusted [b] | | <0.001 |
| p-value: Homogeneity across strata [c] | | 0.236 |

| | | |
|---|---|---|
| Maintenance through Study Week 20 | | |
| Responders | 11 (9.4) | 43 (18.3) |
| Non-responders | 106 (90.6) | 192 (81.7) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 8.9 (1.66, 16.14) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 9.8 (2.58, 17.06) |
| p-value: Adjusted [b] | | 0.008 |
| p-value: Homogeneity across strata [c] | | 0.435 |

CMV = Cytomegalovirus.
CMV infection symptom control data is adjudicated by the Endpoint Adjudication Committee.
Percentage are based on the number of subjects in the Randomized Set.
Subject is considered as a responder based on the maintenance of the effect of CMV viremia clearance, and CMV infection symptom control achieved at the end of Study Week 8 regardless of whether the study assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy, through weeks 12 and 20.
Randomized subjects with no efficacy data are treated as non-responders.
[a] Unadjusted difference in proportion (Maribavir - IAT) and the corresponding 95% CI is computed by the normal approximation method.
[b] Cochran-Mantel-Haenszel (CMH) weighted average approach is used for the adjusted difference in proportion (Maribavir - IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration if homogeneity is met. The minimum risk weight method is used if the homogeneity is not met. Only those with both stratification factors are included in the computation.
[c] Breslow-Day test is used for testing the homogeneity across strata. The stratum-specific difference in proportion is reported only if the p-value for homogeneity across strata is significant.
Cross-reference: Listing 16.2.6.3 and Listing 16.2.6.4.

## Confirmed CMV Viraemia Clearance after 8 Weeks of Study-assigned Treatment and Effect Over Time

Table 34 Analysis of confirmed CMV viraemia clearance response at study week 8, 12, 16 and 20 after receiving 8-week study treatment by treatment group (randomised set)

| CMV Viremia Clearance Response | Investigator Assigned Treatment (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| Number of subjects who had received 8-week study treatment | 37 | 183 |
| At Study Week 8 | | |
| Responders | 22 (18.8) | 129 (54.9) |
| Non-responders | 95 (81.2) | 106 (45.1) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 36.1 (26.57, 45.61) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 36.8 (27.26, 46.40) |
| p-value: Adjusted [b] | | <0.001 |
| p-value: Homogeneity across strata [c] | | 0.201 |
| Maintained Through Study Week 12 | | |
| Responders | 6 (5.1) | 53 (22.6) |
| Non-responders | 111 (94.9) | 182 (77.4) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 17.4 (10.75, 24.10) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 17.8 (10.89, 24.77) |
| p-value: Adjusted [b] | | <0.001 |
| p-value: Homogeneity across strata [c] | | 0.013 |
| Maintained Through Study Week 16 | | |
| Responders | 6 (5.1) | 44 (18.7) |
| Non-responders | 111 (94.9) | 191 (81.3) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 13.6 (7.20, 19.99) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 13.9 (7.21, 20.56) |
| p-value: Adjusted [b] | | <0.001 |
| p-value: Homogeneity across strata [c] | | 0.023 |
| Maintained Through Study Week 20 | | |
| Responders | 5 (4.3) | 43 (18.3) |
| Non-responders | 112 (95.7) | 192 (81.7) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 14.0 (7.87, 20.18) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 14.2 (7.70, 20.75) |
| p-value: Adjusted [b] | | <0.001 |
| p-value: Homogeneity across strata [c] | | 0.032 |

## Confirmed CMV Viraemia clearance and CMV infection symptom control after 8 weeks of study-assigned treatment and effect maintenance over time

Table 35 Analysis of confirmed CMV viraemia clearance and CMV infection symptom control response at study week 8 followed by maintenance through study week 12, 16, and 20 after receiving 8-week study treatment by treatment group (randomised set)

| CMV Viremia Clearance and CMV Infection Symptom Control Response | Investigator Assigned Treatment (N=117) n (%) | Maribavir 400 mg BID (N=235) n (%) |
|---|---|---|
| Number of subjects who had received 8-week study treatment | 37 | 183 |
| At Study Week 8 | | |
| Responders | 22 (18.8) | 129 (54.9) |
| Non-responders | 95 (81.2) | 106 (45.1) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 36.1 (26.57, 45.61) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 36.8 (27.26, 46.40) |
| p-value: Adjusted [b] | | <0.001 |
| p-value: Homogeneity across strata [c] | | 0.201 |
| Maintenance through Study Week 12 | | |
| Responders | 6 (5.1) | 53 (22.6) |
| Non-responders | 111 (94.9) | 182 (77.4) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 17.4 (10.75, 24.10) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 17.8 (10.89, 24.77) |
| p-value: Adjusted [b] | | <0.001 |
| p-value: Homogeneity across strata [c] | | 0.013 |
| Maintenance through Study Week 16 | | |
| Responders | 6 (5.1) | 44 (18.7) |
| Non-responders | 111 (94.9) | 191 (81.3) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 13.6 (7.20, 19.99) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 13.9 (7.21, 20.56) |
| p-value: Adjusted [b] | | <0.001 |
| p-value: Homogeneity across strata [c] | | 0.023 |
| Maintenance through Study Week 20 | | |
| Responders | 5 (4.3) | 43 (18.3) |
| Non-responders | 112 (95.7) | 192 (81.7) |
| Unadjusted Difference in Proportion of Responders (95% CI) [a] | | 14.0 (7.87, 20.18) |
| Adjusted Difference in Proportion of Responders (95% CI) [b] | | 14.2 (7.70, 20.75) |
| p-value: Adjusted [b] | | <0.001 |
| p-value: Homogeneity across strata [c] | | 0.032 |

**Efficacy outcomes maribavir rescue set**

Twenty-two patients entered the maribavir rescue arm after medical monitor review based on the protocol-defined criteria.

Confirmed viraemia clearance at week 8

Of the 22 patients who received maribavir as rescue therapy, 11 (50.0%) patients achieved confirmed CMV viraemia clearance at Week 8 of the maribavir rescue treatment phase and 11 (50.0%) patients were non-responders.

At week 12, eight of the 22 patients achieved confirmed viraemia clearance and CMV infection symptom control in the maribavir rescue arm. Response was maintained in six patients at week 16 and five patients at week 20.

**Exploratory endpoints**

CMV viral load over time

No difference in mean (SD) change from baseline in $\log_{10}$ plasma CMV DNA viral load was seen between the maribavir and IAT group at Week 8 (-1.30 (0.994) vs. -1.32 (1.152), respectively) and week 16 (-1.49 (0.912) vs. -1.39 (1.071), respectively).

Time to viraemia clearance

Overall, 184 (78.3%) patients in the maribavir group and 65 (55.6%) patients in the IAT group achieved confirmed CMV viraemia clearance at any time during the study. The observed median time to first CMV Viraemia clearance (i.e., time to first of two consecutive CMV DNA values <LLOQ) was 17.0 days (range: 5.0 to 114.0 days) in the maribavir group and 20.0 days (range: 6.0 to 111.0 days) in the IAT group. The median (95% CI) time to first confirmed CMV viraemia clearance based on the Kaplan-Meier estimates was shorter for maribavir-treated patients than for patients in the IAT group (maribavir: 22.0 [21.0, 23.0] days; IAT: 29.0 [22.0, 35.0] days, p=0.030).

Time from first CMV viraemia clearance to viraemia recurrence

Overall, 104/184 (56.5%) patients in the maribavir group and 22/65 (33.8%) patients in the IAT group had CMV Viraemia recurrence at any time during the study. The observed median time from first CMV viraemia clearance to CMV viraemia recurrence was 42.0 days (range: 14.0 to 123.0 days) in the maribavir group and 45.5 days (range: 16.0 to 89.0 days) in the IAT group.

**Ancillary analyses**

**Subgroup Analyses of the Primary Endpoint**

Subgroup analyses for the primary endpoint were conducted for the individual IAT, across transplant type (SOT and HSCT), baseline CMV DNA viral load, patients with EAC confirmed symptomatic CMV infection (i.e., CMV syndrome/disease), patients with genotypic resistance to other anti-CMV agents, and patients with antilymphocyte use.

No significant effect of maribavir treatment compared to IAT was seen in patients without baseline resistance to IAT (13%, CI: -6.24, 31.43, p=0.19), while a significant effect in patients with baseline resistance to IAT (44% CI: 31.33, 56.94, p <0.001) was seen. Response rates in the maribavir arm only, were also higher among patients in the maribavir arm with baseline resistance to IAT (63%, CI:54.20, 71.42) compared to patients without resistance (44%, CI: 33.83, 53.67).

In total 29 patients had EAC confirmed symptomatic disease was considerably small (N=29). A numerically trend for a better response in patients with EAC confirmed CMV syndrome/disease at baseline achieved CMV viraemia clearance week 8 in the maribavir group (10/21 (47.6%)) compared to the IAT group (1/8 (12.5%).

Table 36 Subgroup analyses of confirmed CMV viraemia clearance response at study week 8 by treatment group (randomised set)

| | Investigator Assigned Treatment | | Maribavir 400 mg BID | | Adjusted Difference in Proportion of Responders | |
|---|---|---|---|---|---|---|
| | n/N | % (95% CI) | n/N | % (95% CI) | % (95% CI) [a] | p-value [a] |
| Overall | 28/117 | 23.9 (16.20, 31.66) | 131/235 | 55.7 (49.39, 62.10) | 32.8 (22.80, 42.74) | <0.001 |
| Individual Investigator Assigned Treatment | | | | | | |
| Ganciclovir/Valganciclovir | 15/56 | 26.8 (15.19, 38.38) | 131/235 | 55.7 (49.39, 62.10) | 31.7 (18.63, 44.78) | <0.001 |
| Foscarnet | 9/47 | 19.1 (7.90, 30.40) | 131/235 | 55.7 (49.39, 62.10) | 36.4 (23.37, 49.40) | <0.001 |
| Cidofovir | 0/6 | 0 (N/A, N/A) | 131/235 | 55.7 (49.39, 62.10) | N/A | N/A |
| >1 Investigator Assigned Treatment | 4/7 | 57.1 (20.48, 93.80) | 131/235 | 55.7 (49.39, 62.10) | -3.2 (-40.31, 33.96) | 0.867 |
| Transplant Type | | | | | | |
| Solid Organ Transplant (SOT) | 18/69 | 26.1 (15.73, 36.45) | 79/142 | 55.6 (47.46, 63.81) | 30.5 (17.31, 43.61) | <0.001 |
| Hematopoietic Stem Cell Transplant (HSCT) | 10/48 | 20.8 (9.34, 32.32) | 52/93 | 55.9 (45.82, 66.00) | 36.1 (20.92, 51.37) | <0.001 |
| Kidney Transplant [b] | 14/36 | 38.9 (22.96, 54.81) | 47/78 | 60.3 (49.40, 71.12) | 21.0 (1.95, 40.00) | 0.031 |
| CMV DNA Viral Load | | | | | | |
| Low | 21/85 | 24.7 (15.54, 33.87) | 95/153 | 62.1 (54.40, 69.78) | 37.4 (25.41, 49.37) | <0.001 |
| Intermediate/High | 7/32 | 21.9 (7.55, 36.20) | 36/82 | 43.9 (33.16, 54.64) | 21.8 (3.93, 39.67) | 0.017 |
| Resistance Status | | | | | | |
| Yes | 14/69 | 20.3 (10.80, 29.78) | 76/121 | 62.8 (54.20, 71.42) | 44.1 (31.33, 56.94) | <0.001 |
| No | 11/34 | 32.4 (16.63, 48.08) | 42/96 | 43.8 (33.83, 53.67) | 12.6 (-6.24, 31.43) | 0.190 |
| Age Group | | | | | | |
| 18 to 44 Years | 8/32 | 25.0 (10.00, 40.00) | 28/55 | 50.9 (37.70, 64.12) | 26.4 (6.06, 46.74) | 0.011 |
| 45 to 64 Years | 19/69 | 27.5 (17.00, 38.08) | 71/126 | 56.3 (47.69, 65.01) | 29.9 (16.18, 43.64) | <0.001 |
| >=65 Years | 1/16 | 6.3 (0.00, 18.11) | 32/54 | 59.3 (46.15, 72.36) | 53.9 (36.81, 71.08) | <0.001 |
| Enrolling Region | | | | | | |
| North America | 19/71 | 26.8 (16.46, 37.06) | 72/134 | 53.7 (45.29, 62.17) | 26.9 (13.75, 40.11) | <0.001 |
| Europe | 8/39 | 20.5 (7.84, 33.19) | 56/97 | 57.7 (47.90, 67.56) | 42.0 (26.90, 57.05) | <0.001 |
| Asia | 1/7 | 14.3 (0.00, 40.21) | 3/4 | 75.0 (32.57, 100.00) | 56.1 (-25.30, 100.00) | 0.128 |
| Sex | | | | | | |
| Male | 15/65 | 23.1 (12.83, 33.32) | 87/148 | 58.8 (50.85, 66.71) | 35.7 (22.76, 48.58) | <0.001 |
| Female | 13/52 | 25.0 (13.23, 36.77) | 44/87 | 50.6 (40.07, 61.08) | 27.4 (11.35, 43.46) | <0.001 |
| Anti-lymphocyte Use | | | | | | |
| Yes | 12/49 | 24.5 (12.45, 36.53) | 53/100 | 53.0 (43.22, 62.78) | 29.9 (14.30, 45.46) | <0.001 |
| No | 16/68 | 23.5 (13.45, 33.61) | 78/135 | 57.8 (49.45, 66.11) | 35.0 (21.94, 48.01) | <0.001 |
| Baseline Symptomatic CMV Infection by EAC | | | | | | |
| Yes | 1/8 | 12.5 (0.00, 35.42) | 10/21 | 47.6 (26.26, 68.98) | 30.6 (-7.46, 68.57) | 0.112 |
| No | 27/109 | 24.8 (16.67, 32.87) | 121/214 | 56.5 (49.90, 63.18) | 32.5 (22.05, 43.01) | <0.001 |

Subgroup analyses for the key secondary endpoint were provided. The small number of responders for the key secondary endpoint in each treatment group preclude any conclusions based on subgroup analyses.

**Clinical virology**

Genotypic sequencing was performed for all study patient samples with CMV DNA viral load at or above the predefined cut-off level of 500 copies/mL (455 IU/mL) at protocol defined time points at baseline, during the treatment phase, during the study follow-up phase, and at the end of the study.

Central laboratory CMV DNA quantification in the SHP620-303 study was performed using the COBAS®AmpliPrep/ COBAS®TaqMan® CMV test, which is is an FDA-approved *in vitro* nucleic acid amplification test for the quantitative measurement of CMV DNA in human EDTA plasma and which is calibrated to the World Health Organization International Standard for Human CMV for Nucleic Acid Amplification Techniques. Samples ≤ 137 IU/ml were defined as undetectable CMV DNA.

The primary resistance set (PRS) is defined as all patients with at least one known resistance-associated amino acid substitution (RAS) to IAT in pUL97 and/or pUL54 identified at baseline. Patients without identified baseline IAT RASs are designated non-PRS.

The maribavir resistance set (MRS) is defined as all patients with at least one known RAS to maribavir in pUL97 and/or pUL27 at baseline. Patients without identified baseline maribavir RASs are designated non-MRS.

The disposition of patients in the modified randomised set in both treatment arms with and without genotyping data for IAT and maribavir is summarised in the table below.

Table 37 Summary of baseline genotyping testing and resistance to investigator-assigned anti-CMV treatment and maribavir (modified randomised set)

| | IAT-randomized (N=116) n (%) | MBV-randomized (N=234) n (%) | MBV-rescue (N=22) n (%) | All-MBV (N=256) n (%) |
|---|---|---|---|---|
| Subjects with BL GT for IAT RASs in *UL97* and/or *UL54* | 103 (88.8) | 217 (92.7) | 17 (77.3) | 234 (91.4) |
| Subjects without BL GT for IAT RASs in *UL97* and/or *UL54* | 13 (11.2) | 17 (7.3) | 5 (22.7) | 22 (8.6) |
| Subjects in PRS+non-PRS | 103 (88.8) | 217 (92.7) | 17 (77.3) | 234 (91.4) |
| Subjects in PRS | 69 (59.5) | 121 (51.7) | 12 (54.5) | 133 (52.0) |
| Subjects in non-PRS | 34 (29.3) | 96 (41.0) | 5 (22.7) | 101 (39.5) |
| Subjects with BL GT for MBV RASs in *UL97* and/or *UL27* | 100 (86.2) | 214 (91.5) | 17 (77.3) | 231 (90.2) |
| Subjects without BL GT for MBV RASs in *UL97* and/or *UL27* | 16 (13.8) | 20 (8.5) | 5 (22.7) | 25 (9.8) |
| Subjects in MRS+non-MRS | 100 (86.2) | 214 (91.5) | 17 (77.3) | 231 (90.2) |
| Subjects in MRS | 3 (2.6) | 1 (0.4) | 1 (4.5) | 2 (0.8) |
| Subjects in non-MRS | 97 (83.6) | 213 (91.0) | 16 (72.7) | 229 (89.5) |

BL GT=baseline genotype; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment; MRS=maribavir resistance set; MBV=maribavir; PRS=primary resistance set.
Note: Percentages are based on the number of subjects in the modified randomized set (i.e. subjects who received at least one dose of study drug).
In a small number of subjects genotypic analysis of the target genes was not successful due to possible polymorphism(s) within one of the primer binding sites, an insufficient viral load, or PCR inhibitors in the sample.
Source: Resistance Report data listings, Appendix 5, Table 1.1.1 and Appendix 5, Table 2.1.1

A summary of baseline genotyping results by anti-CMV drug and IAT type selected for the modified randomised set is shown below.

Table 38 Summary of baseline genotyping results by anti-CMV Drug and IAT type selected (modified randomised set)

| Resistant to: | IAT Randomized (N=116) | Maribavir Randomized (N=234) | IAT Type | | | | |
|---|---|---|---|---|---|---|---|
| | | | GCV/VGCV (N=56) | Foscarnet (N=47) | Cidofovir (N=6) | GCV/ Foscarnet (N=3) | VGCV/ Foscarnet (N=4) |
| GCV/VGCV | 69 (59.5) | 121 (51.7) | 32 (57.1) | 30 (63.8) | 4 (66.7) | 2 (66.7) | 1 (25.0) |
| Foscarnet | 7 (6.0) | 10 (4.3) | 5 (8.9) | 0 | 1 (16.7) | 1 (33.3) | 0 |
| Cidofovir | 14 (12.1) | 33 (14.1) | 11 (19.6) | 1 (2.1) | 1 (16.7) | 1 (33.3) | 0 |

CMV=cytomegalovirus; GCV=ganciclovir; IAT=investigator-assigned anti-CMV treatment; VGCV=valganciclovir
Source: Resistance Report, Appendix 5, Table 1.1.4

Most patients had CMV encoding IAT RAS at baseline. More patients in the IAT group had virus encoding for baseline IAT RAS in pUL97 (75% vs. 72%), IAT RAS to pUL54 (6% vs. 7%) and in both pUL97 and pUL54 (19% vs. 22%) compared to patients in the maribavir arm.

The most common single baseline IAT RASs identified in pUL97 in the IAT group were A594V (N=11), L595S (N=9), C603W (N=7), F342Y (N=3), M460I (N=2), M460V (N=1), A594S (N=2), H520Q (N=1), and L595F (N=1). Most of this RAS are known to confer a high-level of resistance to ganciclovir/valganciclovir. The F342Y RAS has been reported to cause increases in EC50 for both GCV (6.0-fold) and maribavir (4.5-fold).

The most common single baseline IAT RASs detected in pUL97 in the maribavir group were L595S (N=20), A594V (N=14), C603W (N=6), M460I (N=6), M460V (N=4), C592G (N=4), A594P (N=3), A594T (N=3), H520Q (N=4), and L595F (N=3). Most of this RAS are known to confer a high level of resistance to ganciclovir/valganciclovir.

Treatment response in patients with baseline resistance to IAT

A greater proportion of maribavir-treated patients in the PRS had confirmed viraemia clearance at Week 8 compared to IAT (63% vs 20%, respectively). No significant effect treatment difference was seen in the non-PRS set (32% vs. 44%).

Table 39 Patients achieving confirmed clearance of plasma CMV DNA at the end of study week 8 by analysis group and primary resistance set classification (modified randomised set)

| | IAT-randomized (N=116) m/n (%) | MBV-randomized (N=234) m/n (%) | MBV-rescue (N=22) m/n (%) | All-MBV (N=256) m/n (%) |
|---|---|---|---|---|
| PRS | 14/69 (20.3) | 76/121 (62.8) | 4/12 (33.3) | 80/133 (60.2) |
| Non-PRS | 11/34 (32.4) | 42/96 (43.8) | 3/5 (60.0) | 45/101 (44.6) |
| PRS+non-PRS | 25/103 (24.3) | 118/217 (54.4) | 7/17 (41.2) | 125/234 (53.4) |

CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment; MBV=maribavir; PRS=primary resistance set.
N=number of subjects in the modified randomized set within each analysis group.
n=number of subjects with baseline genotyping data for each category.
m=number of subjects with baseline genotyping data who achieved primary efficacy endpoint for each category (see Section 5.1).
Source: Resistance Report data listings, Appendix 5, Table 1.2.1

Most IAT RAS were located in the pUL97 region, while only a few did have pUL54. No difference in proportion of responders in the maribavir group were seen in the analysis by gene location.

Table 40 PRS patients achieving confirmed clearance of plasma CMV DNA at the end of study week 8 by analysis group and gene location of mutation(s)

| | IAT-randomized (N=116) | MBV-randomized (N=234) | MBV-rescue (N=22) | All-MBV (N=256) |
|---|---|---|---|---|
| Subjects in PRS | 69 | 121 | 12 | 133 |
| Location of IAT RASs | | | | |
| pUL97 or pUL54 | 14/69 (20.3) | 76/121 (62.8) | 4/12 (33.3) | 80/133 (60.2) |
| pUL97 only | 11/52 (21.2) | 53/87 (60.9) | 3/6 (50.0) | 56/93 (60.2) |
| pUL54 only | 2/4 (50.0) | 5/8 (62.5) | 0/1 (0) | 5/9 (55.6) |
| pUL97 and pUL54 | 1/13 (7.7) | 18/26 (69.2) | 1/5 (20.0) | 19/31 (61.3) |

CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment; MBV=maribavir; PRS=primary resistance set; RAS=resistance-associated amino acid substitution
Source: Resistance Report data listings, Appendix 5, Table 1.2.2

**Postbaseline Treatment-emergent Resistance to IAT**

Post-baseline treatment emergent RAS to IAT was more frequently observed in the maribavir group (13%) compared to the IAT group (5%). This effect was consistent for RAS in the pUL97 region (maribavir: 9% and IAT: 3%).

Table 41 Summary of treatment-emergent known resistance-associated amino acid substitutions to investigator-assigned anti-CMV treatments in PRS+non-PRS (modified randomised set)

| | IAT-randomized (N=116) n (%) | MBV-randomized (N=234) n (%) | MBV-rescue (N=22) n (%) | All-MBV (N=256) n (%) |
|---|---|---|---|---|
| Subjects in PRS+non-PRS | 103 | 217 | 17 | 234 |
| Subjects in PRS+non-PRS with post-BL GT | 38 (36.9) | 80 (36.9) | 7 (41.2) | 87 (37.2) |
| New IAT RASs in pUL97 or pUL54[a] | 5 (4.9) | 28 (12.9) | 2 (11.8) | 30 (12.8) |
| pUL97 only | 3 (2.9) | 19 (8.8) | 1 (5.9) | 20 (8.5) |
| pUL54 only | 1 (1.0) | 8 (3.7) | 1 (5.9) | 9 (3.8) |
| pUL97 and pUL54 | 1 (1.0) | 1 (0.5) | 0 | 1 (0.4) |

BL GT=baseline genotype; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment; MBV=maribavir; PRS=primary resistance set; RAS=resistance-associated amino acid substitution.
[a] Includes MBV RASs with cross resistance to IAT.
Source: Resistance Report data listings, Appendix 5, Table 1.3.1

In the maribavir group the following treatment-emergent single treatment emergent IAT RAS were identified; C480F (N=12) and F342Y (N=3). Both are known to confer high-level resistance to maribavir but also confer resistance to ganciclovir/valganciclovir. Single IAT RAS associated with significant increases in $EC_{50}$ to GCV, were also detected in pUL97 A595V, C603F, C595S (each one patient).

IAT RAS in pUL54 were detected more frequently in the maribavir group (N=8) compared to the IAT group (N=1). All detected treatment-emergent RAS in pUL54 confer cross resistance to either foscarnet (S290R, V715M), foscarnet and ganciclovir (N408D, T503I, K513N and A789G) or to all of them (L773V).

**Baseline resistance to maribavir**

Baseline resistance to maribavir was rare and only detected in four patients (IAT: N=3, MBV: N=1). With the exception of one pUL27 RAS (L139R) in the maribavir group, all other mutations were detected in the pUL97 region. pUL97 F342F maribavir RAS was the only RAS detected in the IAT group, which was also detected at baseline in one patient in the maribavir rescue arm.

**Treatment response among patients with baseline resistance to maribavir**

None of the patients in the MRS did respond to treatment. The three patients in the IAT arm with baseline RAS pUL97 F342Y RAS known to confer high-level of resistance to maribavir, did not respond to IAT treatment. No response was seen in the one patient in maribavir group who had CMV with baseline pUL27 L193F maribavir RAS. The clinical relevance of pUL27 L193F remains unclear.

**Postbaseline treatment-emergent resistance to maribavir**

Post-baseline treatment emergent RAS to maribavir were only observed in the maribavir group (21%). Treatment emergent mutations were detected in 60/214 (29%) of the patients treated with maribavir with available genotypic data. In 45/214 patients (21%) RAS to maribavir developed during the first 8 weeks of treatment, while in 17/214 (8%) patients RAS to maribavir developed after treatment cessation. All treatment-emergent RAS to maribavir were identified in pUL97.

The most frequently detected post-bassline RAS to maribavir on treatment were T409M (N=13), C480F (N=9), H411Y (N=5), H411N and F342Y (each N=1). All of these RAS are also known to confer resistance to ganciclovir. Several multiple RAS to maribvir were detected, the most common were T490M+C480F (N=5) and T409M+H411Y (N=7). The impact on maribavir and ganciclovir/valganciclovir $EC_{50}$s of these multiple RAS is missing. Upon request, it was confirmed that there is no plan to further investigate phenotypic resistance, as it is considered that each multiple RAS genotype. Accordingly, this information was included in section 4.4 and 5.1 of the SmPC to indicate that maribavir is no longer susceptible to CMV with this multiple RAS and treatment should be discontinued.

Off treatment, the most frequently detected maribavir RAS was H411Y (N=10), followed by C480F (N=4) and T409M (N=3).

**Postbaseline treatment-emergent resistance to maribavir rescue arm**

Treatment emergent maribavir RAS were detected in CMV of four out of seven patients (24%) in the maribavir rescue arm. All treatment-emergent mutations were detected in pUL97 (H411N (N=1) and T409M (N=2). One patient had virus encoding for a triple-RAS (T409M+H411L+H411Y).

**Treatment response among patients developing maribavir RASs**

Of the 42 patients in the maribavir-randomised analysis group who developed post-baseline maribavir RASs, 41/42 patients (97.6%) did not achieve the primary endpoint, while 1/42 patients (2.4%) did. Of these 42 patients, 18/42 patients (43%) were virologic non-responders (did not achieve viraemia clearance at any time point during the study) and 24/42 patients (57.1%) were virologic responders. Of these 24 virologic responders, 21/24 patients (87.5%) had recurrence on or off treatment.

- **Summary of main efficacy results**

<table>
<tr><td colspan="4"><u>Title:</u> A Phase 3, Multicenter, Randomized, Open label, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Treatment Compared to Investigator-assigned Treatment in Transplant Recipients with Cytomegalovirus (CMV) Infections that are Refractory or Resistant to Treatment with Ganciclovir, Valganciclovir, Foscarnet, or Cidofovir.</td></tr>
<tr><td>Study identifier</td><td colspan="3">SHP-620-303, 2015-004725-13</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">This was a Phase 3, multicentre, randomised, open-label, active-controlled study to assess the efficacy and safety of maribavir compared to IAT in haematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients with CMV infections that are refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, including CMV infections with confirmed resistance to 1 or more anti-CMV agents.<br><br>The study had 3 phases: (1) a screening phase of up to 2 weeks; (2) an 8-week study treatment phase; and (3) a 12-week follow-up phase. All patients were required to visit the site up to 19 times for up to a 22-week period. Patients who entered the maribavir rescue arm could participate in the study for up to 29 weeks.</td></tr>
<tr><td colspan="2">Duration of main phase:<br><br>Duration of Run-in phase:<br><br>Duration of Extension phase:</td><td>20 weeks: 8 weeks of treatment, 12 weeks of follow-up<br><br>not applicable<br><br>not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority</td></tr>
<tr><td rowspan="2">Treatments groups</td><td colspan="2">Maribavir (MBV), 400 mg BID</td><td>Maribavir, 8 weeks, N=235</td></tr>
<tr><td colspan="2">Investigator Assigned Treatment (IAT)</td><td>IAT, 8 weeks, N=117<br><br>One or a prespecified combination of 2 of the available anti-CMV agents from the following were utilised: IV ganciclovir, oral valganciclovir, IV foscarnet, or IV cidofovir. Dose and dose regimen of the IAT were at the discretion of the investigator following best clinical practice for each patient.</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td>CMV Viraemia clearance at study week 8</td><td>Confirmed CMV Viraemia clearance at the end of Week 8, defined as plasma CMV DNA concentration <LLOQ (i.e., <137 IU/mL) per central laboratory result in 2 consecutive post-baseline samples, separated by at least 5 days, regardless of whether the study assigned treatment was discontinued before the end of 8 week treatment phase.</td></tr>
</table>

| | | |
|---|---|---|
| Subgroup analysis of primary efficacy endpoint – SOT recipients | Subgroup analysis - SOT recipients | Subgroup analyses of the primary endpoint was performed for SOT recipients to support the proposed indication claim. |
| Subgroup analysis of primary efficacy endpoint – HSCT recipients | Subgroup analysis – HSCT recipients | Subgroup analyses of the primary endpoint was performed for HSCT recipients to support the proposed indication claim. |
| Subgroup analysis of primary efficacy endpoint – CMV DNA viral load (combined intermediate and high, ⩾ 9100 IU/ml) | Subgroup analysis – CMV DNA viral load (high, intermediate) | Subgroup analyses of the primary endpoint was performed for combined intermediate and high baseline CMV DNA viral load (≥9100 IU/mL). |
| Subgroup analysis of primary efficacy endpoint – CMV DNA viral load (low, <9100 IU/mL) | Subgroup analysis – CMV DNA viral load (low) | Subgroup analyses of the primary endpoint was performed for low baseline CMV DNA viral load (<9100 IU/mL). |
| Subgroup analysis of primary efficacy endpoint – Baseline resistance status (yes) | Subgroup analysis – Baseline resistance status (yes) | Subgroup analyses of the primary endpoint was performed for patients with CMV infection with baseline CMV RAS known to confer resistance to IAT and MBV to support the proposed indication. |
| Subgroup analysis of primary efficacy endpoint – Baseline resistance status (No) | Subgroup analysis – Baseline resistance status (No) | Subgroup analyses of the primary endpoint was performed for patients with CMV infection without baseline CMV RAS known to confer resistance to IAT and MBV to support the proposed indication. |
| Key secondary endpoint | CMV Viraemia clearance and symptom control at the end of study week 8 with maintenance of effect through | Achievement of CMV Viraemia clearance and symptom control at the end of Study Week 8, followed by maintenance of this treatment effect for an additional 8 weeks off treatment (i.e., Follow-up week 16). |

| | | | |
|---|---|---|---|
| | Secondary endpoint | CMV Viraemia clearance after 8 weeks of treatment | Achievement of confirmed CMV Viraemia clearance after 8 weeks of receiving study-assigned treatment. |

| | |
|---|---|
| Database lock | Currently unknown |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** |
|---|---|
| Analysis population and time point description | Intent to treat (ITT)<br>Efficacy analyses during the initial treatment and follow-up phases were conducted using the randomised set (ITT) as primary set.<br>Primary analysis was conducted at Week 8.<br><br>Patients with confirmed CMV Viraemia clearance at the end of Week 8 were considered as responders regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | IAT | MBV |
| | Number of patient | 117 | 235 |
| | Primary endpoint -CMV Viraemia clearance at study week 8 regardless if study-assigned treatment was discontinued before the end of 8-weeks | Number of responders =28 (23.9%) | Number of responders =131 (55.7%) |
| | Subgroup analysis of primary endpoint – CMV Viraemia clearance at study week 8 in patients receiving 8 weeks of study assigned | Number of responders =22 (60%) | Number of responders =129 (71%) |
| | Subgroup analysis - SOT recipients | Number of responders =18/69 (26.1%) | Number of responders =79/142 (55.6%) |
| | Subgroup analysis - HSCT recipients | Number of responders =10/48 (20.8%) | Number of responders =52/93 (55.9%) |

| | | | |
|---|---|---|---|
| | Subgroup analysis - CMV DNA viral load (high, intermedia te) | Number of responders =7/32 (21.9%) | Number of responders =36/82 (43.9%) |
| | Subgroup analysis - CMV DNA viral load (low) | Number of responders =21/85 (24.7%) | Number of responders =95/153 (62.1%) |
| | Subgroup analysis – Resistance Status (yes) | Number of responders =14/69 (20.3%) | Number of responders =76/121 (62.8%) |
| | Subgroup analysis – Resistance Status (No) | Number of responders =11/34 (32.4%) | Number of responders =42/96 (43.8%) |
| Effect estimate per comparison | Primary endpoint-CMV Viraemia clearance at study week 8 | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 32.8% |
| | | 95% Confidence interval | 22.80, 42.74 |
| | | P-value* | <0.001 |
| | Primary endpoint-Subgroup Analysis - SOT recipients | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 30.5% |
| | | 95% Confidence interval | 17.31, 43.61 |
| | | P-value* | <0.001 |
| | Primary endpoint-Subgroup Analysis – HSCT recipients | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 36.1% |
| | | 95% Confidence interval | 20.92, 51.37 |
| | | P-value* | <0.001 |
| | Subgroup Analysis– CMV DNA viral load (low) | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 37.4% |

| | | | |
|---|---|---|---|
| | | 95% Confidence interval | 25.41, 49.37 |
| | | P-value* | <0.001 |
| | Primary endpoint-Subgroup Analysis– CMV DNA viral load (high, intermediate) | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 21.8% |
| | | 95% Confidence interval | 3.93, 39.67 |
| | | P-value* | 0.017 |
| | Primary endpoint-Subgroup Analysis– Baseline resistance status (yes) | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 44.1% |
| | | 95% Confidence interval | 31.33, 56.94 |
| | | P-value* | <0.001 |
| | Primary endpoint-Subgroup Analysis– Baseline resistance status (No) | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 12.6% |
| | | 95% Confidence interval | -6.24, 31.43 |
| | | P-value* | 0.190 |

<table>
<tr><td>Notes</td><td>Reasons for drop-out:<ul><li>The main reasons for discontinuation of the treatment in IAT arm were: adverse events (30.8%) and lack of efficacy (13.7%)</li><li>The main reasons for discontinuation of the treatment in the maribavir arm were adverse events (6.4%) and lack of efficacy (8.9%)</li><li>The completion rate was twice as high in the maribavir group (77.9%) compared to the IAT group (31.6%)</li><li>19% (22 patients) qualified for inclusion to the maribavir rescue arm.</li></ul>Critical findings:<ul><li>The primary endpoint was changed late during the open label study and could have been done in knowledge of data. In the sensitivity analysis of the initial primary endpoint no statistically significant effect was observed.</li><li>Last SAP amendment was finalised after last subject completed</li><li>Differential drop-out rates in the IAT group compared to the maribavir group.</li><li>Response rate in IAT arm lower than observed in clinical practice. The response rate in the IAT arm could have been influenced by the high rate of patients being resistant to their assigned IAT.</li><li>No statistically significant effect of maribavir in patients without resistance was seen.</li><li>A lack of consistency with the overall treatment effect in study 303 was seen between the subgroups of maribavir treated patients who are refractory and those who are resistant to IAT, which is contradictory to the study results of study 202.</li><li>Baseline imbalances between the treatment group concerning the proportion of patient with and without resistance and baseline viral load category</li><li>Definition of refractory CMV used for study enrolment does not comply with definitions of treatment guidelines.</li></ul></td></tr>
<tr><td>Analysis description</td><td>Secondary analysis</td></tr>
<tr><td>Analysis population and time point description</td><td>Intent to treat (ITT)<br>Efficacy analyses during the initial treatment and follow-up phases were conducted using the randomised set (ITT) as primary set.<br>Primary analysis was conducted at Week 8.<br>Patients with confirmed CMV Viraemia clearance at the end of Week 8 were considered as responders regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy.</td></tr>
<tr><td>Descriptive statistics and estimate variability</td><td><table>
<tr><td>Treatment group</td><td>IAT</td><td>MBV</td></tr>
<tr><td>Number of patient</td><td>117</td><td>235</td></tr>
<tr><td>Key secondary endpoint - CMV Viraemia clearance and symptom control at the end of study week 8 with maintenance of effect through study week 16 (responder regardless if treatment discontinuation before week 8)</td><td>Number of responders =12 (10.3%)</td><td>Number of responders =44 (18.7%)</td></tr>
</table></td></tr>
</table>

| | | | |
|---|---|---|---|
| | Key secondary endpoint - CMV Viraemia clearance and symptom control at the end of study week 8 with maintenance of effect through study week 16 in patients who received 8 weeks of study assigned treatment) | Number of responders =6/37 (16.2%) | Number of responders =44/183 (24%) |
| | Key secondary endpoint - Subgroup Analysis – HSCT recipients | Number of responders = 4/48 (8.3%) | Number of responders =25/93 (26.9%) |
| | Key secondary endpoint - Subgroup Analysis – SOT recipients | Number of responders = 8/69 (11.6%) | Number of responders =19/142 (13.4%) |
| | Key secondary endpoint - Subgroup Analysis-CMV DNA viral load (low) | Number of responders = 10/85 (11.8%)<br>95% CI: 4.92, 18.61 | Number of responders =38/153 (24.8%)<br>95% CI: 17.99, 31.68) |
| | Key secondary endpoint - Subgroup Analysis-CMV DNA viral load (high, intermediate) | Number of responders = 2/32 (6.3%)<br>95% CI: 0.00, 14.64 | Number of responders = 6/82 (7.3%)<br>95% CI: 1.68, 12.95 |
| | Key secondary endpoint - Subgroup Analysis-Resistance status (yes) | Number of responders = 6/69 (8.7%)<br>95% CI: 2.05, 15.34 | Number of responders = 18/121 (14.8%)<br>95% CI: (8.54, 21.22) |
| | Key secondary endpoint - Subgroup Analysis-Resistance status (No) | Number of responders = 4/34 (11.8%)<br>95% CI: 0.93, 22.59 | Number of responders = 20/96 (20.8%)<br>95% CI: (12.71, 28.96) |
| | Secondary endpoint – CMV Recurrence | Number of responders =65/117 (57%) | Number of responders =184/235 (57%) |

| | | | |
|---|---|---|---|
| | Secondary endpoint – All-cause mortality | Number of responders =13/117 (11%) | Number of responders =27/235 (12%) |
| Effect estimate per comparison | Key secondary endpoint- CMV Viraemia clearance and symptom control at the end of study week 8 with maintenance of effect through study week 16 (responder regardless if treatment discontinuation before week 8) | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 9.5% |
| | | 95% Confidence Interval | 2.02, 16.88 |
| | | P-value* | 0.013 |
| | Key secondary endpoint subgroup analysis- CMV Viraemia clearance and symptom control at the end of study week 8 with maintenance of effect through study week 16 in patients who received 8 weeks of | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 6.2 |
| | | 95% Confidence interval | -7.54, 19.84 |
| | | P-value* | <0.379 |
| | Key-Secondary endpoint Subgroup Analysis – HSCT recipients | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 19.8% |
| | | 95% Confidence interval | 8.10, 31.42 |
| | | P-value* | <0.001 |
| | Key-Secondary endpoint Subgroup Analysis – SOT recipients | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 2.4% |
| | | 95% Confidence interval | -7.05, 11.03 |
| | | P-value* | 0.62 |

| | | | |
|---|---|---|---|
| | Key-Secondary endpoint Subgroup Analysis – CMV DNA viral load (low) | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 13% |
| | | 95% Confidence interval | 3.31, 22.75 |
| | | P-value* | 0.009 |
| | Key-Secondary endpoint Subgroup Analysis – CMV DNA viral load (high, intermediate) | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 1.0% |
| | | 95% Confidence interval | -9.10, 11.00 |
| | | P-value* | 0.853 |
| | Key-Secondary endpoint Subgroup Analysis – Resistance status (yes) | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 7.3% |
| | | 95% Confidence interval | -2.08, 16.61 |
| | | P-value* | 0.128 |
| | Key-Secondary endpoint Subgroup Analysis – Resistance status (no) | Comparison groups | MBV 400mg BID; IAT |
| | | Adjusted difference in proportion of responders | 10.2% |
| | | 95% Confidence interval | -3.38, 23.87 |
| | | P-value* | 0.141 |

*For p-values presented for primary, key secondary, and secondary endpoints: between-group difference was adjusted for baseline CMV viral load (low, intermediate/high), and transplant type (SOT, HCT) and compared with Cochran–Mantel–Haenszel (CMH) test. For p-values presented for subgroup analysis: Between-group difference was adjusted for applicable baseline CMV viral load (low, intermediate/high), transplant type (SOT, HCT) and compared with CMH test. Patients with confirmed CMV Viraemia clearance at the end of Week 8 were considered as responders regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy (except for those stated).

### *2.6.5.3. Clinical studies in special populations*

Overall 70 patients >65 years of age were treated with maribavir in the Phase 3 study SHP-620-303. Since no further differentiation was presented, the applicant was requested to provide this data. Renal and hepatic impairment studies were conducted (please refer to section "pharmacokinetics").

### *2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)*

Due to differences in study populations, treatment regimens, endpoints, and other study design features, results of the three studies are not directly comparable. Therefore, baseline disease characteristics, and efficacy endpoints for the Phase 3 pivotal study and the Phase 2 supportive studies were only as provided side-by-side comparison.

Table 42 Demographic characteristics across studies supporting efficacy

| Characteristic | Study 303 | | Study 202 | Study 203 | |
|---|---|---|---|---|---|
| | IAT (N=117) | Maribavir 400 mg BID (N=235) | Maribavir 400 BID (N=40) | Maribavir 400 BID (N=40) | Valganciclovir 900 mg BID (N=40) |
| **Age (years)** | | | | | |
| n | 117 | 235 | 40 | 40 | 40 |
| Mean (SD) | 51.5 (12.80) | 53.8 (13.39) | 52.1 (14.25) | 53.0 (14.18) | 54.5 (12.36) |
| Median | 54.0 | 57.0 | 54.5 | 56.5 | 58.5 |
| Min, Max | 19, 77 | 19, 79 | 18, 74 | 29, 76 | 28, 76 |
| **Sex, n (%)** | | | | | |
| Male | 65 (55.6) | 148 (63.0) | 21 (52.5) | 22 (55.0) | 27 (67.5) |
| Female | 52 (44.4) | 87 (37.0) | 19 (47.5) | 18 (45.0) | 13 (32.5) |
| **Race, n (%)** | | | | | |
| White | 87 (74.4) | 179 (76.2) | 32 (80.0) | 37 (92.5) | 32 (80.0) |
| Black or African American | 18 (15.4) | 29 (12.3) | 6 (15.0) | 1 (2.5) | 0 |
| Asian | 7 (6.0) | 9 (3.8) | 2 (5.0) | 1 (2.5) | 4 (10.0) |
| Other | 5 (4.3) | 16 (6.8) [a] | 0 | 0 | 1 (2.5) |

BID=twice daily; IAT=investigator-assigned anti-CMV therapy; max=maximum; min=minimum; N=number of subjects; SD=standard deviation

[a] Race was missing for 2 subjects.

Source: Study 303 CSR, Table 14.1.4.1.1; Study 202 CSR, Table 11.1.4.1.1; Study 203 CSR, Table 11.1.4.1.1

Table 43 Selected baseline CMV disease characteristics across studies supporting efficacy

| Characteristic | Study 303 | | Study 202 | Study 203 | |
|---|---|---|---|---|---|
| | IAT (N=117) | Maribavir 400 mg BID (N=235) | Maribavir 400 BID (N=40) | Maribavir 400 BID (N=40) | Valganciclovir 900 mg BID (N=40) |
| **Transplant type, n (%)** | | | | | |
| Stem Cell[a] | 48 (41.0) | 93 (39.6) | 16 (40.0) | 20 (50.0) | 21 (52.5) |
| Myeloablative | 16 (33.3) | 47 (51.1) | 8 (50.0) | 5 (25.0) | 6 (28.6) |
| Nonmyeloablative | 12 (25.0) | 17 (18.5) | 4 (25.0) | 10 (50.0) | 11 (52.4) |
| Reduced intensity[b] | 17 (35.4) | 28 (30.4) | 6 (37.5 | 5 (23.8) | 4 (19.0) |
| Solid Organ | 69 (59.0) | 142 (60.4) | 24 (60.0) | 20 (50.0) | 19 (47.5) |
| Kidney | 32 (46.4) | 74 (52.1) | 9 (37.5) | 14 (70.0) | 10 (52.6) |
| Lung | 22 (31.9) | 40 (28.2) | 6 (25.0) | 0 | 2 (10.5) |
| Pancreas | 0 | 2 (1.4) | 5 (20.8) | 0 | 0 |
| Heart | 9 (13.0) | 14 (9.9) | 2 (8.3) | 0 | 1 (5.3) |
| Liver | 1 (1.4) | 6 (4.2) | 5 (20.8) | 6 (30.0) | 7 (36.8) |
| Intestine | 0 | 1 (0.7) | 3 (12.5) | 0 | 0 |
| Multiple | 5 (7.2) | 5 (3.5) | 2 (8.3) | 0 | 0 |
| Other | 0 | 0 | 0 | 0 | 0 |
| CMV genetic mutations associated with resistance to prior treatment, n (%)[c] | | | | | |
| Yes (resistant) | 69 (59.5)[d] | 121 (51.7)[d] | 22 (55.0)[d] | NA | NA |
| No (not resistant) mutation | 34 (29.3) | 96 (41.0) | 18 (45.0) | NA | NA |

BID=twice daily; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment; N=number of subjects; NA=not applicable

[a] In Study 303, hematopoietic stem cell transplant was performed.

[b] Reduced intensity conditioning regimen.

[c] In Study 303 at baseline, 17 subjects in the maribavir group and 13 subjects in the IAT group could not be genotyped (central laboratory).

[d] Central laboratory confirmed in Study 303; Investigator-reported in Study 202.

Source: Study 203 CSR, Table 11.1.4.2.1.1, Study 303 CSR, Table 14.1.4.2.1, Study 303 Resistance Report, Appendix 5, Table 1.1.1 and Table 2.1.1

Table 44 Confirmed CMV viraemia clearance response by subgroup across studies 303, 202, and 203

| | Study 303 | | Study 202 | | | Study 203 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Maribavir 400 mg BID N=235 n/m (%) | IAT N=117 n/m (%) | Maribavir 400 mg BID N=40 n/m (%) | Maribavir 800 mg BID N=40 n/m (%) | Maribavir 1200 mg BID N=40 n/m (%) | Maribavir 400 mg BID N=40 n/m (%) | Maribavir 800 mg BID N=40 n/m (%) | Maribavir 1200 mg BID N=39 n/m (%) | Valganciclovir 900 mg BID N=40 n/m (%) |
| **CMV DNA Viral Load** | | | | | | | | | |
| Low | | | | | | | | | |
| <10,000 copies/mL | NA | NA | 19/23 (82.6) | 18/21 (85.7) | 18/23 (78.3) | 24/26 (92.3) | 21/24 (87.5) | 23/28 (82.1) | 20/27 (74.1) |
| <9100 IU/mL | 95/153 (62.1) | 21/85 (24.7) | NA | NA | NA | NA | NA | NA | NA |
| Intermediate/ high | | | | | | | | | |
| ≥10,000 copies/mL | NA | NA | 8/16 (50.0) | 7/19 (36.8) | 8/16 (50.0) | 7/14 (50.0) | 12/16 (75.0) | 5/11 (45.5) | 6/13 (46.2) |
| ≥9100 IU/mL | 36/82 (43.9) | 7/32 (21.9) | NA | NA | NA | NA | NA | NA | NA |
| **Transplant Type** | | | | | | | | | |
| HSCT | 52/93 (55.9) | 10/48 (20.8) | 11/16 (68.8) | 11/16 (68.8) | 11/15 (73.3) | 16/20 (80.0) | 16/21 (76.2) | 14/20 (70.0) | 10/21 (47.6) |
| SOT | 79/142 (55.6) | 18/69 (26.1) | 17/24 (70.8) | 14/24 (58.3) | 16/25 (64.0) | 15/20 (75.0) | 17/19 (89.5) | 14/19 (73.7) | 16/19 (84.2) |
| **Prior Antilymphocyte use[a]** | | | | | | | | | |
| Yes | 53/100 (53.0%) | 12/49 (24.5%) | 9/15 (60.0) | 10/22 (45.5) | 11/16 (68.8) | 16/24 (66.7) | 21/28 (75.0) | 8/16 (50.0) | 14/26 (53.9) |
| No | 78/135 (57.8%) | 16/68 (23.5%) | 19/25 (76.0) | 15/18 (83.3) | 16/24 (66.7) | 15/16 (93.8) | 12/12 (100.0) | 20/23 (87.0) | 12/14 (85.7) |

ALA=anti-lymphocyte antibody; BID=twice daily; CMV=cytomegalovirus; HSCT=hematopoietic stem cell transplant; IAT=investigator-assigned anti-CMV treatment; m=number of subjects in the subgroup; N=number of subjects; NA=not applicable; SOT=solid organ transplant

[a] Use of any antilymphocyte preparations at any time from the most recent transplant until the initiation of study drug.

Note: In Study 303, CMV viremia clearance was assessed at a fixed time point after commencement of therapy (ie, after the 8-week treatment phase). In Study 202 and Study 203, viremia clearance was defined as confirmed undetectable plasma CMV DNA (central laboratory) within 6 weeks, defined as 2 consecutive post-baseline, on-treatment undetectable results (<200 copies/mL) separated by at least 5 days.

Source: Study 303 CSR, Table 14.2.1.10; Study 203 CSR, Table 11.2.8; Study 202 CSR, Table 11.2.7

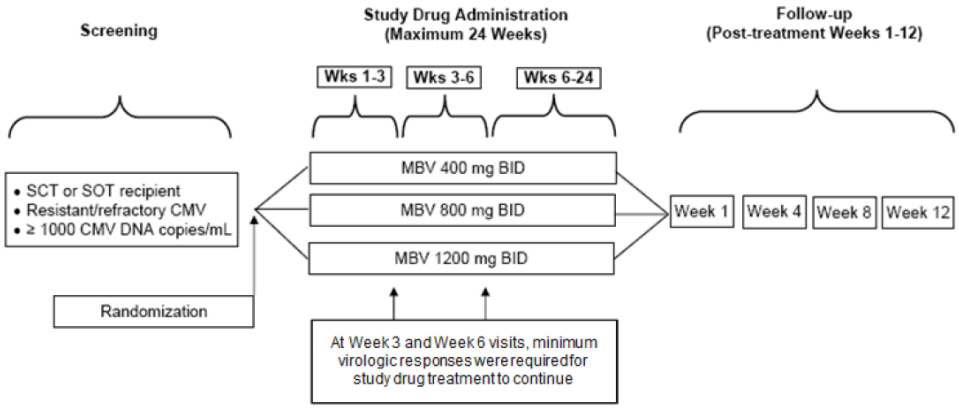
### *2.6.5.5. Supportive studies*

**SHP-620-202**

This was a Phase 2, multi-centre, randomised, dose-ranging, parallel-group study of maribavir for the treatment of CMV infections that were resistant or refractory to treatment with ganciclovir/valganciclovir or foscarnet in SCT or SOT recipients. The study was conducted at 27 sites in the US.

Approximately 120 patients were planned to be randomised in a 1:1:1 allocation ratio to receive oral maribavir at one of 3 dose strengths (400 mg BID, 800 mg BID, or 1200 mg BID) for up to 24 weeks. Randomisation of eligible patients was stratified by transplant type (SCT or SOT). All patients received maribavir, but patients, investigators, and study staff were blinded to dose strength. During the study, patients were followed as either inpatients or outpatients, depending on their condition. An overview of the study design is provided in Figure 6.

All patients must have achieved at least a minimum virologic response at Weeks 3 and 6 for study drug treatment to continue beyond each of these time points. For patients who continued dosing after the Week 6 visit, dosing could continue at the discretion of the investigator through a maximum of 24 weeks in an attempt to decrease CMV DNA to undetectable, and/or to maintain undetectable CMV DNA in an effort to prevent recurrence of CMV infection. These patients underwent study-specific evaluations every 2 weeks through Week 12, and again at Weeks 16, 20, and 24.




BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; MBV=maribavir; SCT=stem cell transplant; SOT=solid organ transplant; Wks=Weeks

Figure 6 Study design of study SHP-620-202

An independent, unblinded data Monitoring Committee (DMC) reviewed available safety and safety-related efficacy data at pre-defined time points during the study.

***Study Participants***

Study participants were male and female stem cell or solid organ transplantation recipients ≥ 12 years of age with documented CMV infection in blood or plasma, with a screening value of ≥1000 DNA copies/mL as determined by quantitative polymerase chain reaction (PCR) or comparable quantitative CMV assay type and had a current CMV infection that was resistant or refractory to treatment.

Resistant CMV was defined as documentation of one or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir and/or foscarnet AND documented failure to achieve >1 log decrease in CMV DNA level in blood/plasma after an interval of 2 or more weeks of treatment with IV ganciclovir, oral valganciclovir, or IV foscarnet (or any combination thereof).

Refractory CMV was defined as documented failure to achieve >1 log decrease in CMV DNA level in blood/plasma after an interval of 2 or more weeks of treatment with IV ganciclovir, oral valganciclovir, or IV foscarnet (or any combination thereof). The definition of "refractory CMV-infection" used in study 202, differs relevantly from the currently accepted guideline definition for the intended target population.

Patients with current CMV infection that was considered resistant or refractory due to inadequate adherence to prior oral anti-CMV treatment and with severe hepatic impairment were excluded from the study. Patients who received drugs with known anti-CMV activity must have been discontinued use at least 14 days before the first dose of study drug.

***Treatments***

Patients received oral maribavir at one of 3 dose strengths (400 mg BID, 800 mg BID, or 1200 mg BID) for a maximum duration of 24 weeks. No reference product was used, but identical placebo tablets were used to blind the dose strengths.

The formulation used in study 202 (formulation III) is not identical to the formulation used in the pivotal phase 3 study 303 (formulation IV).The applied posology (400 mg BID) with the to-be-marketed formulation was only studied in the Phase 3 study and has undergone changes in manufacturing since then. The dose was selected based on *in vitro* antiviral efficacy data, clinical PK data and modelling of the E-R relationships. However, the Pop PK model is currently not considered adequate to support the applied dose.

***Objectives***

The primary objective was to assess the safety and tolerability of different doses of maribavir administered orally for up to 24 weeks for treatment of CMV infections that are resistant or refractory to treatment with ganciclovir/valganciclovir or foscarnet in recipients of stem cell or solid organ transplants. Secondary objectives were to assess the anti-viral activity of different doses of maribavir in this subject population, to evaluate the pharmacokinetics and pharmacodynamics of maribavir in this subject population and to identify a dosing regimen for treatment of CMV infection in future studies.

***Outcomes/endpoints***

The primary endpoint was the proportion of patients with confirmed undetectable plasma CMV DNA (central laboratory) within 6 weeks, defined as 2 consecutive post-baseline, on-treatment undetectable results (<200 copies/mL) separated by at least 5 days.

Secondary endpoints were the proportion of patients with undetectable plasma CMV DNA (central laboratory) at specified visits, the proportion of patients with undetectable blood/plasma CMV at specified visits, the proportion of patients with CMV recurrence at any time during the study and the use of any protocol-specified non-study systemic anti-CMV therapies within 6 weeks and at any time during the study. Time to event endpoints were time to first confirmed undetectable plasma CMV DNA result (central laboratory) within 6 weeks and at any time during the study and time to CMV recurrence during the study.

***Randomisation and blinding (masking)***

Eligible patients were randomised in a 1:1:1 allocation ratio to receive oral maribavir 400 mg BID, 800 mg BID, or 1200 mg BID after stratification by transplant type (SCT or SOT). Prior to dosing, study personnel contacted the interactive voice and web response system (IXRS) to obtain a study drug kit number. The IXRS randomised patients, using a central block randomisation process, across the entire study based on the stratification variable indicated above, and managed resupply of study drug kits to sites as necessary.

All patients received maribavir, but patients, investigators, and study staff were blinded to dose. The treatment assignments of all maribavir patients remained blinded at the site level throughout the study.

***Statistical methods***

All primary and secondary efficacy analyses were performed using the ITT-S and PP Populations. Summary statistics were provided to evaluate the overall treatment effect and by dose groups effects. No statistical comparisons of differences were performed among the different maribavir dose groups.

The antiviral efficacy variables that were determined are listed in section “Outcomes and endpoints”.

The point estimates of the treatment effects (overall and by dose group) and 95% confidence intervals were provided for the primary efficacy endpoint and other binary and numerical endpoints. The Kaplan-Meier method was used to estimate the survival functions using PROC LIFETEST for time-to-event endpoints (overall and by dose group).

Virologic Response by Central or Local Laboratory at Weeks 3 and 6. Minimum virologic response criteria at week 3 was any CMV DNA decline from baseline, at week 6 ≥ 2log decline in CMV DNA from baseline.

The virologic responses at Weeks 3 and 6 were summarised by whether the virologic response was based on central or local laboratory CMV DNA values.

The analyses are acceptable for an early phase exploratory study. Nevertheless, in order make optimal use of the data a reasonable dose-response-regression model would have been expected, although due to the apparent observed flat dose response conclusions would be unlikely to be different. Due to the small number of groups (3), however, only a two-parameter regression model, i.e. a linear model (i.e. linear on the log-odds scale) would allow for interpolation, if a specific time point is used. Using the study data, however, a different conclusion appears unlikely.

A specific challenge in the interpretation of the data is related to the number of missing data imputed by LOCF in the presence of possible recurrence. In addition, treatment discontinuation or switch will play a major role in the interpretation of the data. A large number of patients should have discontinued treatment after week 3 according to the study protocol (i.e. did not meet minimum virologic response) but, apparently, did continue. Since the study was not powered to show an overall dose response and due to the deficiencies in the applied treatment policy and response definitions it seems that the study was not capable to reasonably investigate a relevant dose response. In conclusion, a dose response could neither be demonstrated nor excluded.

***Results***

***Participant flow***

In total, 129 patients screened to participate in the study, 9 were screen failure. One hundred twenty (120) patients were randomised in this study (ITT Population). All patients received at least 1 dose of study drug and were included in the ITT-S Population. Ninety-one (91) patients were included in the PP Population (i.e., met all study entry criteria, had a confirmed detectable plasma CMV DNA level on Day 1 [central laboratory], and received study drug treatment through at least Week 2). One hundred twenty (120) patients were included in the Pharmacokinetic Population (i.e., had plasma samples drawn and tested for maribavir concentrations), and pharmacokinetic profile samples were collected from 33 patients.

Overall, 78% of the patients withdrew from the study. The most common reason was an AE, recovery from CMV infection as judged by the investigator and lack of efficacy. Lack of efficacy was reported most frequently in the 400 mg BID group (400 mg BID: 20%; 800 mg BID: 18%; 1200 mg BID: 15%).

Protocol violations were recorded in nearly all patients. Many violations to inclusion and exclusion criteria were noted (12%). Six patient did not have confirmed viraemia > 1000 IU/mL (400 mg (N=2), 800 mg (N=1) and 1200 mg (N=3)), six patients received prohibited medication (400 mg (N=2), 800 mg (N=1) and 1200 mg (N=3)) or had current CMV infection that was not refractory or resistant to treatment of valganciclovir, ganciclovir or foscarnet (400 mg (N=1), 800 mg (N=1)).

Table 45 Patient disposition (ITT Population)

| | Maribavir 400 mg BID N=40 | Maribavir 800 mg BID N=40 | Maribavir 1200 mg BID N=40 | Maribavir All Doses N=120 |
|---|---|---|---|---|
| ITT-S Population | 40 (100.0) | 40 (100.0) | 40 (100.0) | 120 (100.0) |
| PP Population | 31 (77.5) | 33 (82.5) | 27 (67.5) | 91 (75.8) |
| Reason for exclusion from PP Population [a] | 9 (22.5) | 7 (17.5) | 13 (32.5) | 29 (24.2) |
| Study entry violation | 4 (10.0) | 3 (7.5) | 7 (17.5) | 14 (11.7) |
| No confirmed detectable plasma CMV DNA level on Day 1 | 5 (12.5) | 2 (5.0) | 4 (10.0) | 11 (9.2) |
| Did not receive study drug treatment through at least the Week 2 Visit | 1 (2.5) | 3 (7.5) | 5 (12.5) | 9 (7.5) |
| Pharmacokinetic Population | 40 (100.0) | 40 (100.0) | 40 (100.0) | 120 (100.0) |
| Pharmacokinetic Profile Population | 12 (30.0) | 13 (32.5) | 8 (20.0) | 33 (27.5) |

| | Maribavir 400 mg BID N=40 | Maribavir 800 mg BID N=40 | Maribavir 1200 mg BID N=40 | Maribavir All Doses N=120 |
|---|---|---|---|---|
| Subjects completing treatment | 9 (22.5) | 7 (17.5) | 11 (27.5) | 27 (22.5) |
| Subjects not completing treatment | 31 (77.5) | 33 (82.5) | 29 (72.5) | 93 (77.5) |
| Reason for not completing treatment | | | | |
| Adverse event | 10 (25.0) | 15 (37.5) | 14 (35.0) | 39 (32.5) |
| Lack of efficacy | 8 (20.0) | 7 (17.5) | 6 (15.0) | 21 (17.5) |
| Physician decision | 4 (10.0) | 2 (5.0) | 2 (5.0) | 8 (6.7) |
| Recovery (from CMV infection) | 8 (20.0) | 9 (22.5) | 7 (17.5) | 24 (20.0) |
| Withdrawal by subject | 1 (2.5) | 0 | 0 | 1 (0.8) |
| Subjects completing study | 25 (62.5) | 25 (62.5) | 24 (60.0) | 74 (61.7) |
| Subjects not completing study | 15 (37.5) | 15 (37.5) | 16 (40.0) | 46 (38.3) |
| Reason for not completing study | | | | |
| Death | 10 (25.0) | 12 (30.0) | 10 (25.0) | 32 (26.7) |
| Lost to follow-up | 0 | 1 (2.5) | 0 | 1 (0.8) |
| Physician decision | 5 (12.5) | 1 (2.5) | 2 (5.0) | 8 (6.7) |
| Withdrawal by subject | 0 | 1 (2.5) | 4 (10.0) | 5 (4.2) |

BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; ITT=Intent-to-treat; ITT-S=Intent-to-treat Safety; PP=Per Protocol
Note: Percentages are based on the number of subjects in each treatment group (ITT Population).
[a] Subjects may have more than 1 reason for exclusion from the PP Population; therefore, percentages may not add to 100%.
Source: Section 14, Table 11.1.2.1 and Table 11.1.2.2

**Baseline data**

The median age of the ITT-S Population was 55 years (range: 18-74 years), and the majority of patients were white (79%). The percentage of males and females was 57.5% and 42.5%, respectively. Overall, the distribution of demographic data was similar across treatment groups. However, most patients with hepatic dysfunction were included in the maribavir 400 mg BID group (N=8).

Comparable percentages of SCT and SOT recipients were included within each treatment group (overall maribavir: 39% and 61%, respectively). For all patients except 1, the IXRS and CRF were concordant with respect to transplant type with the exception of one patient in the maribavir 400 mg BID treatment group had SCT documented on the CRF, but SOT documented in IXRS.

Of note, only 55% in the maribavir 400 mg BID group had reported CMV baseline genetic mutations associate with resistance to ganciclovir/valganciclovir or foscarnet, compared to 63% in the maribavir 800 mg BID group and 60% in the maribavir 1200 mg group.

Approximately 13% had CMV disease at baseline, most of them were allocated to the 800 mg and 400 mg BID group.

On Study Day 1, 34% of patients had acute GVHD and 15% of patients had chronic GVHD.

Table 46 Summary of transplant and CMV history (ITT-S population)

| | Maribavir 400 mg BID N=40 | Maribavir 800 mg BID N=40 | Maribavir 1200 mg BID N=40 | Maribavir All Doses N=120 |
|---|---|---|---|---|
| Most recent transplant, n (%) | | | | |
| Stem cell transplant | 16 (40.0) | 16 (40.0) | 15 (37.5) | 47 (39.2) |
| Solid organ transplant | 24 (60.0) | 24 (60.0) | 25 (62.5) | 73 (60.8) |
| Primary underlying disease in ≥5% of all subjects, n (%) | | | | |
| Acute myeloid leukemia | 4 (10.0) | 6 (15.0) | 5 (12.5) | 15 (12.5) |
| Non-Hodgkin's lymphoma | 4 (10.0) | 2 (5.0) | 4 (10.0) | 10 (8.3) |
| Diabetes mellitus | 3 (7.5) | 2 (5.0) | 4 (10.0) | 9 (7.5) |
| Idiopathic pulmonary fibrosis | 3 (7.5) | 2 (5.0) | 3 (7.5) | 8 (6.7) |
| Acute lymphocytic leukemia | 2 (5.0) | 2 (5.0) | 2 (5.0) | 6 (5.0) |
| CMV serostatus, n (%) | | | | |
| D+ R+ | 11 (27.5) | 7 (17.5) | 8 (20.0) | 26 (21.7) |
| D– R+ | 4 (10.0) | 11 (27.5) | 9 (22.5) | 24 (20.0) |
| D+ R– | 20 (50.0) | 20 (50.0) | 22 (55.0) | 62 (51.7) |
| D– R– | 5 (12.5) | 2 (5.0) | 1 (2.5) | 8 (6.7) |
| Days from transplant to first dose of study drug | | | | |
| Mean (SD) | 429.7 (706.95) | 420.2 (643.83) | 583.2 (1743.78) | 477.7 (1140.97) |
| Median (min, max) | 244.0 (16, 4340) | 214.0 (46, 3968) | 223.0 (27, 10615) | 230.0 (16, 10615) |
| Distribution of days from transplant to first dose of study drug, n (%) | | | | |
| 1 to 28 | 1 (2.5) | 0 | 1 (2.5) | 2 (1.7) |
| 29 to 56 | 5 (12.5) | 2 (5.0) | 6 (15.0) | 13 (10.8) |
| 57 to 84 | 3 (7.5) | 5 (12.5) | 1 (2.5) | 9 (7.5) |
| 85 to 182 | 7 (17.5) | 7 (17.5) | 9 (22.5) | 23 (19.2) |
| 183 to 365 | 12 (30.0) | 12 (30.0) | 16 (40.0) | 40 (33.3) |
| >365 | 12 (30.0) | 14 (35.0) | 7 (17.5) | 33 (27.5) |
| Received ALA preparations at any time from transplant until initiation of study drug, n (%) | | | | |
| Yes | 15 (37.5) | 22 (55.0) | 16 (40.0) | 53 (44.2) |
| No | 25 (62.5) | 18 (45.0) | 24 (60.0) | 67 (55.8) |
| Days from last administration of ALA preparations to initiation of study drug | | | | |
| Mean (SD) | 285.2 (268.15) | 249.7 (199.19) | 226.1 (115.78) | 252.1 (197.74) |
| Median (min, max) | 224.0 (27, 1056) | 190.5 (14, 656) | 203.5 (74, 452) | 201.0 (14, 1056) |

| | Maribavir 400 mg BID N=40 | Maribavir 800 mg BID N=40 | Maribavir 1200 mg BID N=40 | Maribavir All Doses N=120 |
|---|---|---|---|---|
| Days from onset of current CMV infection to first dose of study drug | | | | |
| Mean (SD) | 119.7 (111.22) | 113.7 (112.08) | 90.8 (79.95) | 108.0 (102.09) |
| Median (min, max) | 93.5 (16, 540) | 73.5 (13, 530) | 66.5 (19, 413) | 73.5 (13, 540) |
| Distribution of days from onset of current CMV infection to first dose of study drug, n (%) | | | | |
| 1 to 14 | 0 | 1 (2.5) | 0 | 1 (0.8) |
| 15 to 21 | 4 (10.0) | 2 (5.0) | 3 (7.5) | 9 (7.5) |
| 22 to 28 | 3 (7.5) | 6 (15.0) | 6 (15.0) | 15 (12.5) |
| 29 to 56 | 4 (10.0) | 7 (17.5) | 7 (17.5) | 18 (15.0) |
| 57 to 84 | 7 (17.5) | 5 (12.5) | 9 (22.5) | 21 (17.5) |
| 85 to 182 | 13 (32.5) | 12 (30.0) | 10 (25.0) | 35 (29.2) |
| 183 to 365 | 7 (17.5) | 6 (15.0) | 4 (10.0) | 17 (14.2) |
| >365 | 2 (5.0) | 1 (2.5) | 1 (2.5) | 4 (3.3) |
| Number of local laboratory blood/plasma quantitative CMV tests for current CMV infection within 12 weeks prior to randomization, n | 40 | 39 | 40 | 119 |
| Mean (SD) | 10.6 (5.26) | 10.4 (6.01) | 10.4 (5.32) | 10.5 (5.49) |
| Median (min, max) | 10.0 (3, 26) | 11.0 (2, 25) | 10.0 (3, 26) | 10.0 (2, 26) |
| PI reported CMV genetic mutations associated with resistance to ganciclovir/valganciclovir or foscarnet (at time of enrollment), n (%) | | | | |
| Yes | 22 (55.0) | 25 (62.5) | 24 (60.0) | 71 (59.2) |
| No | 18 (45.0) | 15 (37.5) | 16 (40.0) | 49 (40.8) |
| Category of CMV at initiation of study drug | | | | |
| Asymptomatic CMV infection | 24 (60.0) | 26 (65.0) | 27 (67.5) | 77 (64.2) |
| Symptomatic CMV infection | 10 (25.0) | 7 (17.5) | 10 (25.0) | 27 (22.5) |
| Fever >38°C for at least 2 days | 0 | 1 (14.3) | 2 (20.0) | 3 (11.1) |
| New or increased malaise | 8 (80.0) | 6 (85.7) | 10 (100.0) | 24 (88.9) |
| Leukopenia | 4 (40.0) | 3 (42.9) | 7 (70.0) | 14 (51.9) |
| ≥5% atypical lymphocytosis | 0 | 0 | 0 | 0 |
| Thrombocytopenia | 4 (40.0) | 0 | 6 (60.0) | 10 (37.0) |
| ALT or AST elevation to ≥2× ULN | 1 (10.0) | 0 | 0 | 1 (3.7) |
| CMV organ disease | 6 (15.0) | 7 (17.5) | 3 (7.5) | 16 (13.3) |
| CMV pneumonia | 1 (16.7) | 2 (28.6) | 0 | 3 (18.8) |
| CMV gastrointestinal disease | 5 (83.3) | 4 (57.1) | 3 (100.0) | 12 (75.0) |
| CMV hepatitis | 1 (16.7) | 0 | 0 | 1 (6.3) |
| CMV retinitis | 1 (16.7) | 1 (14.3) | 0 | 2 (12.5) |

***Numbers analysed***

A total of 120 patients were planned to be randomised. Protocol-defined analysis populations are shown below. The ITT-S set was used for all primary and secondary efficacy analyses supported by the PP Populations.

***Outcomes and estimation***

Primary efficacy endpoint

Nine patients in the ITT-S had undetectable plasma CMV DNA at baseline (i.e., prior to starting study drug treatment on Day 1). Two were enrolled in the study in violation of inclusion criterion #4: one patient in maribavir 400 mg group and other in maribavir 800 mg group had a screening result of <1000 copies/mL. The remaining 7 patients met inclusion criterion #4 (i.e., had a screening value of ≥ 1000 DNA copies/mL within 7 days prior to randomisation), but their viral loads decreased to undetectable by the time of their Day 1 visit. None of the patients were excluded from the primary efficacy analyses below.

Overall, 67% of patients had confirmed undetectable plasma CMV DNA within 6 weeks after starting study drug treatment. No clear dose-response was seen across the study doses investigated. The

proportion of patients with undetectable plasma CMV DNA was comparable among the 3 treatment groups, with the numerically highest proportion of responders in the 400 mg BID (0.70 [0.53, 0.83]) and 1200 mg BID (0.68 [0.51, 0.81]) groups, followed by the 800 mg BID (0.63 [0.46, 0.77]) group.

Table 47 Analysis of confirmed undetectable plasma CMV DNA within 6 weeks (central laboratory) (ITT-S population)

| | Maribavir 400 mg BID N=40 | Maribavir 800 mg BID N=40 | Maribavir 1200 mg BID N=40 | Maribavir All Doses N=120 |
|---|---|---|---|---|
| Subjects with missing data [a], n (%) | 0 | 0 | 2 (5.0) | 2 (1.7) |
| Subjects with confirmed undetectable plasma CMV DNA, n (%) | | | | |
| Yes | 28 (70.0) | 25 (62.5) | 27 (67.5) | 80 (66.7) |
| No | 12 (30.0) | 15 (37.5) | 11 (27.5) | 38 (31.7) |
| Treatment effect estimate by group | | | | |
| Estimated rate [b] | 0.70 | 0.63 | 0.68 | 0.67 |
| 95% confidence interval [c] | (0.53, 0.83) | (0.46, 0.77) | (0.51, 0.81) | (0.57, 0.75) |

BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; ITT-S=Intent-to-treat Safety
[a] No plasma CMV DNA measurement post-baseline within the assessment period (ie, 6 weeks).
[b] Numerator is the number of "Yes" subjects. Denominator is the number of ITT-S subjects.
[c] Calculated using the exact (Clopper-Pearson) confidence limits for the binomial proportion.
Source: Section 14, Table 11.2.1.1

Secondary efficacy endpoint

The number and estimated rate of patients in the ITT-S Population who achieved undetectable plasma CMV DNA per the central laboratory at each specified visit showed that the proportion of patients with undetectable plasma CMV DNA at baseline was similar among the maribavir dose groups (estimated rate [95% CI]: 400 mg BID (0.10 [0.03, 0.24]), 800 mg BID (0.05 [0.01, 0.17]), and 1200 mg BID (0.08 [0.02, 0.20]). From Week 1 to Week 24, the proportion of patients with undetectable plasma CMV DNA was generally similar among the maribavir dose groups. The same was true throughout the follow-up period (post-treatment Weeks 1-12).

The proportion of patients with undetectable plasma CMV DNA increased weekly to a maximum plateau at study Week 4 for the 400 mg BID cohort and study Week 5 for the 800 mg BID and 1200 mg BID cohorts and did not increase thereafter. Hence, continued treatment with maribavir did not to increase the proportion of responder.

**CMV Recurrence**

No statistically significant difference was seen in terms of patients with CMV recurrence. A numerically lower proportion of patients in the 400 mg BID maribavir group (estimated rate [95% CI]: 0.24 [0.10, 0.44]) had CMV recurrence compared to the 800 mg BID (0.41 [0.22, 0.61]) and 1200 mg BID (0.40 [0.23, 0.59]) groups.

Table 48 Analysis of CMV recurrence at any time during study (ITT-S population)

| | Maribavir 400 mg BID N=40 | Maribavir 800 mg BID N=40 | Maribavir 1200 mg BID N=40 | Maribavir All Doses N=120 |
|---|---|---|---|---|
| Number of subjects achieving confirmed undetectable CMV DNA [a] | 29 | 27 | 30 | 86 |
| Subjects with CMV recurrence, n | | | | |
| Yes [b] | 7 | 11 | 12 | 30 |
| No [c] | 22 | 14 | 17 | 53 |
| Treatment effect estimate by group | | | | |
| Estimated rate [d] | 0.24 | 0.41 | 0.40 | 0.35 |
| 95% CI for estimated rate [e] | (0.10, 0.44) | (0.22, 0.61) | (0.23, 0.59) | (0.25, 0.46) |

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; ITT-S=Intent-to-treat Safety
Note: Results from central laboratory.
[a] Number of subjects with at least 2 consecutive undetectable plasma CMV DNA results separated by at least 5 days, including early withdrawn qualified subjects.
[b] Any recurrence during the study, including early withdrawn subjects who had recurrence before withdrawal from study.
[c] Did not have recurrence during the study, including early withdrawn subjects who did not have recurrence before withdrawal from study.
[d] Numerator is all recurrences. Denominator is the number of subjects achieving confirmed undetectable CMV DNA.
[e] Calculated using the exact (Clopper-Pearson) confidence limits for the binomial proportion.
Source: Section 14, Table 11.2.9.1

**Use of non-study systemic anti-CMV therapies**

More patients in the maribavir 400 mg BID group used non-study anti-CMV treatment compared to the 800 mg BID and 1200 mg BID groups. The estimated treatment effect was numerically lower in the 800 mg BID maribavir group (estimated rate [95% CI]: 0.08 [0.02,0.20]) than the 1200 mg BID (0.15 [0.06, 0.30]) and 400 mg BID (0.20 [0.09, 0.36]) groups.

Table 49 Analysis of use of any non-study systemic anti-CMV therapies after day 1 and within 6 weeks (ITT-S population)

| | Maribavir 400 mg BID N=40 | Maribavir 800 mg BID N=40 | Maribavir 1200 mg BID N=40 | Maribavir All Doses N=120 |
|---|---|---|---|---|
| Use of any non-study systemic anti-CMV therapies, n | | | | |
| No | 32 | 37 | 34 | 103 |
| Yes | 8 | 3 | 6 | 17 |
| Treatment effect estimate by group | | | | |
| Estimated rate | 0.20 | 0.08 | 0.15 | 0.14 |
| 95% CI | (0.09, 0.36) | (0.02, 0.20) | (0.06, 0.30) | (0.08, 0.22) |

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; ITT-S=Intent-to-treat Safety
Source: Section 14, Table 11.2.13.1

**Virologic response by central or local laboratory at weeks 3 and 6**

At week 3 23/40 patients (58%) in the 400 mg BID group met minimal virologic response criteria of any decrease in CMV viral load. At study week 6, 30/40 patients (75%) in the 400 mg BID group met the minimal virological response criteria of ≥ 2 log reduction in CMV DNA.

Table 50 Summary of minimum virologic response criteria at weeks 3 and 6 (ITT-S population)

| | Maribavir 400 mg BID N=40 | Maribavir 800 mg BID N=40 | Maribavir 1200 mg BID N=40 | Maribavir All Doses N=120 |
|---|---|---|---|---|
| **Week 3** | | | | |
| Number of subjects meeting minimum virologic response criteria | 23 | 19 | 22 | 64 |
| Based on central laboratory CMV DNA, n (%) | 21 (91.3) | 19 (100.0) | 21 (95.5) | 61 (95.3) |
| Based on local laboratory CMV DNA, n (%) | 2 (8.7) | 0 | 1 (4.5) | 3 (4.7) |
| **Week 6** | | | | |
| Number of subjects meeting minimum virologic response criteria | 30 | 24 | 28 | 82 |
| Based on central laboratory CMV DNA, n (%) | 27 (90.0) | 23 (95.8) | 25 (89.3) | 75 (91.5) |
| Based on local laboratory CMV DNA, n (%) | 3 (10.0) | 1 (4.2) | 3 (10.7) | 7 (8.5) |

BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; ITT-S=Intent-to-treat Safety
Note: Percentages are based on the number of subjects meeting minimum virologic response criteria in each treatment group.
Source: Section 14, Table 11.2.19

Subgroup analyses were presented, however not powered to show statistically significance. According to the subgroup analysis the response rate in patients with baseline presence of > 1 CMV genetic RAS associated with resistance to ganciclovir/valganncicloviror foscarnet was 64% in the 400 mg BID and was 61% for the overall maribavir group. It is of note that response rates in patients with resistance (202: 64% vs. 303: 44%) and in patients without resistance (202: 78% vs. 303: 13%) were higher than in study 303.

Virology:

Genotypic analyses of CMV was performed for all patients at baseline, for non-responder (not achieve undetectable plasma CMV DNA within 6 weeks after study start) for responders who experienced CMV recurrence during or after maribavir treatment and also for responder patients (if possible).

Treatment emergent UL97 mutations **T409M** and **H411Y** developed fast and frequently on and after maribavir treatment, irrespective of the dose and was associated with non-response and recurrence. In patients who received 400 mg BID 4/6 (67%) patients selected for resistance mutations **H411Y** or **T409M** by treatment Week 24, compared to 6/9 (67%) in the 800 mg BID group and 3/9 (33%) patients who received 1200 mg BID.

The number and range of UL27 mutations in responders and non-responders was similar. Mutation **M418I** was observed de novo in maribavir treated patients, however, the significance of this mutation is unknown.

The presence of UL54 mutations was similar among responder/non-responder. Detected mutations were **S655L, N685S, F669L** and **I833M**. The clinical relevance of these RAS remains unknown and should be monitored in future.

**SHP-620-203**

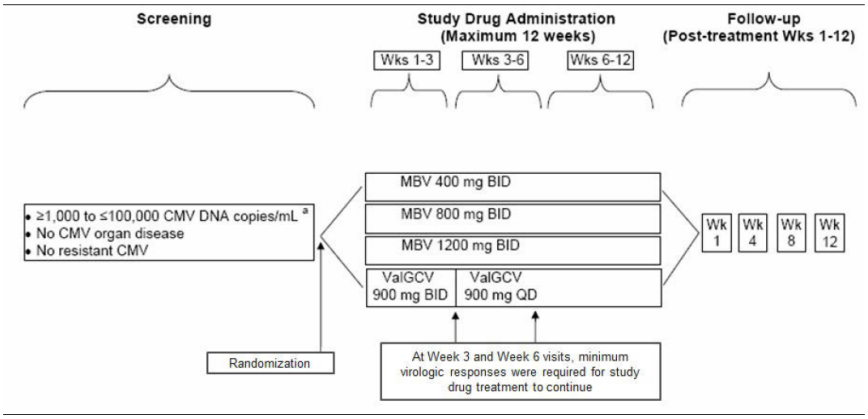
This was a phase 2, multi-centre, randomised, dose-ranging, parallel-group study of maribavir versus valganciclovir for the treatment of CMV infections in HSCT and SOT recipients. The study was conducted at 38 sites in six European countries (Austria, Belgium, Germany, France, Spain, and the UK).

Approximately 160 patients were planned to be randomised in a 1:1:1:1 allocation ratio to receive oral maribavir at 1 of 3 dose strengths (400 mg BID, 800 mg BID, or 1200 mg BID) or valganciclovir (Weeks 1-3: 900 mg BID, after Week 3: 900 mg QD; with dose adjustment for renal function) for up to 12 weeks. To be eligible, patients must not have had CMV organ disease or a CMV infection that was

genotypically resistant to other anti-CMV drugs. Randomisation of eligible patients was stratified by transplant type (SCT or SOT).

Regarding patients assigned to receive maribavir, patients, investigators, and study staff knew that they were receiving maribavir, but were blinded to dose strength; valganciclovir administration was open-label. During the study, patients were followed as either inpatients or outpatients, depending on their condition. An overview of the study design is provided in Figure 7.

Patients must have achieved at least a minimum virologic response at Weeks 3 and 6 for study drug treatment to continue beyond each of these time points. For patients who continued dosing after the Week 6 visit, dosing could continue at the discretion of the investigator through a maximum of 12 weeks in an attempt to decrease CMV DNA to undetectable, and/or to maintain undetectable CMV DNA in an effort to prevent recurrence of CMV infection. These patients underwent study-specific evaluations every 2 weeks through Week 12.




BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; MBV=maribavir; QD=once daily; ValGCV=valganciclovir; Wk(s)=Week(s)

[a] A target of ~25% of all randomized subjects were to have ≥10,000 CMV DNA copies/mL in plasma at baseline.

Figure 7 Study design of study 203

An independent, unblinded Data Monitoring Committee (DMC) reviewed available safety and safety-related efficacy data at predefined time points during the study.

***Study Participants***

Study participants were male and female stem cell or solid organ transplantation recipients ≥ 18 years of age with documented CMV infection in blood or plasma, with a screening value of ≥1000 DNA to < 100.000 copies/mL as determined by quantitative polymerase chain reaction (PCR) or comparable quantitative CMV assay type and without CMV organ disease or a CMV infection that was known to be resistant to ganciclovir/valganciclovir, foscarnet, or cidofovir.

Patients who received drugs with known anti-CMV activity must have been discontinued use at least 14 days before the first dose of study drug.

***Treatments***

Patients received oral maribavir at 1 of 3 dose strengths (400 mg BID, 800 mg BID, or 1200 mg BID) or oral valganciclovir (Weeks 1-3: 900 mg BID, after Week 3: 900 mg QD; with dose adjustment for renal function)

for a maximum duration of 12 weeks. Treatment assignment was known. However, maribavir patients were blinded to dose while valganciclovir administration was open-label.

The formulation used in study 202 (formulation III) is not identical to the formulation used in the pivotal phase 3 study 303 (formulation IV). The applied posology (400 mg BID) with the to-be-marketed formulation was only studied in the Phase 3 study and has undergone changes in manufacturing since then. The dose was selected based on *in vitro* antiviral efficacy data, clinical PK data and modelling of the E-R relationships.

***Objectives***

The primary objective of the study was to assess the safety and tolerability of different doses of maribavir versus valganciclovir, administered orally for up to 12 weeks, for treatment of CMV infections in recipients of stem cell or solid organ transplants who do not have CMV organ disease. The secondary objectives of the study were to assess the antiviral activity of different doses of maribavir versus valganciclovir in this patient population, to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of maribavir in this patient population and to identify a maribavir dosing regimen for treatment of CMV infections in future studies.

***Outcomes/endpoints***

The primary endpoint was the proportion of patients with confirmed undetectable plasma CMV DNA (central laboratory) within 3 weeks and within 6 weeks, defined as 2 consecutive post-baseline, on-treatment undetectable results (<200 copies/mL) separated by at least 5 days.

Secondary endpoints were the proportion of patients with undetectable plasma CMV DNA (central laboratory) at specified visits, the proportion of patients with undetectable blood/plasma CMV at specified visits, the proportion of patients with CMV recurrence at any time during the study and the use of any protocol-specified non-study systemic anti-CMV therapies within 6 weeks. Time to event endpoints were time to first confirmed undetectable plasma CMV DNA result (central laboratory) within 6 weeks and time to CMV recurrence during the study.

***Randomisation and blinding (masking)***

Qualified patients were randomised in a 1:1:1:1 allocation ratio to receive oral maribavir at one of three different dose strengths or oral valganciclovir (collectively, the study drug), after stratification by transplant type (SCT or SOT). To ensure the ability to assess the activity of maribavir at relatively high viral load levels, the study targeted a minimum of approximately 25% of all randomised patients who had ≥10,000 CMV DNA copies/mL in plasma at baseline.

Prior to dosing, study personnel contacted the interactive voice and web response system (IXRS) to obtain a study drug kit number. The IXRS randomised patients using a central block randomisation process across the entire study based on the stratification variable indicated above, and managed resupply of study drug kits to sites as necessary.

Patients assigned to receive maribavir, patients, investigators, and study staff knew that they were receiving maribavir, but were blinded to dose strength; valganciclovir administration was open-label. The treatment assignments of all maribavir patients remained blinded at the site level throughout the study.

***Statistical methods***

All primary and secondary efficacy analyses were performed using the ITT-S and PP Populations. For all efficacy endpoints, the primary comparison of interest was the overall treatment effect evaluated by pooling all maribavir dose groups together versus valganciclovir. The second comparison of interest was to estimate the treatment effect by maribavir dose group versus valganciclovir. Valganciclovir, as

an open-label control group, provided a reference assessment of the treatment effect in the same study population. Summary statistics were provided to evaluate the overall treatment effect and by dose group effects. Statistical comparisons of interest focused primarily on differences between the combined maribavir group versus valganciclovir. In addition, selected efficacy endpoints were modelled as described below.

Unless otherwise specified, all statistical tests were two-sided at the 0.05 level of significance. Baseline plasma CMV DNA and transplantation type were used as covariates to adjust the treatment effect in selected model analyses. No adjustments for multiple comparisons or multiplicity were made.

The antiviral efficacy variables are described in section "Outcomes and endpoints".

The point estimates of the treatment effects (overall and by dose group) and 95% confidence intervals (CIs) were provided for binary and numerical endpoints.

Differences between maribavir (overall) and valganciclovir for binary endpoints measured within 6 weeks were assessed using a logistic regression model (PROC LOGISTIC in SAS) with terms of treatment, baseline plasma CMV DNA, and transplantation type. This was an exploratory analysis; therefore, statistics from the logistic regression model are for summary purposes rather than inferential statistical comparisons among the treatments.

Differences between maribavir (overall) and valganciclovir for all time-to-event endpoints were assessed using Cox proportional hazard model (PROC PHREG in SAS) with terms of treatment, baseline plasma CMV DNA, and transplantation type. EXACT tie handling method was applied for the Cox proportional hazard model analysis. In addition, PROC LIFETEST was used to estimate the survival functions by the Kaplan-Meier method.

Kaplan-Meier survival curves for maribavir (overall and by dose group) vs. valganciclovir are provided. Number of event and censoring information are presented in the summary table and the graph of Kaplan-Meier survival curve.

Differences between maribavir (overall) and valganciclovir for all numerical endpoints at Week 6 were assessed based on an analysis of covariance model (PROC MIXED in SAS) with terms of treatment, baseline plasma CMV DNA, and transplantation type. The model adjusted means and corresponding 95% CIs are provided. The point estimates of the treatment differences and the corresponding 95% CIs are also provided. This was an exploratory analysis; therefore, statistics from the analysis of covariance model are for summary purposes rather than inferential statistical comparisons among the treatments.

All analyses are considered descriptive and exploratory. No confirmatory conclusion can be drawn from the results. The analyses are acceptable for an early phase exploratory study.

***Results***

***Participant flow***

Of the 174 patients screened to participate in this study, 13 were screen failures. One hundred sixty-one (161) patients were randomised in this study (ITT Population,). One patient in the maribavir 1200 mg BID group and one in the valganciclovir 900 mg BID group were randomised but did not receive study drug. The remaining 159 patients received at least one dose of study drug and were included in the ITT-S Population.

Overall, 28% of the patients in the maribavir group and 32% of the patients in the valganciclovir group completed study treatment. The most common reason for discontinuation was an AE, an AE, recovery from CMV infection as judged by the investigator and lack of efficacy. was an AE (400 mg BID: 20%; 800 mg BID: 13%; 1200 mg BID: 25%, valganciclovir: 15%). Recovery from CMV infection as judged

by the investigator (400 mg BID: 33%; 800 mg BID: 55%; 1200 mg BID: 30%, valganciclovir: 34%) and lack of efficacy, which was reported more often in the 400 mg BID group (400 mg BID: 10%; 800 mg BID: 5%; 1200 mg BID: 5%) but was similar between the maribavir and valganciclovir group.

Protocol violations were recoded frequently in 95% of the enrolled patients. Major protocol deviations were noted more frequently the overall maribavir group (13%) compared to the valganciclovir group (8%). Violations of inclusion/exclusion criteria were similar in both treatment groups, while use of prohibited medications was reported only in patients in the maribavir group.

Table 51 Patient disposition study 203

| | Maribavir 400 mg BID n (%) | Maribavir 800 mg BID n (%) | Maribavir 1200 mg BID n (%) | Maribavir All Doses n (%) | Valganciclovir 900 mg BID n (%) | All Subjects n (%) |
|---|---|---|---|---|---|---|
| ITT Population | 40 | 40 | 40 | 120 | 41 | 161 |
| ITT-S Population | 40 (100.0) | 40 (100.0) | 39 (97.5) | 119 (99.2) | 40 (97.6) | 159 (98.8) |
| Subjects randomized but did not receive study drug | 0 | 0 | 1 (2.5) | 1 (0.8) | 1 (2.4) | 2 (1.2) |
| Subjects completing treatment | 13 (32.5) | 8 (20.0) | 13 (32.5) | 34 (28.3) | 13 (31.7) | 47 (29.2) |
| Subjects not completing treatment | 27 (67.5) | 32 (80.0) | 26 (65.0) | 85 (70.8) | 27 (65.9) | 112 (69.6) |
| Reason for not completing treatment | | | | | | |
| Adverse event | 8 (20.0) | 5 (12.5) | 10 (25.0) | 23 (19.2) | 6 (14.6) | 29 (18.0) |
| Lack of efficacy | 4 (10.0) | 2 (5.0) | 2 (5.0) | 8 (6.7) | 3 (7.3) | 11 (6.8) |
| Physician decision | 1 (2.5) | 0 | 0 | 1 (0.8) | 2 (4.9) | 3 (1.9) |
| Recovery (from CMV infection) | 13 (32.5) | 22 (55.0) | 12 (30.0) | 47 (39.2) | 14 (34.1) | 61 (37.9) |
| Sponsor decision | 0 | 1 (2.5) | 0 | 1 (0.8) | 0 | 1 (0.6) |
| Withdrawal by subject | 1 (2.5) | 2 (5.0) | 2 (5.0) | 5 (4.2) | 2 (4.9) | 7 (4.3) |
| Subjects completing study | 36 (90.0) | 36 (90.0) | 34 (85.0) | 106 (88.3) | 34 (82.9) | 140 (87.0) |
| Subjects not completing study | 4 (10.0) | 4 (10.0) | 5 (12.5) | 13 (10.8) | 6 (14.6) | 19 (11.8) |
| Reason for not completing study | | | | | | |
| Death | 1 (2.5) | 1 (2.5) | 3 (7.5) | 5 (4.2) | 3 (7.3) | 8 (5.0) |
| Lost to follow-up | 2 (5.0) | 0 | 0 | 2 (1.7) | 0 | 2 (1.2) |
| Physician decision | 1 (2.5) | 0 | 0 | 1 (0.8) | 0 | 1 (0.6) |
| Withdrawal by subject | 0 | 3 (7.5) | 2 (5.0) | 5 (4.2) | 3 (7.3) | 8 (5.0) |

BID=twice daily; CMV=cytomegalovirus; ITT=Intent-to-treat; ITT-S=Intent-to-treat Safety
Percentages are based on the number of subjects in each treatment group (ITT Population).
Source: Section 14, Table 11.1.2.2

***Baseline data***

Overall, the distribution of demographic data was similar across treatment groups.The median age of the ITT-S Population was 58 years (range: 18-76 years), and the majority of patients were White (91%). The percentage of males (62%) was higher than the percentage of females (38%).

| | Maribavir 400 mg BID (N=40) | Maribavir 800 mg BID (N=40) | Maribavir 1200 mg BID (N=39) | Maribavir All Doses (N=119) | Valganciclovir 900 mg BID (N=40) | All Subjects (N=159) |
|---|---|---|---|---|---|---|
| Age (years) | | | | | | |
| Mean (SD) | 53.0 (14.18) | 54.4 (12.72) | 55.9 (10.69) | 54.4 (12.57) | 54.5 (12.36) | 54.4 (12.48) |
| Median (min, max) | 56.5 (29, 76) | 58.5 (18, 74) | 58.0 (25, 74) | 58.0 (18, 76) | 58.5 (28, 76) | 58.0 (18, 76) |
| Distribution of age (years), n (%) | | | | | | |
| 18 to 44 | 11 (27.5) | 7 (17.5) | 5 (12.8) | 23 (19.3) | 9 (22.5) | 32 (20.1) |
| 45 to 64 | 16 (40.0) | 26 (65.0) | 26 (66.7) | 68 (57.1) | 24 (60.0) | 92 (57.9) |
| 65 to 75 | 12 (30.0) | 7 (17.5) | 8 (20.5) | 27 (22.7) | 6 (15.0) | 33 (20.8) |
| >75 | 1 (2.5) | 0 | 0 | 1 (0.8) | 1 (2.5) | 2 (1.3) |
| Gender, n (%) | | | | | | |
| Female | 18 (45.0) | 13 (32.5) | 17 (43.6) | 48 (40.3) | 13 (32.5) | 61 (38.4) |
| Male | 22 (55.0) | 27 (67.5) | 22 (56.4) | 71 (59.7) | 27 (67.5) | 98 (61.6) |
| Weight (kilograms) | | | | | | |
| Female, N | 17 | 13 | 17 | 47 | 13 | 60 |
| Mean (SD) | 72.1 (14.65) | 62.1 (14.83) | 58.0 (14.43) | 64.2 (15.59) | 62.5 (11.88) | 63.9 (14.79) |
| Median (min, max) | 71.5 (43.0, 98.0) | 60.0 (39.1, 97.0) | 56.6 (39.5, 106.5) | 61.0 (39.1, 106.5) | 66.3 (41.0, 77.6) | 63.1 (39.1, 106.5) |
| Male, N | 22 | 27 | 22 | 71 | 27 | 98 |
| Mean (SD) | 73.5 (10.14) | 76.7 (12.90) | 72.8 (14.27) | 74.5 (12.53) | 76.1 (14.22) | 75.0 (12.96) |
| Median (min, max) | 71.5 (54.2, 98.0) | 74.9 (44.0, 105.8) | 71.3 (51.0, 117.0) | 73.5 (44.0, 117.0) | 74.0 (52.2, 111.3) | 73.7 (44.0, 117.0) |

| | Maribavir 400 mg BID (N=40) | Maribavir 800 mg BID (N=40) | Maribavir 1200 mg BID (N=39) | Maribavir All Doses (N=119) | Valganciclovir 900 mg BID (N=40) | All Subjects (N=159) |
|---|---|---|---|---|---|---|
| Race, n (%) | | | | | | |
| Asian | 2 (5.0) | 1 (2.5) | 0 | 3 (2.5) | 4 (10.0) | 7 (4.4) |
| Black or African American | 1 (2.5) | 2 (5.0) | 0 | 3 (2.5) | 3 (7.5) | 6 (3.8) |
| White | 37 (92.5) | 37 (92.5) | 39 (100.0) | 113 (95.0) | 32 (80.0) | 145 (91.2) |
| Other | 0 | 0 | 0 | 0 | 1 (2.5) [a] | 1 (0.6) [a] |
| Ethnicity, n (%) | | | | | | |
| Hispanic or Latino | 5 (12.5) | 4 (10.0) | 4 (10.3) | 13 (10.9) | 8 (20.0) | 21 (13.2) |
| Not Hispanic or Latino | 35 (87.5) | 34 (85.0) | 35 (89.7) | 104 (87.4) | 31 (77.5) | 135 (84.9) |
| Not Reported/Unknown | 0 | 2 (5.0) | 0 | 2 (1.7) | 1 (2.5) | 3 (1.9) |

BID=twice daily; ITT-S=Intent-to-treat Safety; SD=standard deviation
[a] Moroccan.
Percentages are based on the number of subjects in each treatment group (ITT-S Population).
Source: Section 14, Table 11.1.4.1.1 and Appendix 16.2, Listing 12.3.4.2

**Transplant and CMV history**

Stratification by transplant type resulted in comparable percentages of SCT and SOT recipients within each treatment group (overall maribavir: 51% and 49%, valganciclovir: 53% and 48%, respectively).

The majority of all patients had a primary CMV infection (78%) versus a CMV recurrence (22%). The percentage of patients with a primary infection was 82% in the overall maribavir group and was higher compared to 68% in the valganciclovir group.

On Study Day 1, 26% of patients in the maribavir group and 38% in the valganciclovir group had acute GVHD and 8% in the maribavir group and 19% of patients had chronic GVHD.

Patients with known CMV organ disease or resistant mutations were excluded from the study. This study population represents patients expected to be earlier in the course of their CMV infection compared to the study populations of Studies 202 or 303 and does not cover the proposed target indication.

***Numbers analysed***

A total of 160 patients were planned to be randomised. Protocol-defined analysis populations are shown below. The ITT-S set was used for all primary and secondary efficacy analyses supported by the PP Populations.

***Outcomes and estimation***

Primary efficacy endpoint

Of the 159 patients in the ITT-S Population, fourteen patients (9%) had undetectable plasma CMV DNA at baseline. 10 patients (8%) in the overall maribavir group of which four were enrolled in the 400 mg BID dose group and 4 patients (10%) in the valganciclovir group.

Four patients were enrolled in the study in violation of inclusion criterion #3: one in the maribavir 400 mg group and one in the maribavir 800 mg group had a screening result of <1,000 copies/mL, and two patients in the valganciclovir group were enrolled based on a sample drawn >7 days prior to the initiation of study drug. The remaining 10 patients met inclusion criterion #3 (i.e., had a screening value of 1,000 to 100,000 DNA copies/mL within 7 days prior to the initiation of study drug), but their viral loads decreased to undetectable by the time of their Day 1 visit.

All 14 patients were considered to have achieved confirmed undetectable plasma CMV DNA within 3 and 6 weeks after starting study drug treatment in the primary analysis.

Table 52 Patients with confirmed undetectable plasma CMV DNA ((Central Laboratory) within 3 and 6 weeks (ITT-S population)

| | Maribavir 400 mg BID (N=40) | Maribavir 800 mg BID (N=40) | Maribavir 1200 mg BID (N=39) | Maribavir All Doses (N=119) | Valganciclovir 900 mg BID (N=40) |
|---|---|---|---|---|---|
| **Week 3** | | | | | |
| Subjects with missing data [a], n (%) | 1 (2.5) | 0 | 1 (2.6) | 2 (1.7) | 1 (2.5) |
| Subjects with undetectable plasma CMV DNA, n (%) | | | | | |
| Yes | 26 (65.0) | 23 (57.5) | 23 (59.0) | 72 (60.5) | 22 (55.0) |
| No | 13 (32.5) | 17 (42.5) | 15 (38.5) | 45 (37.8) | 17 (42.5) |
| Treatment effect estimate by group | | | | | |
| Estimated rate [b] | 0.67 | 0.58 | 0.61 | 0.62 | 0.56 |
| 95% CI | (0.50, 0.81) | (0.41, 0.73) | (0.43, 0.76) | (0.52, 0.70) | (0.40, 0.72) |
| Treatment comparison with control [c] | | | | | |
| Odds ratio | 1.79 | 1.20 | 1.27 | 1.42 | |
| 95% CI for the odds ratio | (0.63, 5.08) | (0.44, 3.22) | (0.46, 3.53) | (0.62, 3.24) | |
| p-value | 0.2775 | 0.7218 | 0.6437 | 0.4107 | |
| **Week 6** | | | | | |
| Subjects with missing data [a], n (%) | 1 (2.5) | 0 | 1 (2.6) | 2 (1.7) | 1 (2.5) |
| Subjects with undetectable plasma CMV DNA, n (%) | | | | | |
| Yes | 31 (77.5) | 33 (82.5) | 28 (71.8) | 92 (77.3) | 26 (65.0) |
| No | 8 (20.0) | 7 (17.5) | 10 (25.6) | 25 (21.0) | 13 (32.5) |
| Treatment effect estimate by group | | | | | |
| Estimated rate [b] | 0.79 | 0.83 | 0.74 | 0.79 | 0.67 |
| 95% CI | (0.64, 0.91) | (0.67, 0.93) | (0.57, 0.87) | (0.70, 0.86) | (0.50, 0.81) |
| Treatment comparison with control [c] | | | | | |
| Odds ratio | 2.13 | 2.97 | 1.48 | 2.12 | |
| 95% CI for the odds ratio | (0.72, 6.30) | (0.94, 9.35) | (0.53, 4.16) | (0.91, 4.96) | |
| p-value | 0.1712 | 0.0633 | 0.4528 | 0.0822 | |

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; ITT-S=Intent-to-treat Safety
[a] No plasma CMV DNA measurement post-baseline within the assessment period (i.e., 3 weeks or 6 weeks).
[b] Numerator is the number of "Yes" subjects; denominator is the number of ITT-S subjects with non-missing data.
[c] Logistic regression model for maribavir vs. valganciclovir (SAS PROC LOGISTIC): y = treatment + baseline plasma CMV DNA + transplant type.
Source: Section 14, Table 11.2.1.1

No clear dose-response was seen across the study doses investigated. The proportion of patients with undetectable plasma CMV DNA within 3 weeks after starting study drug treatment was numerically higher in the overall maribavir group than the valganciclovir group: estimate (95% CI), 0.62 (0.52, 0.70) vs. 0.56 (0.40, 0.72); odds ratio, 1.4 (p=0.4107).

Within 6 weeks, the proportion of patients with undetectable plasma CMV DNA was numerically higher in the overall maribavir group than the valganciclovir group: estimate (95% CI), 0.79 (0.70, 0.86) vs. 0.67 (0.50, 0.81); odds ratio, 2.1 (p=0.0822). Among maribavir groups, the proportion of patients with undetectable plasma CMV DNA was numerically highest in the 800 mg BID group (0.83 [0.67, 0.93]) compared with the 400 mg BID (0.79 [0.64, 0.91]) and 1200 mg BID groups (0.74 [0.57, 0.87]).

Secondary efficacy endpoint

One week after starting study drug treatment, the proportion of patients with undetectable plasma CMV DNA was 0.26 (0.18, 0.35) in the overall maribavir group and 0.43 (0.27, 0.59) in the valganciclovir group. At Week 2, the proportion of patients who were undetectable was still numerically lower in the overall maribavir group (0.48 [0.39, 0.57]) than the valganciclovir group (0.53 [0.36, 0.68]).

The proportion of patients with undetectable plasma CMV DNA increased weekly to a maximum plateau at study Week 4 for the 400 mg BID cohort and study Week 5 for the 800 mg BID and 1200 mg BID

cohorts indicating that continued treatment beyond 4-5 weeks did not increase the proportion of responders. If continued treatment was responsible for maintenance of response rate is difficult to interpret considering the high numbers of patients who did have imputed values per LOCF due to discontinuation of the study. Furthermore, LOCF imputation might not be the best option to assess response over time, considering the high number of recurrences observed in CMV patients.

Throughout the follow-up period (post-treatment Weeks 1 to 12), a numerically higher proportion of patients in the overall maribavir group had undetectable plasma CMV DNA compared with the valganciclovir group.

CMV recurrence within the study participation was numerically higher in the overall maribavir group compared to the valganciclovir group estimate (95% CI), 0.22 (0.15, 0.32) vs. 0.18 (0.06, 0.37); odds ratio, 1.3 (p=0.6843).

A dose-related trend was observed among maribavir groups, as the proportion of patients with recurrence was 0.30 (0.16, 0.49), 0.24 (0.11, 0.41), and 0.13 (0.04, 0.30) in the 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively. This indicates that maintenance of response after treatment cessation is lower in patients treated with maribavir 400 mg BID compared to higher doses and valganciclovir.

Table 53 Analysis of CMV recurrence within the study participation period (ITT-S population)

| | Maribavir 400 mg BID (N=40) | Maribavir 800 mg BID (N=40) | Maribavir 1200 mg BID (N=39) | Maribavir All Doses (N=119) | Valganciclovir 900 mg BID (N=40) |
|---|---|---|---|---|---|
| Subjects achieving confirmed undetectable CMV DNA (central lab) [a] | 33 | 34 | 31 | 98 | 28 |
| Subjects with CMV recurrence (central lab) | | | | | |
| Yes [b] | 10 (25.0) | 8 (20.0) | 4 (10.3) | 22 (18.5) | 5 (12.5) |
| No [c] | 23 (57.5) | 26 (65.0) | 26 (66.7) | 75 (63.0) | 23 (57.5) |
| Treatment effect estimate by group | | | | | |
| Estimated rate [d] | 0.30 | 0.24 | 0.13 | 0.22 | 0.18 |
| 95% CI | (0.16, 0.49) | (0.11, 0.41) | (0.04, 0.30) | (0.15, 0.32) | (0.06, 0.37) |
| Treatment comparison with control [e] | | | | | |
| Odds ratio | 1.9 | 1.3 | 0.6 | 1.3 | |
| 95% CI for the odds ratio | (0.52, 6.80) | (0.33, 4.77) | (0.14, 2.77) | (0.41, 3.86) | |
| p-value | 0.3349 | 0.7346 | 0.5301 | 0.6843 | |

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; ITT-S=Intent-to-treat Safety

[a] Subjects with at least 2 consecutive undetectable results separated by at least 5 days, including early withdrawn qualified subjects.

[b] Any recurrence during the study, including early withdrawn subjects who had recurrence before withdrawal from study.

[c] Did not have recurrence during the study and had data after confirmation, including early withdrawn subjects who did not have recurrence before withdrawal from study.

[d] Numerator is number of subjects with recurrence; denominator is number of subjects with confirmed undetectable CMV DNA.

[e] Logistic regression model for maribavir vs. valganciclovir (SAS PROC LOGISTIC): y = treatment + baseline plasma CMV DNA + transplant type.

Source: Section 14, Table 11.2.10.3

Median observed time from confirmed undetectable plasma CMV DNA to CMV recurrence was numerically shorter in the overall maribavir group (72 days) than the valganciclovir group (80 days).

Among maribavir groups, median time from confirmed undetectable plasma CMV DNA to CMV recurrence was numerically longest in the 1200 mg BID group (84 days), followed by the 400 mg BID group (72 days) and the 800 mg BID group (43 days).

Recurrence on treatment (6%) and off treatment (24%) were highest in the 400 mg BID group compared to the 800 mg BID an (6% and 18%) 1200 mg BID group (0% and 13%). Notably, none of the patients in the valganciclovir experienced CMV recurrence while on study drug, while 18% had CMV recurrence off treatment.

Median observed time from last dose of study drug to CMV recurrence was numerically longer in the overall maribavir group (28 days) than the valganciclovir group (23 days). Among maribavir groups,

median time from last dose of study drug to CMV recurrence was numerically longer in the 400 mg BID (28 days) and 1200 mg BID groups (28 days) compared with the 800 mg BID group (8 days).

Patients with recurrence discontinued maribavir due to lack of efficacy and had developed treatment emergent UL97 T409M (known to confer resistance to maribavir). UL27 RAS Q424H was also detected in one patient. Both were not present at baseline.

The proportion of patients who used non-study anti-CMV therapies within 6 weeks was numerically lower in the overall maribavir group than the valganciclovir group: estimate (95% CI), 0.15 (0.09, 0.23) vs. 0.20 (0.09, 0.36); odds ratio, 0.7 (p=0.3920). Among maribavir groups, the proportion of patients who used non-study anti-CMV therapies was numerically lowest in the 800 mg BID group (0.10 [0.03, 0.24]) compared with the 400 mg BID (0.18 [0.07, 0.33]) and 1200 mg BID groups (0.18 [0.08, 0.34]).

The Kaplan-Meier estimate for time to confirmed undetectable plasma CMV DNA within 6 weeks was numerically longer in the overall maribavir group than the valganciclovir group: median (95% CI), 21 days (15 days, 22 days) vs. 17 days (8 days, 25 days); hazard ratio, 1.2 (p=0.4979). Among maribavir groups, the estimated time to confirmed undetectable plasma CMV DNA was numerically shortest in the 400 mg BID group (15 days [15 days, 22 days]), followed by the 1200 mg BID group (21 days [14 days, 22 days]) and the 800 mg BID group (22 days [16 days, 29 days]).

Descriptive subgroup analysis for the primary endpoint and CMV recurrence were provided. Due to the small number of patients in many of the subgroups, meaningful comparisons of the overall maribavir and valganciclovir groups could not be made.

Virology

Genotypic analyses of CMV were performed for all patients at baseline, for non-responder (not achieve undetectable plasma CMV DNA within 6 weeks after study start) for responders who experienced CMV recurrence during or after maribavir treatment and also for responder patients (if possible).

Treatment-emergent UL97 mutation T409M developed fast and frequently in maribavir treated patients and was associated with virological failure. T409M mutations are known to be associated with high-level resistance to maribavir and provided data indicate that they might also confer cross-resistance to valganciclovir. Notably, the presence of treatment-emergent T409M mutation was only detected in those specimens collected from patients who received maribavir at 400 mg or 800 mg BID. It remains unclear whether suboptimal concentrations of maribavir after 400 mg BID might have contributed to the fast development of resistance associated mutations.

A few UL27 gene mutations were described for non-responders or responders with recurrence; however, there appeared to be several of these mutations described for CMV isolated from complete responders (ie. no recurrence) at screening so the clinical relevance remains currently unknown.

Based on the provided resistance data, it seems that T409M RAS develops fast under maribavir treatment and is associated with virological failure, indicating a low barrier of resistance. Doses of 1200 mg BID did not result in treatment emergent development of resistance and seem to yield higher efficacious concentrations than 400 mg BID and 800 mg BID.

## 2.6.6. Discussion on clinical efficacy

The demonstration of the efficacy and safety data for maribavir, rests on one pivotal Phase 3 study (SHP-620-303) and the two supportive Phase 2 studies SHP620-202 and SHP620-203. However, these supportive studies were conducted in two different patient populations with two different formulations

of maribavir than study 303 and study 202 lacks a control arm, thus can only consider supportive of the antiviral activity.

**Dose selection**

The applied posology (400 mg BID) using the to-be-marketed formulation was only studied in the Phase 3 study and has undergone changes in manufacturing since then (please refer to the Q AR). The dose was selected based on in vitro antiviral efficacy data, clinical PK data and modelling of the E-R relationships. However, the Pop PK model is currently not considered adequate to provide ancillary support of the applied dose. Furthermore, the PK data indicate that through exposure after 400 mg maribavir BID dosing is very close to the target minimum effective concentration (please refer to the PD section of this report for details). This may impact the durability of response and facilitate the development of resistance. However, due to the flat dose-response in this exposure interval, higher doses of maribavir are not considered to result in better response rates. Nevertheless, the exposure from the 400 mg BID regimen should be considered on the lower level of the therapeutic index.

***Design and conduct of clinical studies***

**Study SHP 620-303**

The SHP 620-303 study was a multi-centre, randomised, open-label, active-controlled study to assess the efficacy and safety of maribavir compared to investigator-assigned treatment (IAT) in Haematopoetic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients with CMV infections that were refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, including CMV infections with confirmed resistance to 1 or more anti-CMV agents. The primary endpoint was CMV viraemia clearance at the end of study week eight, regardless of whether study-assigned treatment was discontinued before the end of stipulated 8 weeks of therapy. The analysis population included 352 patients (maribavir: 235 patients; IAT: 117 patients).

CMV DNA viraemia clearance as primary endpoint is a valid endpoint. Confirmed clearance of CMV viraemia is an objective and validated surrogate marker. CMV viraemia has been shown to predict development of CMV disease in transplant recipients as well as mortality, has been used in clinical trials and is recommended by international CMV treatment guidelines and is therefore considered acceptable.

The chosen active control arm including anti-CMV drugs ganciclovir, valganciclovir and foscarnet, are empirically used to treat CMV infection and are considered acceptable as active comparator due to ethical reasons.

In assigning a patient to a specific IAT in the IAT group, the investigator was to use all available information to assign the best available therapy for a given patient resulting in a greater heterogeneity of patients in the IAT arm compared to the maribavir arm. As a consequence, a patient in the IAT could not be refractory to their assigned therapy (a requirement for enrolment in study 303) and may or may not have received treatment with a drug to which their CMV was resistant based on the clinical judgment of the investigator. Apparently, no "management algorithm for CMV patients with suspected drug resistance" as recommended by current CMV-guidelines was in place and documentation of the investigator's clinical rational for choosing the IAT is not informative**.**

In total, 23 % of the enrolled study population did not have central laboratory confirmed CMV DNA ≥910 IU/mL and 6 % did not have refractory disease, hence did not meet inclusion criteria for study enrolment.

A triggered GCP inspection for the clinical study SHP620-303 was conducted and showed that the design, outcomes and data presentation of the study are prone to serious criticism. The final integrated GCP report of the sponsor inspection and two clinical sites in Belgium and Germany were recently shared with EMA. At the sponsor site one critical, 12 major and three minor findings were reported. The GCP inspectors stated that the presentation of trial results in the CSR is misleading, as delineation of the different contributing factors to the composite endpoint failed. Major inconsistencies of the presented failure data between the CSR, resistance report and response document and compared to those analysed during the GCP inspection and given in the publicity available FDA errata list were identified, which may impact the data quality. The GCP inspectors highlighted that the presentation of trial results should not be used for assessment without additional information. By clearly distinguishing between potency and tolerability, the trial medication can be assessed appropriately.

Based on the findings of the GCP inspection, the internal validity of study data has been impacted by the lack of sufficient control of bias. Potential bias has been introduced in the statistical analysis by post randomisation changes, major inconsistency of the presented failure data, and the lack of sufficient measures to avoid and control for such bias. Further, the comparator IAT was defined as non-IMP, thus patients would have to co-pay the treatment in some countries like the US. These issues could have negatively impacted the results in the investigator-assigned therapy (IAT) arm and explain the high rate of failures other than lack of virological clearance in the IAT arm. However, overall the data were deemed sufficiently reliable for regulatory decision-making.

**Study SHP 620-202**

The study SHP 620-202 was a phase 2, randomised study to assess the safety and anti-cytomegalovirus (CMV) activity of different doses of maribavir for the treatment of CMV infections that are resistant or refractory to treatment with ganciclovir/valganciclovir or foscarnet in transplant recipients. The primary endpoint was the proportion of patients with confirmed undetectable plasma CMV DNA (central laboratory) within 6 weeks. Patients must have achieved at least a minimum virologic response at Weeks 3 and 6 for continuation of study drug treatment beyond each of these time points. For patients who continued dosing after the Week 6 visit, dosing could continue at the discretion of the investigator through a maximum of 24 weeks. The analysis population included 120 patients (400 mg BID: 40 patients; 800 mg BID: 40 patients 1200 mg BID: 40 patients).

The enrolled study population was similar to the population enrolled in study 303 and the proposed target population of maribavir. However, this was a dose-ranging trial without a control arm. Hence, interpretation of the efficacy results should be done with caution, due to the lack of an adequate control arm, i.e. in the absence of a dose-response relation, this study does not isolate drug effects. The conclusion of this study, however, is that higher doses than the labelled one, are not anticipated to increase antiviral activity or the barrier to resistance.

**Study SHP 620-203**

Study 203 was a Phase 2, multi-centre, randomised, parallel-group, dose ranging study to assess the safety and anti CMV activity of 400 mg, 800 mg and 1200 mg twice daily maribavir versus valganciclovir for up to 12 weeks for the treatment of 159 SOT or HSCT recipients with CMV infection without CMV organ disease or resistant/refractory CMV infection.

The primary efficacy endpoint was confirmed undetectable plasma CMV DNA (central laboratory) within 3 weeks and confirmed undetectable plasma CMV DNA (central laboratory) within 6 weeks. Patients must have achieved at least a minimum virologic response at Weeks 3 and 6 for continuation of study drug treatment beyond each of these time points. For patients who continued dosing after the Week 6 visit, dosing could continue at the discretion of the investigator through a maximum of 12 weeks. The

analysis population included 159 patients (400 mg BID: 40 patients; 800 mg BID: 40 patients, 1200 mg BID: 39 patients and valganciclovir: 40 patients).

Importantly, because study 203 excluded patients with known CMV organ disease and genotypic resistance, the study population was different from the study population in study 303. This study is considered explorative, but supports that maribavir exhibits antiviral activity against CMV.

The formulation used in study 202 and 203 (formulation III) is not identical to the formulation used in the pivotal phase 3 study 303 (formulation IV). In order to show that the differences in the dissolution profiles between the relevant pivotal clinical batches and the commercial batches of the drug product have no clinical relevance a comparison of the results of the food effect study TAK-620-1025 (batch PPQ 4559589) in the fasted state with the results of studies TAK-620-1019 (batch XXVG) and SHP620-115 (batch STDH) was performed. The GMRs for AUC - which is the relevant PK parameter for efficacy - are within the bioequivalence interval of 0.8 to 1.25 indicating that the commercial batch and the batches used during clinical development are comparable.

***Efficacy data and additional analyses***

**SHP620-303**

The definition of refractory used in study 303, i.e. documented failure to achieve ⩾1 log10 decrease in CMV DNA levels after 14 days or longer treatment, is not in line with current clinical treatment guidelines. This definition rather reflects the definition for "probable refractory CMV infection" (Chenaly et al., 2019). The current definition of refractory CMV infection is "CMV viraemia that increases (i.e. ⩾ 1 log increase in CMV DNA levels) after at least 14 days of appropriately dosed antiviral therapy". Furthermore, patients with persistent CMV DNA titres <1000 IU/mL and particular detected but not quantifiable (<137 IU/mL) should not be considered refractory.

The Applicant was asked to clarify how many of the enrolled patients met the following definition of refractory: "CMV viraemia that increases (i.e. ⩾ 1 log increase in CMV DNA levels) after at least 14 days of appropriately dosed antiviral therapy. No information could be given on how many of the enrolled patients met the currently guideline conform definition of refractory, as the viral load data collected prior to screening to determine eligibility (Inclusion Criterion#4) was not collected in the database. Hence, verification of the refractory status of patients enrolled in study 303 is not possible. Furthermore, the study definition of refractory allowed a wide interpretability, the duration of the treatment for the determination of refractory CMV were in part clearly undercut and no specified reference value to document "refractory CMV" was given. It is of note, that the analysed protocol defined population (refractory/resistant) includes participants who do not meet the study definition of refractory/resistant. Due to the lack of documentation of relevant data for defining the "refractory" status and lack of adherence to the study 303 definition of „refractory", it is not possible to verify how many of the patients were "refractory".

The analyses for the primary endpoint showed that the proportion of patients achieving confirmed CMV viraemia clearance at week 8 was higher in the MBV group compared to the IAT group (56% compared to 24%, adjusted difference in proportion of responders: 32.8 % (95%CI: 22.80, 42.74, p=<0.001). Efficacy results for the key secondary endpoint demonstrated that more patients in the maribavir achieved CMV viraemia clearance and CMV infection symptom control at Week 8, with maintenance of this treatment effect through Week 16 compared with patients in the IAT group (19% vs 10%, respectively). The adjusted treatment difference (95% CI) in proportion of responders between the treatment groups was 9.5 (2.02, 16.88), p=0.013.

Concerns regarding potential bias and overestimation were addressed by sensitivity analyses with varying levels of conservativeness, which are in general consistent with the primary analysis. The following may be considered the key sensitivity analyses with respect to the robustness of the efficacy demonstration:

A) Subjects who discontinued prematurely without alternative anti-CMV or maribavir rescue are included as responders if they meet the criteria for confirmed viraemia clearance criteria at the time of discontinuation based on their last available CMV DNA before Week 8.

B) Subjects who either switched to alternative anti-CMV or maribavir rescue or prematurely discontinued with missing data were included as responders if they met the criteria for of confirmed viraemia clearance at time of their treatment switch or at the time of premature discontinuation based on their last available CMV DNA before Week 8.

C) Subjects with confirmed viraemia clearance at the end of study-assigned treatment discontinuation were counted as responders.

All of these analyses show statistically significant superiority for Livtencity.

A very conservative analysis was performed in which subjects with confirmed viraemia clearance at Week 8 regardless of switch to alternative anti-CMV treatment or to maribavir rescue treatment were counted as responders, and subjects who prematurely discontinued from the study or had other reasons for missing data before Week 8 were counted as responders if they met the criteria for confirmed viraemia clearance criteria based on the last available CMV DNA values before Week 8. This shows numerical superiority of Livtencity to its comparator.

Data indicate that the superiority of maribavir to IAT in study 303 is mainly driven by the intolerability of the IAT options. In order to evaluate the potential impact of the differential treatment discontinuation or switch and the change in primary endpoint, a set of sensitivity analyses for the primary and key secondary endpoints was requested. To get more relevant result in terms of a treatment policy estimand, an analysis was requested that uses all available CMV values and imputes the remaining missing values. The provided sensitivity analyses shown that the statistical superiority of maribavir disappears when the actually measured CMV DNA values are used (irrespective of the different intercurrent events) and remaining missing data are imputed using different imputation models.

All analyses were to be provided with and without patients who did not have CMV viral load >910 IU/mL per central lab at the time of randomisation (N=82), patients who were not refractory at baseline (N=21) and should include the six patients in the IAT arm as responders that were assigned to the maribavir rescue arm without meeting the eligibility criteria. Exclusion of these patients from the analyses highlight that responses seen in study 303 may have been influenced by inclusion of patients that did not meet inclusion criteria, as the statistical evidence is further reduced.

However, apparently, CMV values after treatment switch were set to missing despite a large number of participants with measured CMV values after treatment switch. This is of major importance as any post baseline treatment change may have been influenced by the open treatment group assignment.

Notably, the study protocol underwent six amendments including substantial changes of the definition of the primary and key secondary endpoint during the conduct of the study. The initial version of the SAP was finalised on 30 May 2018, i.e. more than 17 months after the first patient was enrolled. Three amendments were generated after that date. Finalisation of the SAP just before database lock at the end of an open-label study, where results are obtained during the study may influence the analysis and, hence, compromise proper type-1 error control. However, as only one patient was enrolled at the time of Amendment 3, it can be concluded that the change of the primary and secondary endpoint and

analysis was not done in in knowledge of any intermediate study outcome. Nevertheless, in the absence of measures to avoid or minimise bias, it cannot be excluded that due to post-randomisation changes significant bias to the statistical analysis was introduced that may have led to a potential structural disadvantage for the IAT arm. This was also highlighted during the GCP inspection. Overall, however, data are sufficiently robust for decision-making.

Concerning the key secondary endpoint, all patients who achieved CMV viraemia clearance at week 8 also had CMV infection symptom control at week 8 (maribavir: 131 patients, IAT 28 patients). More patients in the maribavir achieved CMV viraemia clearance and CMV infection symptom control at Week 8, with maintenance of this treatment effect through Week 16 compared with patients in the IAT group (19% vs 10%, respectively). The adjusted treatment difference (95% CI) in proportion of responders between the treatment groups was 9.5 (2.02, 16.88), p=0.013.

The clinical judgement of CMV symptom control was categorised by the investigator and verified by an EAC after the study completion and therefore the analysis was prone to bias considering the open label of the study. In addition, the definition of symptomatic CMV infection was changed late during the open-label study to include both tissue-invasive CMV disease and CMV syndrome.

The CMV symptom status relative to baseline in symptomatic patients (i.e., resolution, improvement, no change, or worsening) and the emergence of new CMV disease during the study (in previously asymptomatic patients or patients with ongoing CMV disease) was confirmed by an independent and blinded EAC. Only a small number of patients (N=29) had EAC confirmed CMV symptomatic disease. Imbalances concerning the distribution of patients with EAC confirmed symptomatic infection across treatment arms (IAT: 8 patients (6.8%), maribavir: 21 (8.9 %). In the maribavir group, 10/21 (47.6%) patients with CMV syndrome/disease at baseline per the EAC achieved CMV viraemia clearance at Week 8 compared with 1/8 (12.5%) patients in the IAT group.

The EAC confirmed 22 cases of new onset symptomatic CMV infection in 21 patients (maribavir: 14 [6.0%) patients; IAT: 7 [6.0%] patients). All patients with new onset symptomatic CMV infection at Week 8 (MBV: 7 patients, IAT: 5 patients) were non-responders for the primary endpoint. Interestingly, more patients who were primary responders had new onset symptomatic CMV infection, 5/14 maribavir-treated patients compared to none in the IAT treated patients. Hence, it seems that recurrence of CMV disease after cessation of therapy is more common in patients treated with maribavir. This would be in line with the data and sensitivity analysis related to the key secondary endpoint, indicating that sustainability of viraemia clearance and symptom control is not substantial with maribavir treatment, compatible with a low barrier to resistance.

This is further illustrated by the fact that recurrence of CMV viraemia during study 303 was seen in 57% of the maribavir treated patients and in 34% of the IAT treated patients. Of these, 18% in the maribavir group had recurrence of CMV viraemia while on-treatment compared to 12% in the IAT group. Recurrence of CMV viraemia during follow up was seen in 39% of patients in the maribavir group and in 22% of the patients in the IAT group.

No effect of maribavir on mortality was seen. A similar percentage of patients in each treatment group died during the study (maribavir: 27 [11.5%] patients; IAT: 13 [11.1%] patients). Median time to death was shorted in the maribavir compared to the IAT group.

Subgroup analyses for the primary and key secondary endpoint were not powered to demonstrate statistical significance; hence interpretation of the data should be done with caution.

According to the study protocol, central lab testing was not required for randomisation and local testing was sufficient. However, based on central lab results 82 patients were included in the study although they did not meet the inclusion criteria of >910 IU/mL. It is of note that the central lab (COBAS) assay used in study 303 for CMV viral load determination was consistently 0.5 log less sensitive than local

laboratory results. In addition, the COBAS assay was the less sensitive assay on the market, which was already known at the time of study initiation (Preiksaitiset al, 2016 Clinical Infectious Disease). A sensitivity analysis of the primary efficacy endpoint excluding those 82 patients who failed to achieve >910 IU/mL on both the central and the local lab testing, was provided, which still showed superiority of maribavir, although reduced.

Subgroup analyses by transplant type (HCST or SOT) indicate no difference concerning efficacy.

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Subgroup analyses by transplant type (HCST or SOT) indicate no difference concerning efficacy.

**Clinical virology**

Genotypic sequencing was performed for study patient samples with CMV DNA viral load at and above the predefined cut-off level of 500 copies/mL (455 IU/mL) at protocol defined time points at baseline, during the treatment phase, during the study follow-up phase, and at the end of the study. Patients with at least one known resistance-associated amino acid substitution (RAS) to IAT in pUL97 and/or pUL54 identified at baseline were included in the primary resistance set (PRS), while patients without identified baseline IAT RASs were designated to the non-PRS set ("refractory"). Similarily, all patients with at least one known RAS to maribavir in pUL97 and/or pUL27 at baseline were included in the maribavir resistance set (MRS), while patients without identified baseline maribavir RASs were designated non-MRS.

Despite attempts to genotype all patient samples at baseline, some baseline samples could not be genotyped. Bassline genotypic results for PRS were available for 89% of the patients in the IAT arm and for 93% in the maribavir arm. Baseline genotypic results for MRS were available for 86% in the IAT arm and 92% in the maribavir arm.

Baseline imbalances were noted between the treatment arms. More patients in the IAT arm (60%) had baseline resistance to at least one IAT, compared to patients in the maribavir arm (52%). Consequently, more patients in the maribavir arm (41%) had no baseline resistance to IAT compared to patients in the IAT arm (29%).

In the virus of four patients baseline RAS known to confer resistance to maribavir were identified (IAT: 3 patients, MBV group: 1 patient).

**Primary resistance set (PRS) outcome:**

More than half of the patients (57%) identified as having one or more baseline RASs known to confer resistance to ganciclovir/valganciclovir received ganciclovir/valganciclovir as the IAT.

Most patients had CMV encoding IAT RAS at baseline. More patients in the IAT group had virus encoding for baseline IAT RAS in pUL97 (75% vs. 72%), IAT RAS to pUL54 (6% vs. 7%) and in both pUL97 and pUL54 (19% vs. 22%) compared to patients in the maribavir arm.

The most common single baseline IAT RASs identified in pUL97 in the IAT group were **A594V**, **L595S** , **C603W, F342Y**, **M460I**, **M460V**, **C592G**, **H520Q** and **L595F**. Most of this RAS are known to confer a high-level of resistance to ganciclovir/valganciclovir. The **F342Y** RAS has been reported to cause increases in $EC_{50}$ for both GCV (6.0-fold) and maribavir (4.5-fold).

The most common single baseline IAT RASs detected in pUL97 in the maribavir group were **L595S**, **A594V**, **C603W, M460I**, **M460V**, **C592G**, **A594P**, **A594T**, **H520Q**, and **L595F**. Most of this RAS are known to confer a high level of resistance to ganciclovir/valganciclovir. With respect to multiple IAT RASs, the double pUL97 **A594V+L595S** RAS was detected with the highest frequency. Individually, both of these IAT RASs are associated with GCV resistance.

Results of the maribavir rescue arm indicate that response in patients who switch to maribavir was limited and not sustained. Furthermore, development of treatment emergent RAS to maribavir was seen in many patients.

Post-baseline treatment emergent RAS to IAT was more frequently observed in the maribavir group (13%) compared to the IAT group (5%). This effect was consistent for RAS to IAT in the pUL97 (maribavir: 9% and IAT: 3%). This is cause of concern, as it suggests that maribavir not only selects for RAS to maribavir but also for IAT RAS with a potential to confer cross-resistance. Considering that treatment-emergent RAS under IAT were less commonly selected than with maribavir, maribavir seems to have a lower barrier to resistance development to IAT than IATs themselves.

Overall, 44/235 patients (19%) in the maribavir arm had treatment emergent RAS to IAT. Of these 28 patients (55%) had C480F or the F342Y RAS, both of which are cross-resistant to both ganciclovir/valganciclovir and maribavir. Notably, only 8/44 (18%) patients with treatment emergent RAS to IAT achieved the primary endpoint. At present it remains unclear, if the 24 patients with treatment emergent C480F or the F342Y RAS, both of which are cross-resistant to both ganciclovir/valganciclovir and maribavir did or did not achieve the primary endpoint.

Important identified treatment-emergent IAT RAS in the maribavir group were: C480F and F342Y, both confer high-level resistance to maribavir but also confer resistance to ganciclovir/valganciclovir and A594V, C603W, L595F/S all confer high-level resistance to ganciclovir.

Furthermore, IAT RAS in pUL54 were detected more frequently in the maribavir group (N=8) compared to the IAT group (N=1). While all treatment-emergent RAS in pUL54 only account for one patient each, they do confer cross resistance to either foscarnet (S290R, V715M), cidofovir and ganciclovir (N408D, T503I, K513N and A789G) or to all of them (L773V).

These findings indicate that maribavir treatment may select for RAS conferring potential cross-resistance to IAT.

**Maribavir resistance set (MRS) outcome:**

Baseline resistance to maribavir was uncommon. With the exception of one pUL27 RAS (**L193R**) in the maribavir group, all other mutations were detected in the pUL97 region. pUL97 **F342YF** maribavir RAS was the only RAS detected in the IAT group, which was also detected at baseline in the one patient in the maribavir rescue arm.

None of the patients with CMV encoding baseline RAS to maribavir did respond to treatment. Results of the patients in the IAT group indicate that pUL97 **F342Y** RAS confers cross-resistance to IAT, as no response was seen among the three patients. Furthermore, **F342Y** at baseline was associated with non-response in the one patient in the maribavir rescue arm.

No response was seen in the one patient in maribavir group who had CMV with baseline pUL27 **L193F** maribavir RAS. The clinical relevance of pUL27 **L193F** remains unclear.

Treatment emergent RAS to maribavir were only observed in maribavir treated patients, i.e. 60/214 (29%). Of these 21% had RAS to maribavir detected on–treatment, while 8% were found to have maribavir RAS after treatment cessation. Of the 42 patients in the maribavir-randomised analysis group who developed post-baseline maribavir RASs, 41/42 patients (98%) did not achieve the primary endpoint, while one patient did. Of these 42 patients, 18/42 patients (43%) were virologic non-responders (did not achieve viraemia clearance at any time point during the study) and 24/42 patients (57%) were virologic responders. Of these 24 virologic responders, 21/24 patients (88%) had recurrence on or off treatment.

All treatment-emergent RAS to maribavir were identified in pUL97, indicating that this is the major region responsible for conferring resistance to maribavir. The most frequently detected post-bassline RAS to maribavir on treatment were T409M, C480F, H411Y, H411N and F342Y. Mutations F342Y and C480Fare also known to confer resistance to ganciclovir. In addition, several multiple RAS to maribavir were detected, the most common were T409M+C480F and T409M+H411Y. The impact on maribavir and ganciclovir/valganciclovir $EC_{50}$s of these multiple RAS is currently unclear.

Off treatment, the most frequently detected maribavir RAS was H411Y, C480F and T409M.

These data indicate that maribavir has a low barrier to resistance, as resistance development occurred fast during treatment and also after treatment cessation. Development of multiple RAS was seen frequently on treatment. The clinical impact of double mutations remain unclear but it is anticipated that they are associated with non-response. Therefore, this information is reflected in the SmPC.

**Study SHP620-202**

Data do not indicate a dose-response effect across the three doses tested. Within six weeks, 70% of the patients in the 400 mg BID group, 63% in the 800 mg group and 68% in the 1200 mg BID maribavir group had undetectable CMV DNA. It is of note, that the nine patients in the ITT-S who had undetectable plasma CMV DNA at baseline (i.e., prior to starting study drug treatment on Day 1) were counted as responders in the primary efficacy analysis.

Data over time indicate that the proportion of patients with undetectable plasma CMV DNA increased weekly to a maximum plateau at study Week 4 for the 400 mg BID cohort and study Week 5 for the 800 mg BID and 1200 mg BID cohorts and did not increase thereafter. These results indicate that continued beyond 6 weeks did not result in an increase of responders.

No statistically significant difference was seen in terms of CMV recurrence. A numerically lower proportion of patients in the 400 mg BID maribavir group (estimated rate [95% CI]: 0.24 [0.10, 0.44]) had CMV recurrence compared to the 800 mg BID (0.41 [0.22, 0.61]) and 1200 mg BID (0.40 [0.23, 0.59]) groups.

Time to undetectable CMV DNA within six weeks was numerically shorter in the 1200 mg BID group, compared to the 400 mg BID and 800 mg BID group. Time from undetectable CMV DNA to CMV recurrence was numerically shorter in the 400 mg BID group (36 days) and the 800 mg BID group (36 days) compared to the 1200 mg BID group (82 days). Recurrence occurred predominantly on study drug and were associated with treatment-emergent UL97 RAS.

Notably, the response rate in patients with baseline presence of > 1 CMV genetic RAS associated with resistance to ganciclovir/valganciclovir or foscarnet was 64% in the 400 mg BID and 61% for the overall maribavir group. It is of note that response rates in patients with resistance (202: 64% vs. 303: 44%) and in patients without resistance (202: 78% vs. 303: 63%) were generally higher than in study 303.

**Study SHP620-203**

Efficacy data of study 203 do not indicate a dose-response effect between the three doses tested. The proportion of patients with undetectable plasma CMV DNA within 3 weeks was numerically higher in the overall maribavir group than the valganciclovir group: estimate (95% CI), 0.62 (0.52, 0.70) vs. 0.56 (0.40, 0.72); odds ratio, 1.4 (p=0.4107), however no statistically significant effect was seen. Among maribavir groups, the proportion of patients with undetectable plasma CMV DNA was numerically highest in the 400 mg BID group (0.67 [0.50, 0.81]) compared with the 800 mg BID (0.58 [0.41, 0.73]) and 1200 mg BID groups (0.61 [0.43, 0.76]). A similar trend was observed within 6 weeks.

## 2.6.7. Conclusions on the clinical efficacy

This application is based on the pivotal trial -303. This has demonstrated the efficacy of maribavir in the target population. However, due to a low barrier to resistance, the durability of response may be limited.

## 2.6.8. Clinical safety

The clinical safety database includes data from two Phase 2 and one Phase 3 studies of maribavir as a CMV treatment in transplant recipients, three Phase 2 and 3 studies of maribavir for CMV prevention in transplant recipients, 17 Phase 1 studies, and 1 taste assessment study.

The focus of the safety data provided is placed on pivotal Study 303, which provides the safety experience most relevant to the target population. Data from Phase 2 and Phase 1 studies were not integrated into safety analysis due to the differences in patient populations and/or study designs as well as differences in dosages and treatment duration across the studies. Studies 202 and 203 are considered supportive of the target indication.

### *2.6.8.1. Patient exposure*

A total of 1,555 patients have been exposed to maribavir across a broad range of doses (50 mg to 2400 mg daily) and a range of treatment durations (single dose up to 24 weeks) in 23 completed clinical studies. This total includes:

- 495 transplant recipients with CMV infection treated with maribavir 400 mg BID to 1200 mg BID (800 mg/day to 2400 mg /day) for 8 weeks to 24 weeks (Phase 3 study 303 for 8 weeks, Phase 2 study 202 for up to 24 weeks, Phase 2 study 203 for up to 12 weeks).
- 680 patients in three Phase 2 and 3 CMV prevention studies in transplant recipients who received maribavir doses of 100 mg BID, 400 mg QD, or 400 mg BID (200 mg/day to 800 mg/day) for 12 weeks to 24 weeks
- 380 patients in Phase 1 studies

### *2.6.8.2. Adverse events*

**Overview of adverse events**

**Phase 3 study 303**

Patients in the maribavir group were exposed to study-assigned treatment for approximately 50% longer than patients in the IAT group: mean (SD) exposure of 52.5 (11.81) days in the maribavir group and 36.0 (18.06) days in the IAT group based on the number of days between first and last exposure to study-assigned treatment. Exposure based on the number of days actually exposed to study-assigned treatment was 50% longer for maribavir than for IAT: mean (SD) exposure of 48.6 (13.82) days in the maribavir group and 31.2 (16.91) days in the IAT group. This difference in exposure should be considered when comparing the incidence of AEs in the 2 treatment groups.

In the following table an overview of treatment-emergent adverse events during the on-treatment observation period by treatment group is given.

Table 54 Overall treatment-emergent adverse events during the on-treatment observation period by treatment group and IAT type (safety set)

| Category | IAT (N=116) n (%) m | Maribavir 400 mg BID (N=234) n (%) m | IAT Type | | | |
|---|---|---|---|---|---|---|
| | | | Ganciclovir/ Valganciclovir (N=56) | Foscarnet (N=47) | Cidofovir (N=6) | >1 IAT (N=7) |
| Any TEAE | 106 (91.4) 712 | 228 (97.4) 1648 | 51 (91.1) 273 | 43 (91.5) 371 | 5 (83.3) 26 | 7 (100.0) 42 |
| Any treatment-related TEAE | 57 (49.1) 176 | 141 (60.3) 270 | 23 (41.1) 49 | 29 (61.7) 116 | 2 (33.3) 6 | 3 (42.9) 5 |
| Any TESAE | 43 (37.1) 61 | 90 (38.5) 154 | 21 (37.5) 27 | 20 (42.6) 31 | 2 (33.3) 3 | 0 |
| Any treatment-related TESAE | 17 (14.7) 19 | 12 (5.1) 16 | 7 (12.5) 7 | 9 (19.1) 10 | 1 (16.7) 2 | 0 |
| Any severe TEAE | 44 (37.9) 86 | 75 (32.1) 140 | 22 (39.3) 53 | 19 (40.4) 28 | 2 (33.3) 4 | 1 (14.3) 1 |
| Any treatment-related severe TEAE | 24 (20.7) 36 | 9 (3.8) 17 | 15 (26.8) 25 | 8 (17.0) 10 | 1 (16.7) 1 | 0 |
| Any TEAE leading to discontinuation of study-assigned treatment | 37 (31.9) 51 | 31 (13.2) 39 | 18 (32.1) 28 | 17 (36.2) 20 | 2 (33.3) 3 | 0 |
| Any treatment-related TEAE leading to discontinuation of study-assigned treatment | 27 (23.3) 41 | 11 (4.7) 17 | 15 (26.8) 25 | 11 (23.4) 14 | 1 (16.7) 2 | 0 |
| Any TESAE leading to discontinuation of study-assigned treatment | 17 (14.7) 17 | 20 (8.5) 24 | 6 (10.7) 6 | 10 (21.3) 10 | 1 (16.7) 1 | 0 |
| Any treatment-related TESAE leading to discontinuation of study-assigned treatment | 9 (7.8) 9 | 5 (2.1) 8 | 3 (5.4) 3 | 6 (12.8) 6 | 0 | 0 |
| Any TEAE leading to study discontinuation | 9 (7.8) 10 | 17 (7.3) 18 | 4 (7.1) 5 | 5 (10.6) 5 | 0 | 0 |
| Any treatment-related TEAE leading to study discontinuation | 2 (1.7) 3 | 3 (1.3) 3 | 2 (3.6) 3 | 0 | 0 | 0 |
| Any TESAE leading to death | 6 (5.2) 6 | 16 (6.8) 16 | 2 (3.6) 2 | 4 (8.5) 4 | 0 | 0 |
| Any treatment-related TESAE leading to death | 1 (0.9) 1 | 1 (0.4) 1 | 1 (1.8) 1 | 0 | 0 | 0 |
| Any TEAE of special interest | 74 (63.8) 172 | 187 (79.9) 488 | 39 (69.6) 78 | 29 (61.7) 79 | 2 (33.3) 6 | 4 (57.1) 9 |
| Any treatment-related TEAE of special interest | 34 (29.3) 53 | 127 (54.3) 192 | 20 (35.7) 27 | 12 (25.5) 22 | 1 (16.7) 3 | 1 (14.3) 1 |

AESI=adverse event of special interest; BID=twice daily; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event; N=number of subjects; n=number of subjects experiencing the event; m=number of events

Percentages were based on the number of subjects in the safety set within each column. A continuing non-AESI that changed in severity was collected as 1 event at the highest level of severity; an AESI that changed in severity was collected as 1 event at each severity level. The AESI class listed in the study protocol was identified by mapping of the MedDRA preferred terms defined by the sponsor medical lead (see Table 10).

Intravenous ganciclovir and oral valganciclovir were combined, as the change between the 2 was allowed.

Subjects were counted once per category per treatment.

The on-treatment observation period started at the time of study-assigned treatment initiation through 7 days after the last dose of study-assigned treatment or through 21 days if cidofovir was used, or until the maribavir rescue treatment initiation or until the nonstudy CMV treatment initiation, whichever was earlier.

Treatment-emergent adverse events were defined as any adverse event occurring during the on-treatment observation period.

Adverse Events were coded using MedDRA, Version 23.0.

Source: Section 14, Table 14.3.1.1.1

The AE profile for the overall study observation period and in the rescue set (n=22) was similar to that of the on-treatment observation period.

**Phase 2 study 202**

In the table below an overview of treatment-emergent adverse events observed during Phase 2 study 202 is presented.

Table 55 Summary of adverse events (study 202)

| | Maribavir 400 mg BID N=40 n (%) | Maribavir 800 mg BID N=40 n (%) | Maribavir 1200 mg BID N=40 n (%) | Maribavir All Doses N=120 n (%) |
|---|---|---|---|---|
| N (%) of subjects with ≥1 AE | | | | |
| All | 40 (100.0) | 40 (100.0) | 40 (100.0) | 120 (100.0) |
| Related to study drug[a] | 31 (77.5) | 32 (80.0) | 30 (75.0) | 93 (77.5) |
| N of reported AEs | | | | |
| All | 490 | 462 | 466 | 1418 |
| Related to study drug | 70 | 84 | 107 | 261 |
| N (%) of subjects with ≥1 TEAE[b] | | | | |
| All | 40 (100.0) | 40 (100.0) | 40 (100.0) | 120 (100.0) |
| Related to study drug | 31 (77.5) | 32 (80.0) | 30 (75.0) | 93 (77.5) |
| N of reported TEAEs | | | | |
| All | 468 | 445 | 443 | 1356 |
| Related to study drug | 70 | 84 | 105 | 259 |
| N (%) of subjects who had an AE with an outcome of death | | | | |
| All | 10 (25.0) | 12 (30.0) | 10 (25.0) | 32 (26.7) |
| Related to study drug | 0 | 1 (2.5) | 0 | 1 (0.8) |
| N (%) of subjects with SAEs | | | | |
| All | 29 (72.5) | 30 (75.0) | 26 (65.0) | 85 (70.8) |
| Related to study drug | 8 (20.0) | 7 (17.5) | 5 (12.5) | 20 (16.7) |
| N (%) of subjects with treatment-emergent SAEs | | | | |
| All | 28 (70.0) | 27 (67.5) | 26 (65.0) | 81 (67.5) |
| Related to study drug | 8 (20.0) | 7 (17.5) | 5 (12.5) | 20 (16.7) |
| N (%) of subjects who discontinued study drug due to AEs | | | | |
| All | 11 (27.5) | 17 (42.5) | 13 (32.5) | 41 (34.2) |
| Related to study drug | 3 (7.5) | 8 (20.0) | 4 (10.0) | 15 (12.5) |
| N (%) of subjects with AEs causing interruptions of study drug | | | | |
| All | 6 (15.0) | 5 (12.5) | 9 (22.5) | 20 (16.7) |
| Related to study drug | 2 (5.0) | 3 (7.5) | 5 (12.5) | 10 (8.3) |

AE=adverse event; BID=twice daily; CSR=clinical study report; SAE=serious adverse event; TEAE=treatment-emergent adverse event

[a] Related adverse events are those considered of possible, probable, or definite relationship to study drug by the investigator; events with missing, unknown, or unrecorded relationship were assumed to be related.

[b] Treatment-emergent adverse events are those events that occurred on or after study drug administration through 7 days after the last dose of study drug, or are events that occurred prior to study drug administration and recurred with increased severity after taking study drug through 7 days after the last dose of study drug.

Note: Study 202 was a Phase 2, randomized study to assess the safety and anti- CMV activity of different doses of maribavir for treatment of CMV infections that are resistant or refractory to treatment with ganciclovir/ valganciclovir or foscarnet in transplant recipients.

Note: Percentages are based on the number of subjects within each treatment group.

Source: Study 202 CSR, Table 54

**Phase 2 study 203**

In the table below an overview of treatment-emergent adverse events observed during Phase 2 study 203 is presented.

Table 56 Summary of adverse events (study 203)

| | Maribavir 400 mg BID (N=40) n (%) | Maribavir 800 mg BID (N=40) n (%) | Maribavir 1200 mg BID (N=39) n (%) | Maribavir All Doses (N=119) n (%) | Valganciclovir 900 mg BID (N=40) n (%) |
|---|---|---|---|---|---|
| N (%) of subjects with ≥1 AE | | | | | |
| All | 39 (97.5) | 38 (95.0) | 39 (100.0) | 116 (97.5) | 34 (85.0) |
| Related to study drug[a] | 25 (62.5) | 25 (62.5) | 30 (76.9) | 80 (67.2) | 9 (22.5) |
| N of reported AEs | | | | | |
| All | 273 | 305 | 317 | 895 | 238 |
| Related to study drug | 45 | 54 | 79 | 178 | 13 |
| N (%) of subjects with ≥1 TEAE[b] | | | | | |
| All | 39 (97.5) | 38 (95.0) | 39 (100.0) | 116 (97.5) | 33 (82.5) |
| Related to study drug | 25 (62.5) | 25 (62.5) | 30 (76.9) | 80 (67.2) | 9 (22.5) |
| N of reported TEAEs | | | | | |
| All | 259 | 256 | 299 | 814 | 196 |
| Related to study drug | 45 | 54 | 78 | 177 | 12 |
| N (%) of subjects who had an AE with an outcome of death | | | | | |
| All | 2 (5.0) | 1 (2.5) | 3 (7.7) | 6 (5.0) | 3 (7.5) |
| Related to study drug | 0 | 0 | 0 | 0 | 0 |
| N (%) of subjects with SAEs | | | | | |
| All | 18 (45.0) | 20 (50.0) | 21 (53.8) | 59 (49.6) | 15 (37.5) |
| Related to study drug | 3 (7.5) | 1 (2.5) | 9 (23.1) | 13 (10.9) | 2 (5.0) |
| N (%) of subjects with treatment-emergent SAEs | | | | | |
| All | 16 (40.0) | 17 (42.5) | 19 (48.7) | 52 (43.7) | 13 (32.5) |
| Related to study drug | 3 (7.5) | 1 (2.5) | 8 (20.5) | 12 (10.1) | 1 (2.5) |
| N (%) of subjects who discontinued study drug due to AEs | | | | | |
| All | 12 (30.0) | 5 (12.5) | 10 (25.6) | 27 (22.7) | 5 (12.5) |
| Related to study drug | 5 (12.5) | 4 (10.0) | 7 (17.9) | 16 (13.4) | 4 (10.0) |
| N (%) of subjects with AEs causing interruptions of study drug | | | | | |
| All | 3 (7.5) | 1 (2.5) | 6 (15.4) | 10 (8.4) | 2 (5.0) |
| Related to study drug | 1 (2.5) | 1 (2.5) | 4 (10.3) | 6 (5.0) | 1 (2.5) |

AE=adverse event; BID=twice daily; CSR=clinical study report; SAE=serious adverse event; TEAE=treatment-emergent adverse event

[a] Related adverse events are those considered of possible, probable, or definite relationship to study drug (maribavir or valganciclovir) by the investigator; events with missing, unknown, or unrecorded relationship were assumed to be related.

[b] Treatment-emergent adverse events are those events that occurred on or after study drug (maribavir or valganciclovir) administration through 7 days after the last dose of study drug or are events that occurred prior to study drug administration and recurred with increased severity after taking study drug through 7 days after the last dose of study drug.

Note: Study 203 was a Phase 2, randomized, dose-ranging study to assess the safety and anti-CMV activity of maribavir versus valganciclovir for treatment of CMV infections in transplant recipients who do not have CMV organ disease.

Note: Percentages are based on the number of subjects within each treatment group.

Source: Study 203 CSR, Table 48

***Ancillary studies***

**Cytomegalovirus Prevention Studies**

Study 1263-300

Throughout the full study follow-up period (ie, 12-month database), deaths were reported in 26% (59/223) of patients in the placebo group and in 31% (139/451) of patients in the maribavir group. The proportion of patients with a treatment-emergent SAE was similar among placebo- and maribavir-treated patients (44% in both treatment groups). Similar proportions of patients in both treatment groups discontinued study drug due to an AE (placebo 19%; maribavir 17%).

Ninety-six percent (213/223) of placebo-treated patients and 98% (440/451) of maribavir treated patients reported a TEAE during the study. The majority of TEAEs were not considered related to study drug by the investigator: 93% (1408/1513) in the placebo group and 91% (3169/3469) in the maribavir group. In both treatment groups, the majority of TEAEs were of mild or moderate severity (82% [1246/1513] in the placebo group and 83% [2894/3469] in the maribavir 100 mg BID group).

The proportion of severe events was 15% (220/1513) in the placebo group versus 13% (450/3469) in the maribavir group; the proportion of events of maximal severity was 3% (47/1513) in the placebo group versus 4% (125/3469) in the maribavir group.

Study 1263-301

This study was stopped early when the Data Monitoring Committee (DMC) determined there was an imbalance between the maribavir and ganciclovir groups in the incidence of CMV infections during the study.

Deaths were reported in 4% (6/156) of patients in the ganciclovir group and in 6% (9/147) of patients in the maribavir group. The proportion of patients with a treatment-emergent SAE was similar among ganciclovir- and maribavir-treated patients (49% and 48%, respectively). Study drug was discontinued due to an AE in 9% of ganciclovir patients and 18% of maribavir patients (with the difference driven largely by higher CMV infection rates in the maribavir group).

Ninety-seven percent (152/156) of ganciclovir-treated patients and 95% (140/147) of maribavir-treated patients reported a TEAE during the study. The majority of TEAEs were not considered related to maribavir/placebo by the investigator: 91% (1095/1205) in the ganciclovir group and 90% (977/1087) in the maribavir group. In both treatment groups, the majority of TEAEs were of mild or moderate severity (91% [1098/1205] in the ganciclovir group and 93% [1006/1087] in the maribavir group). The proportions of sever events were 8% (97/1205) in the ganciclovir group and 7% (74/1087) in the maribavir group; the proportions of events of maximal severity were <1% (10/1205) in the ganciclovir group and <1% (7/1087) in the maribavir group.

Study 1263-200

Deaths were reported in 21% (6/28) of placebo-treated patients and in 12% (10/82) of maribavir-treated patients. The proportion of patients with a treatment-emergent SAE was similar among placebo- and maribavir-treated patients (43% and 39%, respectively). More patients receiving maribavir discontinued study drug due to an adverse event than those receiving placebo (40% and 21%, respectively). However, it should be noted that the study design called for the discontinuation of study drug upon occurrence of CMV infection or disease requiring treatment, and this occurred most frequently in the placebo group (54%, 15/28). Had these patients continued study drug, it is possible that subsequent AEs might have led to discontinuation within the 12-week evaluation time frame.

Ninety-nine percent (109/110) of patients reported a TEAE during the study. The majority of adverse events were not considered related to study drug by the investigator: 96% (125/130) in the placebo group and 88% (426/485) in the combined maribavir groups. Across all treatment groups, the majority of TEAEs were of mild or moderate severity: 81% (105/130) in the placebo group, 83% (131/158) in the maribavir 100 mg BID group, 84% (145/172) in the maribavir 400 mg QD group, and 79% (122/155) in the maribavir 400 mg BID group.

**Phase 1 studies**

In the 14 studies in healthy patients, there were no deaths or SAEs. Three maribavir-treated patients and no placebo-treated patients discontinued treatment due to an AE. One subject was discontinued due to an AE following dosing with moxifloxacin in a single-dose crossover study.

The majority of TEAEs that occurred in Phase 1 studies in healthy patients were mild or moderate in severity. The most common TEAE in single- and multiple-dose Phase 1 studies in healthy patients was dysgeusia. In general, dysgeusia was reported as a bitter or metallic taste and was considered related to maribavir administration by the investigators. No patients were withdrawn from treatment because of dysgeusia. Dysgeusia usually started within 1 hour after maribavir dosing and resolved within approximately 8 hours after dosing in the single-dose studies (range, 0.5 hours to 25 hours) and

within 1 day after the last dose in the multiple-dose studies. Other frequently occurring TEAEs included headache and nausea; these events occurred less frequently than dysgeusia and were also mostly mild to moderate in severity.

In the 3 studies in HIV-infected patients and patients with AIDs, no deaths occurred. There were 5 patients (3 maribavir-treated and 2 placebo-treated) who experienced SAEs, none of which were considered to be related to the study treatment by the investigator. Seven patients discontinued treatment due to an AE, with rash being the most frequently occurring AE resulting in discontinuation (n=5). The majority of TEAEs were mild or moderate in severity. As was found in the Phase 1 studies in healthy patients, the most frequently occurring TEAE in patients with HIV infection or AIDS was dysgeusia. The characteristics of these events were similar to those described above for healthy patients in the Phase 1 studies. Abnormal laboratory findings were generally consistent with those expected for patients with AIDS or HIV infection. Results of vital sign measurements and ECGs in these patients were generally unremarkable.

Study 1263-108 (Thorough QT/QTc Study)

One subject was discontinued from treatment due to an adverse event (upper respiratory tract infection) which occurred after receiving moxifloxacin 400 mg. All TEAEs were mild in severity. The most frequently reported TEAE was dysgeusia, which was dose related (80% of patients during treatment with maribavir 1200 mg, 22% of patients during treatment with maribavir 100 mg, 2% of patients during treatment with moxifloxacin, and no placebo-treated patients). The second most frequent TEAE was contact dermatitis, reported in 2-12% of patients across the 4 treatments. All of these events were attributed to ECG patch application and were considered not related to study drug by the investigator.

Treatment-emergent AEs occurring in 2 or more patients during a given treatment included: nausea (10% of maribavir 1200 mg patients, 2% of maribavir 100 mg patients, and no moxifloxacin or placebo patients); headache (2% of maribavir 1200 mg patients, 6% of maribavir 100 mg patients, and no moxifloxacin or placebo patients); and pharyngolaryngeal pain (4% of maribavir 100 mg patients, 2% of moxifloxacin patients, and no maribavir 1200 mg or placebo patients). Other TEAEs occurred in 1 subject during a given treatment. There were no clinically meaningful trends noted in median change from baseline in vital signs following any of the 4 treatments or across treatments. None of the patients had standard 12-lead ECG findings that were considered clinically significant by the investigator. No maribavir- or placebo-treated subject had a QTcIb or QTcF >450 msec or increases from baseline in these parameters that were >30 msec.

**Common adverse events**

**Phase 3 study 303**

The table below displays TEAE preferred terms reported in ≥5% of patients in either the maribavir or the IAT group during the on-treatment observation period.

Table 57 Frequently occurring (in at least 5% of patients in the maribavir or IAT group) treatment-emergent adverse events during the on-treatment observation period by preferred term, treatment group, and selected IAT type (safety set)

| | | | IAT Type | |
|---|---|---|---|---|
| Category | IAT (N=116) n (%) m | Maribavir 400 mg BID (N=234) n (%) m | Ganciclovir/ Valganciclovir (N=56) n (%) m | Foscarnet (N=47) n (%) m |
| Any TEAE | 106 (91.4) 712 | 228 (97.4) 1648 | 51 (91.1) 273 | 43 (91.5) 371 |
| Dysgeusia | 4 (3.4) 4 | 87 (37.2) 92 | 2 (3.6) 2 | 0 |
| Nausea | 25 (21.6) 28 | 50 (21.4) 60 | 8 (14.3) 9 | 14 (29.8) 16 |
| Diarrhoea | 24 (20.7) 31 | 44 (18.8) 54 | 13 (23.2) 13 | 9 (19.1) 13 |
| Vomiting | 19 (16.4) 20 | 33 (14.1) 48 | 7 (12.5) 7 | 8 (17.0) 9 |
| Anaemia | 14 (12.1) 15 | 29 (12.4) 32 | 4 (7.1) 5 | 9 (19.1) 9 |
| Fatigue | 10 (8.6) 10 | 28 (12.0) 29 | 7 (12.5) 7 | 3 (6.4) 3 |
| Pyrexia | 17 (14.7) 20 | 24 (10.3) 28 | 6 (10.7) 7 | 9 (19.1) 11 |
| CMV viraemia | 6 (5.2) 6 | 24 (10.3) 26 | 4 (7.1) 4 | 1 (2.1) 1 |
| Neutropenia | 26 (22.4) 39 | 22 (9.4) 51 | 19 (33.9) 23 | 7 (14.9) 16 |
| Immunosuppressant drug level increased | 1 (0.9) 1 | 21 (9.0) 22 | 1 (1.8) 1 | 0 |
| Taste disorder | 1 (0.9) 1 | 21 (9.0) 21 | 0 | 1 (2.1) 1 |
| Acute kidney injury | 11 (9.5) 13 | 20 (8.5) 22 | 1 (1.8) 1 | 10 (21.3) 12 |
| Headache | 15 (12.9) 16 | 19 (8.1) 21 | 6 (10.7) 6 | 8 (17.0) 9 |
| Abdominal pain | 3 (2.6) 3 | 18 (7.7) 21 | 2 (3.6) 2 | 1 (2.1) 1 |
| Decreased appetite | 9 (7.8) 9 | 18 (7.7) 20 | 4 (7.1) 4 | 4 (8.5) 4 |
| Dizziness | 5 (4.3) 5 | 17 (7.3) 20 | 1 (1.8) 1 | 2 (4.3) 2 |
| Oedema peripheral | 9 (7.8) 11 | 17 (7.3) 18 | 3 (5.4) 4 | 5 (10.6) 6 |
| Blood creatinine increased | 5 (4.3) 5 | 13 (5.6) 14 | 1 (1.8) 1 | 3 (6.4) 3 |
| Dyspnoea | 8 (6.9) 8 | 13 (5.6) 14 | 5 (8.9) 5 | 3 (6.4) 3 |
| Arthralgia | 3 (2.6) 3 | 13 (5.6) 13 | 1 (1.8) 1 | 2 (4.3) 2 |
| Cough | 7 (6.0) 7 | 13 (5.6) 13 | 3 (5.4) 3 | 3 (6.4) 3 |
| CMV infection reactivation | 3 (2.6) 3 | 12 (5.1) 13 | 3 (5.4) 3 | 0 |
| Thrombocytopenia | 7 (6.0) 8 | 11 (4.7) 11 | 5 (8.9) 6 | 2 (4.3) 2 |
| Hypomagnesaemia | 10 (8.6) 10 | 9 (3.8) 10 | 2 (3.6) 2 | 7 (14.9) 7 |
| Constipation | 7 (6.0) 8 | 9 (3.8) 9 | 4 (7.1) 4 | 2 (4.3) 3 |
| Hypertension | 8 (6.9) 9 | 9 (3.8) 9 | 1 (1.8) 1 | 6 (12.8) 7 |
| Hypokalaemia | 11 (9.5) 11 | 8 (3.4) 10 | 1 (1.8) 1 | 9 (19.1) 9 |
| Abdominal pain upper | 6 (5.2) 7 | 8 (3.4) 8 | 5 (8.9) 6 | 0 |
| Leukopenia | 8 (6.9) 9 | 7 (3.0) 7 | 7 (12.5) 8 | 1 (2.1) 1 |
| Pain in extremity | 6 (5.2) 6 | 5 (2.1) 5 | 5 (8.9) 5 | 1 (2.1) 1 |

BID=twice daily; IAT=investigator assigned anti-CMV treatment; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects; n=number of subjects experiencing the event; m=number of events; TEAE=treatment-emergent adverse event

Percentages were based on the number of subjects in the safety set within each column.

Intravenous ganciclovir and oral valganciclovir were combined as the change between the 2 was allowed.

The table was sorted by the preferred term in a descending order of frequency by maribavir group.

Subjects were counted once per preferred term per treatment.

The on-treatment observation period started at the time of study-assigned treatment initiation through 7 days after the last dose of study-assigned treatment or through 21 days if cidofovir was used, or until the maribavir rescue treatment initiation or until the nonstudy CMV treatment initiation, whichever was earlier. Treatment-emergent adverse events were defined as any adverse event occurring during the on-treatment observation period.

Adverse Events were coded using MedDRA, Version 23.0.

Source: Section 14, Table 14.3.1.3.1

**Phase 2 study 202**

In the table below, TEAEs occurring in ≥7.5% of patients in the overall maribavir group in Phase 2 study 202 are provided.

Table 58 Treatment-emergent adverse events occurring in ≥7.5% of patients in the overall maribavir group (study 202)

| Preferred Term | Maribavir 400 mg BID N=40 n (%) | Maribavir 800 mg BID N=40 n (%) | Maribavir 1200 mg BID N=40 n (%) | Maribavir All Doses N=120 n (%) |
|---|---|---|---|---|
| Subjects with any TEAE | 40 (100.0) | 40 (100.0) | 40 (100.0) | 120 (100.0) |
| Dysgeusia | 24 (60.0) | 25 (62.5) | 29 (72.5) | 78 (65.0) |
| Nausea | 15 (37.5) | 12 (30.0) | 14 (35.0) | 41 (34.2) |
| Vomiting | 11 (27.5) | 13 (32.5) | 11 (27.5) | 35 (29.2) |
| Cytomegalovirus infection | 6 (15.0) | 12 (30.0) | 10 (25.0) | 28 (23.3) |
| Diarrhoea | 5 (12.5) | 13 (32.5) | 10 (25.0) | 28 (23.3) |
| Fatigue | 8 (20.0) | 10 (25.0) | 7 (17.5) | 25 (20.8) |
| Anaemia | 7 (17.5) | 7 (17.5) | 10 (25.0) | 24 (20.0) |
| Oedema peripheral | 11 (27.5) | 6 (15.0) | 6 (15.0) | 23 (19.2) |
| Headache | 9 (22.5) | 4 (10.0) | 6 (15.0) | 19 (15.8) |
| Renal impairment | 3 (7.5) | 7 (17.5) | 9 (22.5) | 19 (15.8) |
| Rash | 7 (17.5) | 6 (15.0) | 3 (7.5) | 16 (13.3) |
| Constipation | 5 (12.5) | 5 (12.5) | 5 (12.5) | 15 (12.5) |
| Pneumonia | 6 (15.0) | 4 (10.0) | 5 (12.5) | 15 (12.5) |
| Pyrexia | 6 (15.0) | 6 (15.0) | 3 (7.5) | 15 (12.5) |
| Cough | 5 (12.5) | 6 (15.0) | 2 (5.0) | 13 (10.8) |
| Decreased appetite | 3 (7.5) | 5 (12.5) | 4 (10.0) | 12 (10.0) |
| Dehydration | 5 (12.5) | 4 (10.0) | 3 (7.5) | 12 (10.0) |
| Hypokalaemia | 2 (5.0) | 4 (10.0) | 6 (15.0) | 12 (10.0) |
| Immunosuppressant drug level increased | 4 (10.0) | 2 (5.0) | 6 (15.0) | 12 (10.0) |
| Urinary tract infection | 6 (15.0) | 3 (7.5) | 3 (7.5) | 12 (10.0) |
| Depression | 2 (5.0) | 8 (20.0) | 1 (2.5) | 11 (9.2) |
| Dyspnoea | 4 (10.0) | 2 (5.0) | 5 (12.5) | 11 (9.2) |
| Hypotension | 5 (12.5) | 5 (12.5) | 1 (2.5) | 11 (9.2) |
| Pruritus | 5 (12.5) | 1 (2.5) | 5 (12.5) | 11 (9.2) |
| Abdominal pain | 3 (7.5) | 4 (10.0) | 3 (7.5) | 10 (8.3) |
| Clostridium difficile infection | 4 (10.0) | 2 (5.0) | 4 (10.0) | 10 (8.3) |
| Hyperkalaemia | 2 (5.0) | 3 (7.5) | 5 (12.5) | 10 (8.3) |
| Acute graft versus host disease | 2 (5.0) | 4 (10.0) | 3 (7.5) | 9 (7.5) |
| Back pain | 4 (10.0) | 1 (2.5) | 4 (10.0) | 9 (7.5) |
| Dizziness | 1 (2.5) | 5 (12.5) | 3 (7.5) | 9 (7.5) |
| Weight decreased | 2 (5.0) | 3 (7.5) | 4 (10.0) | 9 (7.5) |

BID=twice daily; CSR=clinical study report; TEAE=treatment-emergent adverse event

Note: Study 202 was a Phase 2, randomized study to assess the safety and anti- CMV activity of different doses of maribavir for treatment of CMV infections that are resistant or refractory to treatment with ganciclovir/ valganciclovir or foscarnet in transplant recipients.

Note: Subjects may have reported more than 1 event (preferred term); therefore, percentages may not add to 100%. Subjects are counted once within each preferred term.

Source: Study 202 CSR, Table 56

**Phase 2 study 203**

In the table below, TEAEs occurring in ≥7.5% of patients in the overall maribavir group in Phase 2 study 203 are provided.

Table 59 Treatment-emergent adverse events reported in ≥7.5% of patients in any treatment group (study 203)

| Preferred Term | Maribavir 400 mg BID (N=40) | Maribavir 800 mg BID (N=40) | Maribavir 1200 mg BID (N=39) | Maribavir All Doses (N=119) | Valganciclovir 900 mg BID (N=40) |
|---|---|---|---|---|---|
| Number (%) of subjects with any TEAE | 39 (97.5) | 38 (95.0) | 39 (100.0) | 116 (97.5) | 33 (82.5) |
| Dysgeusia | 18 (45.0) | 16 (40.0) | 14 (35.9) | 48 (40.3) | 1 (2.5) |
| Nausea | 9 (22.5) | 7 (17.5) | 11 (28.2) | 27 (22.7) | 6 (15.0) |
| Diarrhoea | 7 (17.5) | 7 (17.5) | 10 (25.6) | 24 (20.2) | 4 (10.0) |
| Vomiting | 4 (10.0) | 8 (20.0) | 12 (30.8) | 24 (20.2) | 4 (10.0) |
| Cough | 5 (12.5) | 6 (15.0) | 6 (15.4) | 17 (14.3) | 5 (12.5) |
| Oedema peripheral | 3 (7.5) | 9 (22.5) | 5 (12.8) | 17 (14.3) | 7 (17.5) |
| Urinary tract infection | 5 (12.5) | 5 (12.5) | 6 (15.4) | 16 (13.4) | 4 (10.0) |
| Decreased appetite | 4 (10.0) | 5 (12.5) | 5 (12.8) | 14 (11.8) | 1 (2.5) |
| Headache | 4 (10.0) | 4 (10.0) | 6 (15.4) | 14 (11.8) | 1 (2.5) |
| Anaemia | 2 (5.0) | 7 (17.5) | 3 (7.7) | 12 (10.1) | 1 (2.5) |
| Dyspnoea | 3 (7.5) | 3 (7.5) | 6 (15.4) | 12 (10.1) | 2 (5.0) |
| Nasopharyngitis | 7 (17.5) | 5 (12.5) | 0 | 12 (10.1) | 2 (5.0) |
| Pyrexia | 4 (10.0) | 3 (7.5) | 4 (10.3) | 11 (9.2) | 0 |
| Weight decreased | 6 (15.0) | 2 (5.0) | 3 (7.7) | 11 (9.2) | 3 (7.5) |
| Immunosuppressant drug level increased | 2 (5.0) | 2 (5.0) | 6 (15.4) | 10 (8.4) | 0 |
| Abdominal pain | 2 (5.0) | 3 (7.5) | 4 (10.3) | 9 (7.6) | 3 (7.5) |
| Constipation | 2 (5.0) | 3 (7.5) | 4 (10.3) | 9 (7.6) | 2 (5.0) |
| Cytomegalovirus infection | 5 (12.5) | 3 (7.5) | 1 (2.6) | 9 (7.6) | 2 (5.0) |
| Renal failure | 3 (7.5) | 1 (2.5) | 5 (12.8) | 9 (7.6) | 0 |
| Hypokalaemia | 2 (5.0) | 1 (2.5) | 5 (12.8) | 8 (6.7) | 2 (5.0) |
| Oral herpes | 3 (7.5) | 2 (5.0) | 3 (7.7) | 8 (6.7) | 0 |
| Abdominal pain upper | 4 (10.0) | 2 (5.0) | 1 (2.6) | 7 (5.9) | 1 (2.5) |

| Preferred Term | Maribavir 400 mg BID (N=40) | Maribavir 800 mg BID (N=40) | Maribavir 1200 mg BID (N=39) | Maribavir All Doses (N=119) | Valganciclovir 900 mg BID (N=40) |
|---|---|---|---|---|---|
| Acute graft versus host disease | 3 (7.5) | 1 (2.5) | 3 (7.7) | 7 (5.9) | 3 (7.5) |
| Fatigue | 2 (5.0) | 3 (7.5) | 2 (5.1) | 7 (5.9) | 1 (2.5) |
| Rash | 2 (5.0) | 4 (10.0) | 1 (2.6) | 7 (5.9) | 3 (7.5) |
| Hypotension | 2 (5.0) | 2 (5.0) | 2 (5.1) | 6 (5.0) | 3 (7.5) |
| Tremor | 1 (2.5) | 1 (2.5) | 4 (10.3) | 6 (5.0) | 1 (2.5) |
| Asthenia | 1 (2.5) | 3 (7.5) | 1 (2.6) | 5 (4.2) | 1 (2.5) |
| Dry mouth | 1 (2.5) | 2 (5.0) | 2 (5.1) | 5 (4.2) | 3 (7.5) |
| Hepatic enzyme increased | 2 (5.0) | 3 (7.5) | 0 | 5 (4.2) | 3 (7.5) |
| Hypertension | 3 (7.5) | 0 | 2 (5.1) | 5 (4.2) | 1 (2.5) |
| Nephrogenic anaemia | 1 (2.5) | 1 (2.5) | 3 (7.7) | 5 (4.2) | 0 |
| Neutropenia | 1 (2.5) | 3 (7.5) | 1 (2.6) | 5 (4.2) | 2 (5.0) |
| Pneumonia | 2 (5.0) | 1 (2.5) | 2 (5.1) | 5 (4.2) | 3 (7.5) |
| Dysuria | 1 (2.5) | 0 | 3 (7.7) | 4 (3.4) | 1 (2.5) |
| Leukopenia | 2 (5.0) | 2 (5.0) | 0 | 4 (3.4) | 3 (7.5) |
| Malaise | 0 | 0 | 4 (10.3) | 4 (3.4) | 0 |
| Dry skin | 3 (7.5) | 0 | 0 | 3 (2.5) | 1 (2.5) |
| Metabolic acidosis | 0 | 0 | 3 (7.7) | 3 (2.5) | 0 |
| Paraesthesia | 0 | 0 | 3 (7.7) | 3 (2.5) | 1 (2.5) |
| Weight increased | 2 (5.0) | 1 (2.5) | 0 | 3 (2.5) | 3 (7.5) |
| Bacterial sepsis | 0 | 0 | 1 (2.6) | 1 (0.8) | 3 (7.5) |
| Vaginal discharge*F | 0 | 1 (7.7) | 0 | 1 (2.1) | 0 |
| Vulvovaginal mycotic infection*F | 0 | 1 (7.7) | 0 | 1 (2.1) | 0 |
| Bronchitis | 0 | 0 | 0 | 0 | 3 (7.5) |
| Vulvovaginal dryness*F | 0 | 0 | 0 | 0 | 1 (7.7) |

BID=twice daily; CSR=clinical study report; TEAE=treatment-emergent adverse event

Note: Study 203 was a Phase 2, randomized, dose-ranging study to assess the safety and anti-CMV activity of maribavir versus valganciclovir for treatment of CMV infections in transplant recipients who do not have CMV organ disease.

Note: Unless denoted with a *, percentages are based on the number of subjects in each treatment group. For terms followed by (*M) or (*F), percentages are based on the number of males or females in each treatment group. Subjects may have reported more than one event (preferred term); therefore, percentages may not add to 100%. Subjects are counted once within each preferred term.

Source: Study 203 CSR, Table 49

## Related Treatment-emergent Adverse Events

### Phase 3 study 303

In the table below TEAEs considered related to study-assigned treatment occurring in at least 5% of patients during the on-treatment observation period of the Phase 3 study 303 are provided.

Table 60 Treatment-emergent adverse events considered related to study-assigned treatment by the investigator during the on-treatment observation period by system organ class, preferred term, and treatment group – events occurring in at least 5% of patients in either treatment group or for either IAT type (ganciclovir/valganciclovir or foscarnet) (safety set)

| System Organ Class<br>Preferred Term | IAT (N=116)<br>n (%) m | Maribavir 400 mg BID (N=234)<br>n (%) m | IAT Type<br>Ganciclovir/ Valganciclovir (N=56)<br>n (%) m | IAT Type<br>Foscarnet (N=47)<br>n (%) m |
|---|---|---|---|---|
| Any related TEAE | 57 (49.1) 176 | 141 (60.3) 270 | 23 (41.1) 49 | 29 (61.7) 116 |
| **Blood and lymphatic system disorders** | 25 (21.6) 48 | 7 (3.0) 15 | 17 (30.4) 35 | 8 (17.0) 13 |
| Anaemia | 9 (7.8) 10 | 3 (1.3) 3 | 3 (5.4) 4 | 6 (12.8) 6 |
| Febrile neutropenia | 4 (3.4) 4 | 0 | 4 (7.1) 4 | 0 |
| Leukopenia | 5 (4.3) 5 | 0 | 4 (7.1) 4 | 1 (2.1) 1 |
| Neutropenia | 16 (13.8) 22 | 4 (1.7) 11 | 14 (25.0) 18 | 2 (4.3) 4 |
| Thrombocytopenia | 6 (5.2) 7 | 0 | 4 (7.1) 5 | 2 (4.3) 2 |

| System Organ Class<br>Preferred Term | IAT<br>(N=116)<br>n (%) m | Maribavir<br>400 mg BID<br>(N=234)<br>n (%) m | IAT Type<br>Ganciclovir/<br>Valganciclovir<br>(N=56)<br>n (%) m | IAT Type<br>Foscarnet<br>(N=47)<br>n (%) m |
|---|---|---|---|---|
| **Gastrointestinal disorders** | 15 (12.9) 26 | 37 (15.8) 69 | 2 (3.6) 2 | 11 (23.4) 20 |
| Diarrhoea | 6 (5.2) 7 | 9 (3.8) 9 | 1 (1.8) 1 | 4 (8.5) 5 |
| Nausea | 11 (9.5) 11 | 20 (8.5) 22 | 1 (1.8) 1 | 8 (17.0) 8 |
| Vomiting | 5 (4.3) 5 | 18 (7.7) 23 | 0 | 4 (8.5) 4 |
| **General disorders and administration site conditions** | 9 (7.8) 11 | 7 (3.0) 7 | 0 | 9 (19.1) 11 |
| Oedema peripheral | 4 (3.4) 5 | 0 | 0 | 4 (8.5) 5 |
| **Investigations** | 9 (7.8) 14 | 20 (8.5) 22 | 2 (3.6) 4 | 6 (12.8) 7 |
| Immunosuppressant drug level increased | 0 | 14 (6.0) 14 | 0 | 0 |
| **Metabolism and nutrition disorders** | 11 (9.5) 25 | 6 (2.6) 8 | 2 (3.6) 3 | 8 (17.0) 21 |
| Hypocalcaemia | 5 (4.3) 5 | 0 | 1 (1.8) 1 | 4 (8.5) 4 |
| Hypokalaemia | 5 (4.3) 5 | 1 (0.4) 3 | 0 | 4 (8.5) 4 |
| Hypomagnesaemia | 5 (4.3) 5 | 0 | 1 (1.8) 1 | 4 (8.5) 4 |
| **Nervous system disorders** | 9 (7.8) 12 | 104 (44.4) 115 | 1 (1.8) 1 | 8 (17.0) 11 |
| Dysgeusia | 1 (0.9) 1 | 84 (35.9) 89 | 1 (1.8) 1 | 0 |
| Headache | 4 (3.4) 4 | 2 (0.9) 2 | 0 | 4 (8.5) 4 |
| Taste disorder | 1 (0.9) 1 | 20 (8.5) 20 | 0 | 1 (2.1) 1 |
| **Renal and urinary disorders** | 15 (12.9) 22 | 4 (1.7) 6 | 0 | 13 (27.7) 19 |
| Acute kidney injury | 9 (7.8) 11 | 4 (1.7) 5 | 0 | 9 (19.1) 11 |
| Renal impairment | 3 (2.6) 5 | 0 | 0 | 3 (6.4) 5 |

BID=twice daily; IAT=investigator-assigned anti-CMV treatment; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects; n=number of subjects experiencing the event; m=number of events; TEAE=treatment-emergent adverse event

Percentages were based on the number of subjects in the safety set within each column.

Intravenous ganciclovir and oral valganciclovir were combined as the change between the 2 was allowed.

Subjects were counted once per system organ class and once per preferred term per treatment. If a subject had more than 1 TEAE of the same preferred term, the most related was counted.

The on-treatment observation period started at the time of study-assigned treatment initiation through 7 days after the last dose of study-assigned treatment or through 21 days if cidofovir was used, or until the maribavir rescue treatment initiation or until the nonstudy CMV treatment initiation, whichever was earlier. Treatment emergent adverse events were defined as any adverse event occurring during the on-treatment observation period.

Adverse Events were coded using MedDRA, Version 23.0.

Source: Section 14, Table 14.3.1.5.1

**Phase 2 study 202**

Treatment-emergent adverse events considered by the investigator to be related to maribavir that occurred in 2 or more patients in Phase 2 study 202 are summarised in the table below.

Table 61 Related treatment-emergent adverse events occurring in 2 or more patients in the overall maribavir group (study 202)

| Preferred Term | Maribavir 400 mg BID N=40 n (%) | Maribavir 800 mg BID N=40 n (%) | Maribavir 1200 mg BID N=40 n (%) | Maribavir All Doses N=120 n (%) |
|---|---|---|---|---|
| Subjects with any related TEAEs | 31 (77.5) | 32 (80.0) | 30 (75.0) | 93 (77.5) |
| Dysgeusia | 24 (60.0) | 25 (62.5) | 29 (72.5) | 78 (65.0) |
| Nausea | 7 (17.5) | 8 (20.0) | 10 (25.0) | 25 (20.8) |
| Cytomegalovirus infection | 2 (5.0) | 7 (17.5) | 2 (5.0) | 11 (9.2) |
| Immunosuppressant drug level increased | 3 (7.5) | 2 (5.0) | 6 (15.0) | 11 (9.2) |
| Diarrhoea | 0 | 3 (7.5) | 6 (15.0) | 9 (7.5) |
| Rash | 3 (7.5) | 2 (5.0) | 3 (7.5) | 8 (6.7) |
| Vomiting | 1 (2.5) | 2 (5.0) | 5 (12.5) | 8 (6.7) |
| Anaemia | 3 (7.5) | 2 (5.0) | 2 (5.0) | 7 (5.8) |
| Pruritus | 3 (7.5) | 0 | 3 (7.5) | 6 (5.0) |
| Deceased appetite | 1 (2.5) | 2 (5.0) | 2 (5.0) | 5 (4.2) |
| Fatigue | 1 (2.5) | 1 (2.5) | 2 (5.0) | 4 (3.3) |
| Headache | 0 | 1 (2.5) | 3 (7.5) | 4 (3.3) |
| Dyspepsia | 2 (5.0) | 1 (2.5) | 0 | 3 (2.5) |
| Renal impairment | 1 (2.5) | 0 | 2 (5.0) | 3 (2.5) |
| Blood creatinine increased | 0 | 1 (2.5) | 1 (2.5) | 2 (1.7) |
| Dizziness | 0 | 2 (5.0) | 0 | 2 (1.7) |
| Flushing | 0 | 0 | 2 (5.0) | 2 (1.7) |
| Insomnia | 0 | 1 (2.5) | 1 (2.5) | 2 (1.7) |
| Local swelling | 0 | 1 (2.5) | 1 (2.5) | 2 (1.7) |
| Malaise | 0 | 0 | 2 (5.0) | 2 (1.7) |
| Thrombocytopenia | 1 (2.5) | 1 (2.5) | 0 | 2 (1.7) |
| Vertigo | 1 (2.5) | 1 (2.5) | 0 | 2 (1.7) |
| Weight decreased | 0 | 0 | 2 (5.0) | 2 (1.7) |

BID=twice daily; CSR=clinical study report; TEAE=treatment-emergent adverse event

Note: Study 202 was a Phase 2, randomized study to assess the safety and anti- CMV activity of different doses of maribavir for treatment of CMV infections that are resistant or refractory to treatment with ganciclovir/ valganciclovir or foscarnet in transplant recipients.

Note: Percentages are based on the number of subjects in each treatment group. Subjects may have reported more than 1 event (preferred term); therefore, percentages may not add to 100%. Subjects are counted once within each preferred term.

Source: Study 202 CSR, Table 57

**Phase 2 study 203**

Treatment-emergent adverse events considered by the investigator to be related to maribavir that occurred in 2 or more patients in Phase 2 study 203 are summarised in the table below.

Table 62 Treatment-emergent adverse events related to study drug reported by 2 or more patients in any treatment group (study 203)

| Preferred Term | Maribavir 400 mg BID (N=40) | Maribavir 800 mg BID (N=40) | Maribavir 1200 mg BID (N=39) | Maribavir All Doses (N=119) | Valganciclovir 900 mg BID (N=40) |
|---|---|---|---|---|---|
| Number (%) of subjects with any related TEAEs | 25 (62.5) | 25 (62.5) | 30 (76.9) | 80 (67.2) | 9 (22.5) |
| Dysgeusia | 18 (45.0) | 16 (40.0) | 14 (35.9) | 48 (40.3) | 0 |
| Nausea | 5 (12.5) | 4 (10.0) | 7 (17.9) | 16 (13.4) | 0 |
| Vomiting | 2 (5.0) | 4 (10.0) | 8 (20.5) | 14 (11.8) | 0 |
| Anaemia | 0 | 6 (15.0) | 1 (2.6) | 7 (5.9) | 0 |
| Abdominal pain upper | 3 (7.5) | 2 (5.0) | 1 (2.6) | 6 (5.0) | 0 |
| Decreased appetite | 3 (7.5) | 0 | 2 (5.1) | 5 (4.2) | 0 |
| Diarrhoea | 2 (5.0) | 0 | 3 (7.7) | 5 (4.2) | 1 (2.5) |
| Immunosuppressant drug level increased | 0 | 1 (2.5) | 3 (7.7) | 4 (3.4) | 0 |
| Weight decreased | 1 (2.5) | 1 (2.5) | 2 (5.1) | 4 (3.4) | 0 |
| Gastrointestinal toxicity | 1 (2.5) | 0 | 2 (5.1) | 3 (2.5) | 0 |
| Hepatic enzyme increased | 0 | 3 (7.5) | 0 | 3 (2.5) | 2 (5.0) |
| Dry mouth | 0 | 2 (5.0) | 0 | 2 (1.7) | 0 |
| Hypokalaemia | 0 | 0 | 2 (5.1) | 2 (1.7) | 0 |
| Oral herpes | 0 | 0 | 2 (5.1) | 2 (1.7) | 0 |
| Leukopenia | 0 | 1 (2.5) | 0 | 1 (0.8) | 3 (7.5) |
| Neutropenia | 0 | 0 | 1 (2.6) | 1 (0.8) | 2 (5.0) |

BID=twice daily; CSR=clinical study report; TEAE=treatment-emergent adverse event

Note: Study 203 was a Phase 2, randomized, dose-ranging study to assess the safety and anti-CMV activity of maribavir versus valganciclovir for treatment of CMV infections in transplant recipients who do not have CMV organ disease.

Note: Percentages are based on the number of subjects in each treatment group. Subjects may have reported more than one event (preferred term); therefore, percentages may not add to 100%. Subjects are counted once within each preferred term.

Source: Study 203, Table 50

## AEs of special interest (AESIs)

### *Taste disturbance*

**Phase 3 study 303**

Taste disturbance (dysgeusia) as an AESI class occurred more frequently in maribavir-treated patients than for patients in the IAT group during the on-treatment observation period (maribavir: 108 [46.2%] patients; IAT: 5 [4.3%] patients). Taste disturbance (dysgeusia) was considered related to maribavir in 44.0% of patients (1.7% of patients who received IAT), but was Grade 1 or 2 in severity for all patients and was not reported as a treatment-emergent SAE for any subject. The most frequently reported preferred terms within this AESI class (>1% of patients) were dysgeusia (maribavir: 87 [37.2%] patients; IAT: 4 [3.4%] patients) and taste disorder (maribavir: 21 [9.0%] patients: IAT: 1 [0.9%] patient) (Section 14, Table 14.3.1.15.1). Preferred terms within the AESI category of taste disturbance (dysgeusia) led to discontinuation of treatment for 2 (0.9%) maribavir treated patients and no patients in the IAT group.

Time to event analyses showed dysgeusia resolved either during treatment with maribavir or shortly after discontinuation of treatment. For the 119 patients who had dysgeusia (or similar terms) while on maribavir treatment, the event(s) resolved during treatment for 44 (37.0%) patients, with an observed median duration of dysgeusia while on treatment of 43 days (range: 7 to 59 days). The Kaplan-Meier estimate of time to resolution of dysgeusia while on treatment was 58 days. For the 75 patients who had dysgeusia (or similar terms) that was ongoing at the time of the last dose of maribavir, the event(s) resolved for 67 (89.3%) patients, with an observed median duration of dysgeusia off treatment of 6 days. The median Kaplan-Meier estimate of time to resolution of dysgeusia following discontinuation of study drug was 7 days (95% CI: 4 to 8 days).

**Phase 2 study 202**

The most frequently reported TEAE associated with maribavir in this study was dysgeusia (taste disturbance), with the proportions showing some evidence of dose dependence (60%, 63%, and 73% in the maribavir 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively). Two patients reported either ageusia or hypogeusia in addition to dysgeusia. Except for 1 event that was severe, all other reports of taste disturbance were of mild to moderate severity.

The majority of TEAEs of dysgeusia were reported with descriptions that included "metallic taste" or "bitter taste." All events associated with taste disturbance were considered by the investigator to be related to maribavir treatment. One patient had maribavir discontinued due to an AE of dysgeusia. Three other patients had maribavir treatment interrupted due to dysgeusia. One of these patients (1200 mg BID) had a subsequent event of dysgeusia that resulted in maribavir dose adjustment.

**Phase 2 study 203**

Dysgeusia was the most frequently reported TEAE among maribavir-treated patients: 45.0% of maribavir 400 mg BID patients, 40.0% of maribavir 800 mg BID patients, and 35.9% of maribavir 1200 mg BID patients. By comparison, dysgeusia occurred in 1 (2.5%) valganciclovir patient. It is noted that the proportion of patients with dysgeusia decreased as maribavir dose increased. Other events associated with taste disturbance, including ageusia and hypogeusia, were each reported by 1 patient (0.8%) in the overall maribavir group compared with no reports in the valganciclovir group. All events of taste disturbance were of mild or moderate severity. All events associated with taste disturbance were considered by the investigator to be related to maribavir. The event of dysgeusia in the valganciclovir-treated patient was not considered to be treatment related.

The majority of TEAEs of dysgeusia were reported with descriptions that included "metallic taste" or "bitter taste." None of the events associated with taste disturbance led to discontinuation or interruption of study drug, and 1 patient (maribavir 800 mg BID) had a taste disturbance event that resulted in dose adjustment.

***Nausea/diarrhoea/vomiting***

**Phase 3 study 303**

Nausea, vomiting, diarrhoea as an AESI class occurred for a similar percentage of patients in the maribavir and IAT groups during the on-treatment observation period (maribavir: 78 [33.3%] patients; IAT: 44 [37.9%] patients) despite the longer duration of exposure to maribavir. The TEAEs in this AESI class were considered related to treatment for 12.8% of patients in the maribavir group and 11.2% of patients in the IAT group and were reported as SAEs for 2.6% of patients in each treatment group. Most patients had TEAEs in the AESI class of nausea, vomiting, and diarrhoea that were Grade 1 or 2 in severity; 2.1% of maribavir-treated patients and 3.4% of patients in the IAT group had Grade 3 TEAEs of nausea, vomiting, and/or diarrhoea. One (0.4%) maribavir-treated patient had a Grade 4 event (diarrhoea), which was the maximum intensity reported. For patients in the IAT group, at least 1 TEAE mapping to this AESI class occurred across all IAT types: ganciclovir/valganciclovir (33.9%), foscarnet (40.4%), and >1 IAT (57.1%).

**Phase 2 study 202**

In the maribavir 400 mg BID group, events of nausea (37.5%), vomiting (27.5%), and diarrhoea (12.5%) were frequently reported. There was no evidence that the occurrence of nausea and vomiting were related to maribavir dose. Diarrhoea occurred more frequently in the 2 higher maribavir dose groups (32.5% of patients in the 800 mg BID group and 25.0% of patients in the 1200 mg BID group). The majority of these GI events were of mild or moderate severity. For 9 patients, 1 or more of these

3 GI events were severe (two 400 mg BID patients, two 800 mg BID patients, and five 1200 mg BID patients).

Three patients (2.5%) discontinued from maribavir due to nausea, vomiting, and/or diarrhoea, one of whom had active nausea at the study start. Nausea led to interruption of maribavir treatment in 4 patients (3.3%), 3 of whom were receiving the 1200 mg BID dose, and vomiting lead to interruption of maribavir treatment in 1 patient who was receiving the 1200 mg BID dose. Gastrointestinal toxicity (including reasons specified as nausea or vomiting) accounted for the majority (8 of 15) of dose adjustments to maribavir that occurred during the study.

**Phase 2 study 203**

A total of 14 patients (35.0%) who received maribavir 400 mg BID and 10 patients (25.0%) who received valganciclovir reported a GI disorders of nausea, diarrhoea, or vomiting. The percentages of patients reporting GI events of nausea and diarrhoea were higher in the maribavir 400 mg BID group (22.5% and 17.5% for each event, respectively) compared with the valganciclovir group (15% and 10% for each event, respectively), while similar proportions of patients in the 2 groups (10.0%) reported vomiting. There was some evidence that the occurrence of vomiting and diarrhoea was related to maribavir dose. Vomiting occurred in 10.0% of patients in the 400 mg BID group, 20.0% of patients in the 800 mg BID group, and 30.8% of patients in the 1200 mg BID group (compared with 10.0% of patients in the valganciclovir group). Diarrhoea occurred in 17.5% of patients in the 400 and 800 mg BID groups and 25.6% of patients in the 1200 mg BID group (compared with 10.0% of patients in the valganciclovir group). The majority of these GI events were of mild or moderate severity.

Study drug discontinuation or interruption due to nausea, vomiting or diarrhoea was rare in all treatment groups. While dose adjustment was required infrequently for maribavir patients (10 of 119 patients [8.4%]), GI toxicity was the most frequently occurring reason for maribavir dose adjustment (5 of the 10 patients whose dose was adjusted for toxicity).

***Immunosuppressant drug level increased***

Based on the results from clinical drug interaction study 1263-105, coadministration with maribavir may increase the concentration of tacrolimus and other immunosuppressants (eg, cyclosporine, everolimus and sirolimus) that have a narrow therapeutic index.

**Phase 3 study 303**

The higher percentage of maribavir-treated patients with immunosuppressant drug concentration level increased during the on-treatment observation period compared with patients who received IAT was consistent with the known PK effects of maribavir (maribavir: 21 [9.0%] patients; IAT: 1 [0.9%] patient). The increased drug level of immunosuppressant was considered related to maribavir for 14 (6.0%) patients and was reported as a treatment-emergent SAE for 1 (0.4%) maribavir-treated patient.

**Phase 2 study 202**

Treatment-emergent AEs of increased immunosuppressant drug levels occurred in 10% (12/120) of maribavir-treated patients. Eleven of the 12 patients for whom this TEAE was reported had high to toxic levels of tacrolimus and 1 patient (400 mg BID group) had elevated sirolimus levels (refer to the Study 202 CSR, Section 10.6). The occurrence of TEAEs of increased immunosuppressant drug levels appeared to be dose related, with the highest proportion of patients with increased immunosuppressant drug level events in the 1200 mg BID dose group (15.0% of patients), compared with 10% of patients in the 400 mg BID dose group and 5% of patients in the 800 mg BID dose group. For the majority of patients with increased immunosuppressant drug level events, these events were

mild to moderate in severity; for 3 patients, these events were severe. Maribavir was discontinued for 1 patient (1200 mg BID) due to acute kidney injury secondary to increased tacrolimus levels. No patient had maribavir treatment interrupted due to a TEAE of increased immunosuppressant drug levels.

**Phase 2 study 203**

Treatment-emergent increased immunosuppressant drug levels occurred in 5% of patients (n=2) in the maribavir 400 and 800 mg BID dose groups and in 15.4% of patients (n=6) in the maribavir 1200 mg group; no patient in the valganciclovir group was reported to have increased immunosuppressant drug levels. Nine of these 10 maribavir-treated patients had high to toxic levels of tacrolimus and 1 patient had cyclosporine intoxication. It is noted that the highest proportion of patients with increased immunosuppressant drug level events occurred in the 1200 mg BID dose group (15.4% of patients). For the majority of patients with increased immunosuppressant drug level events, these events were mild to moderate in severity; for 2 patients in the 1200 mg BID group, these events were severe. For 1 of the 10 patients with increased immunosuppressant drug level events, the study drug was discontinued due to the AE of worsening cachexia, which was described as the result of clinical aggravation due to the rise in tacrolimus levels. Maribavir treatment was interrupted for 1 patient (0.8%) who was receiving 800 mg BID due to a TEAE of increased immunosuppressant drug level.

***Rash***

**Phase 3 study 303**

Rash as a medical concept was reported more frequently in the maribavir group (7.3%) than in the IAT group (2.6%). Rash was mild for all but 3 maribavir-treated patients, and all TEAEs in the medical concept of rash were considered by the investigator as not related to treatment with maribavir. There were no SAEs of rash reported during the study.

**Phase 2 study 202**

Treatment-emergent rash was reported for 7 (17.5%) maribavir 400 mg BID patients, 6 (15.0%) 800 mg BID patients, and 3 (7.5%) 1200 mg BID patients. It is noted that the occurrence of rash decreased as maribavir dose increased. Eight of the 16 patients had rash that was considered by the investigator to be related to maribavir. All events of rash were of mild or moderate severity, and none resulted in any patient discontinuing maribavir treatment. Two patients had maribavir temporarily interrupted for a mild rash. There were no SAEs of rash reported during the study.

**Phase 2 study 203**

Treatment-emergent rash was reported with similar frequencies across all treatment groups: 2 (5.0%) maribavir 400 mg BID patients, 4 (10.0%) maribavir 800 mg patients, 1 (2.6%) maribavir 1200 mg patient, and 3 (7.5%) valganciclovir-treated patients. The occurrence of rash did not appear to be related to maribavir dose. Two of the 7 maribavir-treated patients had rash that was considered by the investigator to be related to the study drug (1 patient each in the 800 and 1200 mg BID groups. Rash was not considered related to valganciclovir treatment. All events of rash were of mild or moderate severity, and none resulted in discontinuation from the study drug in any treatment group. One patient in the maribavir 1200 mg BID group had study drug temporarily interrupted for a mild rash. None of the events of rash were reported as SAEs.

***Neutropenia***

**Phase 3 study 303**

Neutropenia as an AESI class was less common for maribavir-treated patients than for IAT during the on-treatment observation period (maribavir: 24 [10.3%] patients; IAT: 30 [25.9%] patients). Treatment-related neutropenia (as an AESI class) was reported for 1.7% of maribavir-treated patients. In contrast, by IAT type, neutropenia as an AESI class occurred for 22 (39.3%) ganciclovir/valganciclovir-treated patients (with 32.1% considered treated related) and 8 (17.0%) foscarnet-treated patients (with 4.3% considered treatment related). Neutropenia (as an AESI class) was reported as a treatment-emergent SAE for 2 (0.9%) maribavir-treated patients (neither considered related) compared with 7 (12.5%) ganciclovir/valganciclovir-treated patients (considered related for 2 [3.6%] patients).

***Tissue-invasive CMV disease/syndrome***

**Phase 3 study 303**

During the on-treatment observation period, TEAEs in the AESI class of tissue-invasive CMV disease/syndrome were reported for 3.4% of patients in each treatment group (maribavir: 8; IAT: 4) despite the longer duration of exposure to maribavir. Preferred terms for tissue-invasive CMV disease/syndrome reported during the on-treatment observation period included the following:

- CMV syndrome: maribavir: 3 (1.3%) patients (SAE for 2 [0.9%] patients); IAT: 1 (0.9%) patient
- CMV chorioretinitis: maribavir: 2 (0.9%) patients (SAEs); IAT: 1 (0.9%) patient (SAE)
- CMV colitis: maribavir: 1 (0.4%) patient (SAE); IAT: 1 (0.9%) patient
- CMV mucocutaneous ulcer: maribavir: 1 (0.4%) patient (SAE); IAT: 0 patients
- CMV GI infection: maribavir: 1 (0.4%) patient; IAT: 0 patients
- CMV enteritis: maribavir: 0 patients; IAT: 1 (0.9%) patient

Tissue-invasive CMV disease/syndrome was considered related to treatment for 1 maribavir-treated patient (CMV syndrome).

***Invasive fungal or bacterial or viral infections***

**Phase 3 study 303**

A higher proportion of maribavir-treated patients than IAT-treated patients had TEAEs mapping to the AESI class of invasive fungal or bacterial or viral infections during the on-treatment observation period (maribavir: 55 [23.5%] patients; IAT: 22 [19.0%] patients). This disparity appears to be related to the longer duration of exposure to maribavir compared to IAT. The infections were reported as treatment-emergent SAEs for 23 (9.8%) patients in the maribavir group and 6 (5.2%) patients in the IAT group. However, none of the infections (TEAEs or SAEs) in the maribavir group were considered related to treatment; whereas, infection was considered related to IAT for 1 patient (encephalitis viral). For the IAT group, patients with TEAEs within this AESI class received either ganciclovir/valganciclovir (12.5%) or foscarnet (29.8%). One patient received >1 IAT. Infections reported for more patients in the maribavir group than in the IAT group included preferred terms of the following:

- Pneumonia (8 vs 2 patients)
- BK virus infection (5 vs 4 patients)
- Enterococcal infection and herpes zoster (5 vs 0 patients)
- Staphylococcal bacteraemia (4 vs 2 patients)

- Encephalitis CMV, enterococcal bacteraemia, and Epstein-Barr virus infection reactivation (3 vs 1 patient)
- Cystitis viral (3 vs 0 patients)
- Aspergillus infection and Epstein-Barr viraemia (2 vs 1 patient)
- Epstein-Barr virus infection, Escherichia sepsis, human polyomavirus infection, pneumocystis jirovecii pneumonia, septic shock, Staphylococcal infection, and varicella zoster virus infection (2 vs 0 patients)

Bronchopulmonary aspergillosis, clostridium difficile colitis, clostridium difficile infection, cystitis klebsiella, Enterobacter infection, Escherichia bacteraemia, herpes zoster meningoencephalitis, meningitis enteroviral, parvovirus B19 infection, pneumonia cryptococcal, pneumonia haemophilus, pneumonia mycoplasmal, pseudomonal bacteraemia, pseudomonal sepsis, pulmonary tuberculosis, stenotrophomonas infection, systemic candida, and tuberculosis (1 vs 0 patients).

***GVHD***

**Phase 3 study 303**

At baseline, the percentage of patients with acute GVHD was numerically higher for patients in the maribavir group versus the IAT group (9.8% vs 6.8%). This may have contributed to the difference in the incidence rates of acute GVHD between treatment groups during the study. Twenty-one (9.0%) maribavir-treated patients had a TEAE of new or worsening GVHD during the on-treatment observation period compared with 5 (4.3%) patients in the IAT group. One-third of the maribavir-treated patients (7/21 patients) with treatment-emergent GVHD during the on-treatment observation period reported acute GVHD at baseline compared with one-fifth (1/5 patients) of the IAT group.

The GVHD was considered related to study-assigned treatment for 2 (0.9%) patients in the maribavir group (preferred terms of GVHD and acute GVHD in intestine) and none in the IAT group. The maribavir-treated patient with the TEAE of acute GVHD in intestine that was considered related to study-assigned treatment had Grade III GVHD at baseline.

***Graft rejection***

**Phase 3 study 303**

Graft rejection as an AESI class occurred for a similar percentage of patients in the maribavir and IAT groups during the on-treatment observation period (3.4% and 2.6%, respectively). Transplant rejection (type of transplant not specified) occurred for 6 maribavir-treated patients (SAE for 1 patient) and 2 patients who received foscarnet. Lung transplant rejection occurred for 1 maribavir-treated patient and 1 patient who received foscarnet. Transplant failure (HSCT) occurred for 1 maribavir-treated patient. None of these TEAEs were considered related to study-assigned treatment.

## Serious adverse events and deaths

**Serious adverse events**

**Phase 3 study 303**

In the table below TESAEs reported for 2 or more patients during the on-treatment observation period of Phase 3 study 303 are outlined.

Table 63 Treatment-emergent serious adverse events during the on-treatment observation period reported for 2 or more patients in either treatment group (maribavir or IAT) by system organ class, preferred term, treatment group, and selected IAT type (safety set) (study 303)

| System Organ Class<br>Preferred Term | IAT<br>(N=116)<br>n (%) m | Maribavir<br>400 mg BID<br>(N=234)<br>n (%) m | IAT Type<br>Ganciclovir/<br>Valganciclovir<br>(N=56)<br>n (%) m | IAT Type<br>Foscarnet<br>(N=47)<br>n (%) m |
|---|---|---|---|---|
| Any TESAE | 43 (37.1) 61 | 90 (38.5) 154 | 21 (37.5) 27 | 20 (42.6) 31 |
| **Blood and lymphatic system disorders** | 7 (6.0) 7 | 9 (3.8) 11 | 7 (12.5) 7 | 0 0 |
| Anaemia | 0 0 | 3 (1.3) 3 | 0 0 | 0 0 |
| Febrile neutropenia | 4 (3.4) 4 | 2 (0.9) 2 | 4 (7.1) 4 | 0 0 |
| Neutropenia | 3 (2.6) 3 | 0 0 | 3 (5.4) 3 | 0 0 |
| Thrombocytopenia | 0 0 | 2 (0.9) 2 | 0 0 | 0 0 |
| **Gastrointestinal disorders** | 6 (5.2) 7 | 13 (5.6) 15 | 2 (3.6) 2 | 3 (6.4) 4 |
| Abdominal pain | 0 0 | 3 (1.3) 3 | 0 0 | 0 0 |
| Diarrhoea | 0 0 | 4 (1.7) 4 | 0 0 | 0 0 |
| Gastrointestinal haemorrhage | 1 (0.9) 1 | 3 (1.3) 3 | 0 0 | 1 (2.1) 1 |
| Nausea | 2 (1.7) 2 | 2 (0.9) 2 | 0 0 | 2 (4.3) 2 |
| Vomiting | 2 (1.7) 2 | 1 (0.4) 1 | 0 0 | 1 (2.1) 1 |
| **General disorders and administration site conditions** | 3 (2.6) 3 | 12 (5.1) 12 | 0 0 | 3 (6.4) 3 |
| General physical health deterioration | 0 0 | 2 (0.9) 2 | 0 0 | 0 0 |
| Pyrexia | 2 (1.7) 2 | 3 (1.3) 3 | 0 0 | 2 (4.3) 2 |
| **Immune system disorders** | 0 0 | 5 (2.1) 6 | 0 0 | 0 0 |
| GVHD in GI tract | 0 0 | 2 (0.9) 3 | 0 0 | 0 0 |
| **Infections and infestations** | 17 (14.7) 20 | 53 (22.6) 60 | 12 (21.4) 14 | 4 (8.5) 5 |
| Bacteraemia | 1 (0.9) 1 | 2 (0.9) 2 | 1 (1.8) 1 | 0 0 |
| CMV chorioretinitis | 1 (0.9) 1 | 2 (0.9) 2 | 1 (1.8) 1 | 0 0 |
| CMV infection | 4 (3.4) 4 | 6 (2.6) 6 | 3 (5.4) 3 | 0 0 |
| CMV infection reactivation | 0 0 | 2 (0.9) 2 | 0 0 | 0 0 |
| CMV syndrome | 0 0 | 2 (0.9) 2 | 0 0 | 0 0 |
| CMV viraemia | 3 (2.6) 3 | 7 (3.0) 7 | 3 (5.4) 3 | 0 0 |
| Encephalitis CMV | 1 (0.9) 1 | 3 (1.3) 3 | 0 0 | 1 (2.1) 1 |
| Escherichia sepsis | 0 0 | 2 (0.9) 2 | 0 0 | 0 0 |
| Herpes zoster | 0 0 | 2 (0.9) 2 | 0 0 | 0 0 |
| Pneumonia | 1 (0.9) 1 | 2 (0.9) 2 | 0 0 | 1 (2.1) 1 |
| Pneumonia cytomegaloviral | 1 (0.9) 1 | 2 (0.9) 2 | 1 (1.8) 1 | 0 0 |
| Septic shock | 0 0 | 2 (0.9) 2 | 0 0 | 0 0 |
| Staphylococcal bacteraemia | 0 0 | 2 (0.9) 2 | 0 0 | 0 0 |
| **Investigations** | 1 (0.9) 1 | 6 (2.6) 6 | 0 0 | 1 (2.1) 1 |
| Weight decreased | 0 0 | 2 (0.9) 2 | 0 0 | 0 0 |
| **Metabolism and nutrition disorders** | 2 (1.7) 2 | 4 (1.7) 4 | 0 0 | 1 (2.1) 1 |
| Failure to thrive | 0 0 | 2 (0.9) 2 | 0 0 | 0 0 |
| Hypokalaemia | 2 (1.7) 2 | 0 0 | 0 0 | 1 (2.1) 1 |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | 3 (2.6) 3 | 4 (1.7) 4 | 1 (1.8) 1 | 2 (4.3) 2 |
| Leukemia recurrent | 2 (1.7) 2 | 1 (0.4) 1 | 1 (1.8) 1 | 1 (2.1) 1 |

| System Organ Class<br>Preferred Term | IAT<br>(N=116)<br>n (%) m | Maribavir<br>400 mg BID<br>(N=234)<br>n (%) m | IAT Type<br>Ganciclovir/<br>Valganciclovir<br>(N=56)<br>n (%) m | IAT Type<br>Foscarnet<br>(N=47)<br>n (%) m |
|---|---|---|---|---|
| **Psychiatric disorders** | 1 (0.9) 1 | 2 (0.9) 2 | 0 0 | 1 (2.1) 1 |
| Mental status changes | 0 0 | 2 (0.9) 2 | 0 0 | 0 0 |
| **Renal and urinary disorders** | 6 (5.2) 6 | 9 (3.8) 9 | 0 0 | 6 (12.8) 6 |
| Acute kidney injury | 4 (3.4) 4 | 8 (3.4) 8 | 0 0 | 4 (8.5) 4 |
| **Respiratory, thoracic and mediastinal disorders** | 5 (4.3) 5 | 11 (4.7) 13 | 2 (3.6) 2 | 3 (6.4) 3 |
| Dyspnoea | 1 (0.9) 1 | 2 (0.9) 2 | 1 (1.8) 1 | 0 0 |
| Hypoxia | 1 (0.9) 1 | 2 (0.9) 2 | 0 0 | 1 (2.1) 1 |
| Respiratory failure | 1 (0.9) 1 | 3 (1.3) 3 | 0 0 | 1 (2.1) 1 |
| **Vascular disorders** | 1 (0.9) 1 | 3 (1.3) 3 | 0 0 | 1 (2.1) 1 |
| Deep vein thrombosis | 0 0 | 2 (0.9) 2 | 0 0 | 0 0 |

BID=twice daily; CMV=cytomegalovirus; GI=gastrointestinal; GVHD=graft-versus-host-disease; IAT=investigator-assigned anti-CMV treatment; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects; n=number of subjects experiencing the event; m=number of events; TESAE=treatment-emergent serious adverse event

Percentages were based on the number of subjects in the safety set within each column.

Intravenous ganciclovir and oral valganciclovir were combined as the change between the 2 was allowed.
Subjects were counted once per category and once per preferred term per treatment.

The on-treatment observation period started at the time of study-assigned treatment initiation through 7 days after the last dose of study-assigned treatment or through 21 days if cidofovir was used, or until the maribavir rescue treatment initiation or until the non-study CMV treatment initiation, whichever was earlier. SAEs were defined as any treatment-emergent SAE occurring during the on-treatment observation period.

Adverse Events were coded using MedDRA, Version 23.0.

Source: Study 303 CSR, Table 14.3.1.6.1

**Phase 2 study 202**

Treatment-emergent SAEs occurred in similar proportions of patients in the 3 dose groups (ie, 65-70% of patients). Anaemia was the most frequently occurring SAE in the 400 mg BID group (10% [n=4]); anaemia was not reported for patients in the other dose groups. Cytomegalovirus infection was the next most frequently occurring SAE in the 400 mg BID group, with the incidence of CMV infection increasing with maribavir dose (8%, 13%, and 15% in the 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively). Other SAEs in the 400 mg BID group occurred in 2 or fewer patients. The SAEs that occurred in the 800 mg BID and 1200 mg BID groups were similar to those that occurred in the 400 mg BID group and occurred with similar frequency.

Eight patients in the 400 mg BID group (20%), 7 patients in the 800 mg BID group (17.5%), and 5 patients in the 1200 mg BID group (12.5%) had treatment-emergent SAEs that were considered by the investigator to be related to maribavir therapy. Per the study protocol, events of new CMV infection or reactivation were to be recorded as an AE or SAE, as appropriate. Treatment-related SAEs of CMV infection (new or worsening CMV viraemia) were reported for two 400 mg BID patients and three 800 mg BID patients. Anaemia (2 patients) was the only other treatment-related SAE reported by 2 patients in the 400 mg BID group. Treatment-related SAEs in the 800 and 1200 mg BID groups were similar in frequency to those occurring in the 400 mg BID group.

**Phase 2 study 203**

The median exposure to maribavir at any dose (43.5 days to 45 days) was longer than the median exposure to valganciclovir (30 days). As a result, the proportions of maribavir patients reporting SAEs are likely to be higher than the proportions of valganciclovir patients reporting SAEs. Treatment-emergent SAEs occurred in 40% (n=16) of patients in the maribavir 400 mg BID group and 32.5% (n=13) of patients in the valganciclovir group. There was no obvious association with maribavir dose. Acute GVHD in the maribavir 1200 mg BID group and bacterial sepsis in the valganciclovir group were the only 2 events that occurred in 3 patients; all other SAEs occurred in 2 or fewer patients in each treatment group.

Treatment-emergent SAEs considered by the investigator to be related to the study drug occurred in three maribavir 400 mg BID patients, one maribavir 800 mg BID patients, eight maribavir 1200 mg BID patients, and one valganciclovir patient. Per the study protocol, events of new CMV infection or reactivation were to be recorded as an AE or SAE, as appropriate. Three cases of CMV reactivation were classified as treatment-related SAEs; this event was reported by 1 patient each from the maribavir 400 mg BID, maribavir 800 mg BID, and valganciclovir groups. Diarrhoea was the only treatment-related SAE that occurred in 2 patients in a particular treatment group (maribavir 1200 mg BID); all other treatment-related SAEs occurred in 1 patient in each treatment group.

**Deaths**

**Phase 3 study 303**

A total of 40 patient deaths were reported for this study. This included 2 patients in the maribavir group who died within the first week of treatment (i.e, before receiving a sufficient course of therapy) as well as 4 patients (2 in each treatment group) who died more than 20 weeks after the first dose of study-assigned treatment (i.e, after the 20-week study observation period). These 4 late-occurring deaths were captured because they were associated with SAEs that were ongoing when the patients concluded participation in the study.

With respect to the onset of SAEs that resulted in death:

- 38/350 (10.9%) patients experienced fatal SAEs with onset in the overall study observation period (i.e, on-treatment or during post-treatment follow-up): 26 (11.1)% in the maribavir group and 12 (10.3%) patients in the IAT group. Most SAE preferred terms leading to death were reported for 1 patient each. The most common SAEs leading to death were due to respiratory failure or relapse or progression of underlying disease.
- 22/350 (6.3%) patients had fatal treatment-emergent SAEs with onset during the on-treatment observation period: 16 (6.8%) patients in the maribavir group and 6 (5.2%) patients in the IAT group. There was no consistent pattern of fatal treatment-emergent SAEs within or between treatment groups. The only fatal treatment-emergent SAEs reported for more than 1 patient in the on-treatment observation period were as follows:
  - Respiratory failure (maribavir: 2 patients; IAT: 1 patient [foscarnet]),
  - Acute myeloid leukaemia (recurrent) (maribavir: 1 patient; IAT:1 patient [foscarnet])
  - Leukaemia (recurrent) (maribavir: 1 patient; IAT: 1 patient [ganciclovir/valganciclovir])
- Fatal treatment-emergent SAEs due to CMV infection of any type during the on-treatment observation period were reported for 2 (0.9%) maribavir-treated patients (CMV colitis and CMV syndrome) and 1 (0.9%) patient in the IAT group who received foscarnet (CMV encephalitis).
- 16/350 (4.6%) patients had fatal SAEs with onset >7 days after the last dose (ie, during the follow-up period): 10 (4.3%) patients in the maribavir group and 6 (5.2%) patients in the IAT group. These post-treatment fatal SAEs are consistent with progression of disease in the population under study. Fatal SAEs due to CMV infection of any type in the post-treatment period were reported for 2 (0.9%) maribavir treated patients (CMV encephalitis for both patients) and 2 (1.7%) patients in the IAT group (CMV pneumonia and CMV enterocolitis).
- 1/22 (4.5%) patients who received maribavir as rescue therapy after failing IAT had a fatal treatment-emergent SAE in the maribavir rescue period.
- 1/234 (0.4%) patients died after receiving maribavir, however the onset of the fatal adverse event was prior to the first dose (recurrence of Hodgkin’s disease, classified as severe in

intensity, 3 days before taking the first dose of maribavir). This patient died approximately 3 months after initiating maribavir (cause of death: relapse Hodgkin's disease).

Fatal treatment-emergent SAEs were considered related to study-assigned treatment for 1 (0.4%) maribavir-treated patient (drug-drug interaction with outcome of sudden death on day 7, treatment with maribavir until day 4, concomitant medication voriconazole followed by posaconazole (for upper respiratory tract infection with Aspergillus) and domperidone (for anorexia), no autopsy, no additional laboratory, physical exam, ECG, or radiographic information was available beyond the baseline study visit, the Sponsor disagrees with the investigator's assessment and considers that while there was potential for drug-drug interactions resulting in fatal arrhythmia, those interactions do not reasonably include the investigational product (maribavir), rather, the most likely agents involved were domperidone (for anorexia) and posaconazole) and 1 (0.9%) IAT-treated patient (febrile neutropenia, pneumonia, and tuberculosis).

**Phase 2 study 202**

A total of 32 deaths were reported in this study: 10 (25%), 12 (30%), and 10 (25%) patients died in the 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively. No particular AE (i.e, preferred term) resulted in more than 2 deaths in any treatment group.

One death due to multi-organ failure in the 800 mg BID group was considered by the investigator to be possibly related to maribavir therapy (medical history significant for non-Hodgkin's lymphoma, chronic renal failure, and graft pancreatitis after receiving a pancreas transplant).

**Phase 2 study 203**

A total of 9 patients died in this study: 2 (5%), 1 (2.5%), and 3 (7.7%) patients died in the maribavir 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively, and 3 (7.5%) patients in the valganciclovir 900 mg BID group. No particular AE (i.e, preferred term) resulted in more than 1 deaths in any treatment group. None of the SAEs resulting in death were considered to be treatment related.

### *2.6.8.3. Laboratory findings*

Overall, a similar percentage of patients in the maribavir and IAT groups of the Phase 3 study 303 had a shift in creatinine to NCI CTCAE Grade 3 or 4 at the last on-study assessment and at the last on-study observation. However, shifts in creatinine to Grade 3 or 4 in the IAT group occurred exclusively in foscarnet-treated patients. The median time to first maximum post baseline NCI CTCAE Grade 3 or 4 increase in creatinine during the on-treatment observation period was similar in both treatment groups (maribavir: 20.5 days [range: 14 to 58 days]; IAT: 22.5 days [range: 14 to 31 days]).

Median change from baseline in liver function parameters, cholesterol, triglycerides, albumin, glucose, and creatine kinase were minimal at the last on-treatment assessment and the last on-study observation. At the last on-treatment assessment, shifts from a lower NCI CTCAE grade to Grade 3 or 4 occurred for >2% of maribavir-treated patients for increases in GGT (maribavir: 10.4%; IAT: 8.8%), glucose (maribavir: 4.4%; IAT: 0%), ALT (maribavir: 3.2%; IAT: 0%), triglycerides (maribavir: 4.1%; IAT: 1.0%), and total bilirubin (maribavir: 2.3%; IAT: 1.0%). Shifts from a lower NCI CTCAE Grade to Grade 3 or 4 for other liver function parameters, cholesterol, albumin, and creatine kinase occurred infrequently during the on-treatment observation period and the overall study period.

### *2.6.8.4. Safety in special populations*

**Age, Sex, and Race**

The incidence and types of TEAEs commonly reported during the on-treatment observation period of the Phase 3 study 303 were generally similar regardless of age, sex, or race.

The analysis based on age was performed by age categories of 18 to 44 years, 45 to 64 years, and ≥65 years in Study 303. In the 18 to 44 age group treated with maribavir, at least 1 TEAE was reported for 96.4% (53/55) patients. Similarly, in the 45 to 64 age group treated with maribavir, 96.8% (121/125) patients had at least 1 TEAE and 100% (54/54) of patients in the ≥65 age group treated with maribavir had at least 1 TEAE. In all age groups, dysgeusia was the most commonly reported TEAE and occurred with similar frequency (34.5% in the 18 to 44 age group, 39.2% in the 45 to 64 age group, and 35.2% in the ≥65 age group).

Of the 147 males in the maribavir group, 96.6% had at least 1 TEAE compared to 98.9% (86/87) females in the maribavir group. For both sexes, dysgeusia was the most commonly reported TEAE (40.8% in males and 31.0% in females).

In the table below AEs reported in Phase 3 Study 303 are summarised.

Table 64 Summary of adverse events by age group in study 303 (safety set)

| MedDRA Terms | Age <65 N (%) | | Age 65-74 N (%) | | Age 75-84 N (%) | |
|---|---|---|---|---|---|---|
| | IAT | Maribavir | IAT | Maribavir | IAT | Maribavir |
| No of subjects | 100 | 180 | 14 | 50 | 2 | 4 |
| Total AEs | 60 (60.0) | 154 (85.6) | 7 (50.0) | 42 (84.0) | 1 (50.0) | 4 (100.0) |
| AE leading to drop-out | 28 (28.0) | 25 (13.9) | 1 (7.1) | 3 (6.0) | 1 (50.0) | 2 (50.0) |
| Psychiatric disorders | 12 (12.0) | 20 (11.1) | 1 (7.1) | 6 (12.0) | 0 | 1 (25.0) |
| Nervous system disorders | 30 (30.0) | 103 (57.2) | 1 (7.1) | 29 (58.0) | 0 | 1 (25.0) |
| Accidents and injuries | 5 (5.0) | 19 (10.6) | 0 | 5 (10.0) | 0 | 0 |
| Cardiac disorders | 6 (6.0) | 13 (7.2) | 0 | 2 (4.0) | 0 | 0 |
| Vascular disorders | 10 (10.0) | 22 (12.2) | 4 (28.6) | 4 (8.0) | 0 | 2 (50.0) |
| Cerebrovascular disorders | 0 | 0 | 0 | 0 | 0 | 0 |
| Infections and infestations | 41 (41.0) | 103 (57.2) | 6 (42.9) | 30 (60.0) | 1 (50.0) | 2 (50.0) |
| Anticholinergic syndrome | 0 | 0 | 0 | 0 | 0 | 0 |
| Quality of life decreased [a] | 0 | 0 | 0 | 0 | 0 | 0 |
| Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures | 5 (5.0) | 25 (13.9) | 1 (7.1) | 3 (6.0) | 0 | 1 (25.0) |
| Dizziness | 4 (4.0) | 15 (8.3) | 1 (7.1) | 2 (4.0) | 0 | 0 |
| Fall | 0 | 3 (1.7) | 0 | 0 | 0 | 0 |
| Orthostatic Hypotension | 0 | 3 (1.7) | 0 | 0 | 0 | 1 (25.0) |
| Syncope | 0 | 3 (1.7) | 0 | 1 (2.0) | 0 | 0 |
| Depressed level of consciousness | 0 | 1 (0.6) | 0 | 0 | 0 | 0 |
| Spinal fracture | 1 (1.0) | 0 | 0 | 0 | 0 | 0 |
| Other AE appearing more frequently in older patients | | | | | | |
| Nausea | 22 (22.0) | 35 (19.4) | 3 (21.4) | 13 (26.0) | 0 | 2 (50.0) |
| Fatigue | 9 (9.0) | 20 (11.1) | 1 (7.1) | 6 (12.0) | 0 | 2 (50.0) |
| Taste disorder | 1 (1.0) | 14 (7.8) | 0 | 7 (14.0) | 0 | 0 |
| Abdominal pain | 3 (3.0) | 12 (6.7) | 0 | 6 (12.0) | 0 | 0 |

| MedDRA Terms | Age <65 N (%) | | Age 65-74 N (%) | | Age 75-84 N (%) | |
|---|---|---|---|---|---|---|
| | IAT | Maribavir | IAT | Maribavir | IAT | Maribavir |
| Oedema peripheral | 7 (7.0) | 11 (6.1) | 2 (14.3) | 6 (12.0) | 0 | 0 |
| Headache | 15 (15.0) | 10 (5.6) | 0 | 8 (16.0) | 0 | 1 (25.0) |
| Pleural effusion | 2 (2.0) | 2 (1.1) | 1 (7.1) | 4 (8.0) | 0 | 0 |
| SAEs | N of SAEs | N of SAEs | N of SAEs | N of SAEs | N of SAEs | N of SAEs |
| Total | 70 | 180 | 10 | 51 | 3 | 4 |
| Fatal | 9 | 21 | 2 | 7 | 1 | 0 |
| Hospitalization/prolong existing hospitalization | 61 | 163 | 7 | 46 | 3 | 4 |
| Life-threatening | 11 | 9 | 0 | 8 | 0 | 0 |
| Disability/ incapacity | 0 | 2 | 0 | 4 | 0 | 0 |
| Other (medically significant) | 5 | 22 | 3 | 5 | 0 | 1 |

AE=adverse event; CMV=cytomegalovirus; HRQOL=Health-related Quality of Life; IAT=investigator assigned treatment; MedDRA=medical dictionary for regulatory activities; N=number of subjects; n=number of subjects experiencing the event; SAE=serious adverse event; SF-36v2=Short-Form-36 version 2; TEAE=treatment-emergent adverse event.

Percentages are based on the number of subjects in the Safety set within each column.

Subjects were counted once per category per treatment. The on-treatment observation period started at the time of study treatment initiation through 7 days after the last dose of study treatment or through 21 days if cidofovir is used, or until the maribavir rescue treatment initiation or until the non-study CMV treatment initiation, whichever was earlier. TEAEs were defined as any adverse event occurring during the on-treatment observation period.

[a]Health-related Quality of Life in the study was assessed using the SF-36v2 which is a validated generic measure of general health status. The overall observed changes for SF-36v2 assessments were minimal and did not reflect meaningful improvement or deterioration in HRQOL, including the elderly patients in the trial

Adverse Events were coded using MedDRA, Version 23.0.

Source: Table st00549 14.3.1.3.1 AE Other 303 Q137; Study 303 CSR Listing 16.2.7.1; Table st00549 14.3.1.1.1 AE Special 303 Q137

The subgroups based on race comprised White, Black/African American, Asian, and others. Since meaningful interpretation of the results for the Asian and other populations was limited by the small number of patients, these results are not presented. In the subgroup of White patients who received maribavir, 98.3% (175/178) of patients had at least 1 TEAE, which was similar to that reported for Black/African American patients (93.1%, 27/29).

**Renally Impaired Patients**

The pharmacokinetics of maribavir following a single 400 mg dose have been characterised in patients with varying degrees of renal impairment: mild (creatinine clearance [CrCl] 50 mL/minute to 80 mL/minute); moderate (CrCl 30 mL/minute to <50 mL/minute); and severe (CrCl <30 mL/minute), and compared with patients of similar age, weight, and sex with normal renal function (i.e, CrCl >80 mL/minute) (Study 1263-101).

Mean PK parameter estimates based on total or unbound plasma maribavir concentrations for patients with normal renal function (creatinine clearance >80 mL/min), mild/moderate renal impairment, and severe renal impairment were similar. Mild, moderate, or severe renal impairment does not affect the PK of maribavir. Because maribavir has demonstrated time-independent PK, the results from this single-dose renal impairment study are applicable to multiple BID doses of maribavir.

Maribavir has not been studied in patients with end-stage renal disease (CrCl less than 10 mL/min), including patients on dialysis.

**Hepatically Impaired Patients**

Even though maribavir is primarily eliminated by hepatic metabolism, no clinically significant effect of moderate hepatic impairment (Child-Pugh Class B score of 7-9) was observed on total or unbound maribavir PK parameters following a single dose 200 mg of maribavir. Compared to the healthy control patients, AUC0-∞ and Cmax were 26% and 35% higher, respectively, for maribavir, in patients with moderate hepatic impairment. The trend observed with the unbound maribavir PK parameters was consistent with that observed with the total PK parameters, though the extend was less. Because exposure to maribavir was approximately dose proportional following a single dose from 50 to 1600 mg and following multiple doses up to 2400 mg per day and maribavir has demonstrated time-independent PK, the results from this single-dose hepatic impairment study are applicable to multiple BID doses of maribavir.

The modest increase in maribavir exposure in patients with moderate hepatic impairment is not considered clinically significant, therefore, no dose adjustment is needed for patients with mild or moderate hepatic impairment. Maribavir has not been studied in patients with severe hepatic impairment.

### *2.6.8.5. Immunological events*

No specific information is provided for immunological events. For cases of GVHD and graft rejection, please see section AESIs.

### *2.6.8.6. Safety related to drug-drug interactions and other interactions*

Regarding cases of immunosuppressant drug level increased, please see section AESIs.

### *2.6.8.7. Discontinuation due to adverse events*

**Phase 3 study 303**

During the on-treatment observation period, TEAEs leading to discontinuation of study-assigned treatment were reported for a greater proportion of patients in the IAT group (31.9%) than in the maribavir group (13.2%). Treatment discontinuation due to TEAEs by IAT type was 32.1% for ganciclovir/valganciclovir, 36.2% for foscarnet, and 33.3% for cidofovir.

**Phase 2 study 202**

In Phase 2 study 202, 34% of patients were discontinued from maribavir due to an AE. The highest rate of discontinuation occurred in the 800 mg BID group (43%), with generally comparable rates occurring in the 400 mg BID (28%) and 1200 mg BID (33%) groups.

**Phase 2 study 203**

In Phase 2 study 203, 30% (n=12) of patients in the maribavir 400 mg BID group had TEAEs that led to discontinuation of study drug, compared with 12.5% (n=5) of valganciclovir patients. The proportions of TEAEs leading to study drug discontinuation were not related to maribavir dose.

### *2.6.8.8. Post marketing experience*

N/A

## 2.6.9. Discussion on clinical safety

**Safety Database**

The clinical safety database includes data from two Phase 2 and one Phase 3 studies of maribavir as a CMV treatment in transplant recipients, three Phase 2 and 3 studies of maribavir for CMV prevention in transplant recipients, 17 Phase 1 studies, and 1 taste assessment study.

The results from pivotal study 303 are regarded as primary safety data. Data from Phase 2 and Phase 1 studies were not integrated into safety analysis due to the differences in patient populations and/or study designs as well as differences in dosages and treatment duration across the studies, which is agreed.

The overall safety population consists of 1,555 patients which have been exposed to maribavir across a broad range of doses (50 mg to 2400 mg daily) and a range of treatment durations (single dose up to 24 weeks) in 23 completed clinical studies. Overall, 495 transplant recipients with CMV infection were treated with maribavir 400 mg BID to 1200 mg BID (800 mg/day to 2400 mg /day) for 8 weeks to 24 weeks. Of these, 234 patients received maribavir 400 mg BID for up to 8 weeks in Phase 3 study 303. In Phase 2 study 202, 40 patients were treated with maribavir 400 mg BID for up to 24 weeks and in Phase 2 study 203, 40 patients received maribavir 400 mg BID for up to 12 weeks. Overall, the size of the safety database is considered acceptable.

It is notable that the assessment and isolation of the adverse effects profile of maribavir in -303 study is hampered by the open-label design and by the heterogeneity of IAT agents in the comparator arm, each of which has a complicated side effects profile, including haematological and renal events; the same goes for valganciclovir in the -203 study. Furthermore, the background disease is different in patients post SOT and post HSCT.

**Adverse events**

**Phase 3 study 303**

During the on-treatment observation period of the Phase 3 study 303, 97.4% of the patients in the maribavir group and 91.4% of the patients in the IAT group had at least one TEAE. The high incidence of TEAEs in both treatment groups is in accordance with the expected rate in a post-transplant population. The higher incidence in the maribavir group could be explained by the longer treatment period. When comparing the overall study observation period the rate of TEAEs in the maribavir group and IAT group is 99.1% and 96.6%, respectively.

The most frequently reported TEAE during the Phase 3 study 303 was dysgeusia, which occurred predominantly in maribavir-treated patients (maribavir: 37.2%; IAT: 3.4%).

Maribavir (400 mg BID) was shown to increase the whole blood trough concentration of tacrolimus by 57% in a clinical drug interaction study. Accordingly, drug levels of immunosuppressants were monitored during Phase 3 study 303. As expected, the TEAE of immunosuppressant drug level increased was reported in a higher proportion of patients in the maribavir group (9.0%) compared to the IAT group (0.9%).

Neutropenia was the most frequently reported TEAE in the IAT group during the on-treatment observation period. It occurred at a lower incidence for maribavir-treated patients than for IAT (9.4% vs 22.4%). In line with the known safety profile, neutropenia occurred predominantly in patients who received ganciclovir/valganciclovir (33.9%). Febrile neutropenia (0.9% and 7.1%), leukopenia (3.0% and 12.5%), and thrombocytopenia (4.7% and 8.9%) occurred less frequently in maribavir-treated patients than in ganciclovir/valganciclovir-treated patients.

The incidence of anaemia was 12.4% for maribavir-treated patients, 12.1% for IAT overall, 7.1% for ganciclovir/valganciclovir-treated patients, and 19.1% for foscarnet-treated patients. The proportion of patients with anaemia considered related to treatment was lower for maribavir-treated patients than for patients who received either ganciclovir/valganciclovir or foscarnet (maribavir: 1.3%; IAT: 7.8%; ganciclovir/valganciclovir: 5.4%; foscarnet: 12.8%). According to the non-clinical safety considerations in pivotal repeat-dose oral toxicity studies in rats (6 months) and monkeys (12 months), one of the major findings was reversible regenerative anaemia. Therefore, the Applicant was requested to present an in-depth analysis of cases with anaemia observed during treatment with maribavir 400 mg BID (from Phase 3 study 303 and from Phase 2 studies 202 and 203). Overall, no clear relationship between treatment with maribavir and the event of anaemia can be concluded based on the analysis provided. In all reported cases alternative aetiology of anaemia including patient's medical history and concomitant use of medications with known adverse reaction of anaemia was present. Nevertheless, the issue should be closely evaluated in the upcoming PSURs.

Maribavir-treated patients had a lower incidence of TEAEs than foscarnet-treated patients for the TEAEs frequently reported in foscarnet-treated patients: acute kidney injury (8.5% and 21.3%), hypokalaemia (3.4% and 19.1%), headache (8.1% and 17.0%), hypomagnesaemia (3.8% and 14.9%), hypertension (3.8% and 12.8%), peripheral oedema (7.3% and 10.6%), hypophosphataemia (1.7% and 10.6%), and paraesthesia (1.7% and 10.6%).

The following TEAEs were more frequently reported in maribavir-treated patients compared to IAT group: abdominal pain (7.7% vs. 2.6%), arthralgia (5.6% vs. 2.6%), dizziness (7.3% vs. 4.3%), mental status changes (2.6% vs. 0.9%). Therefore, the Applicant was requested to provide more information about the cases with abdominal pain, arthralgia, dizziness and mental status changes after treatment with maribavir. Overall, all reported cases had alternative etiologies that may have been attributed to the event such as medical history, concurrent AEs and concomitant medications where these events are known adverse reactions. No clear signal could be identified based on these cases. Nevertheless, upper abdominal pain is suggested for inclusion in section 4.8 of the SmPC, which is agreed.

Treatment-related TEAEs occurred in a higher proportion of maribavir-treated patients than in patients who received IAT (maribavir: 60.3%; IAT: 49.1%) during the on-treatment observation period. This observed difference was driven largely by reports of the TEAE of dysgeusia.

The Applicant provided an overview of TEAEs considered related to study-assigned treatment occurring in more than one patient during the on-treatment observation period of the Phase 3 study 303. Overall, TEAEs considered related to study-assigned treatment in the SOCs Blood and lymphatic system disorders, General disorders and administration site conditions, Metabolism and nutrition disorders and Renal and urinary disorders were less commonly reported in the maribavir group compared to IAT group. In particular, cases of anaemia (1.3% vs. 7.8%), neutropenia (1.7% vs. 13.8%), thrombocytopenia (0% vs. 5.2%) and acute kidney injury (1.7% vs. 7.8%) considered related to treatment were less reported after treatment with maribavir compared to IAT. In contrast, more TEAEs considered related to study-assigned treatment were detectable in the maribavir group in the SOC Nervous system disorders, which is driven by cases with dysgeusia (35.9% vs. 0.9%) and the SOC infections and infestations (5.1% vs. 2.6), which is driven by cases of CMV infection (0.9%, 0%) and viraemia (3.8%, 0.9%). Furthermore, cases of immunosuppressant drug level increased were reported more frequently in the maribavir group (6.0 vs. 0%).

The rate of deaths in the Phase 3 study 303 (maribavir group 11.5%, IAT group 11.2%) was comparable between treatment groups.

The safety profile of maribavir in the phase II studies was consistent with that in study 303.

Due to the open label design there is potential bias, as known adverse reactions of the comparator treatment are reported as related to IAT regardless of other possible causes, whereas TEAEs after treatment with maribavir could have been reported more reservedly as related to treatment. This was also highlighted by the EMA GCP inspectors during the GCP inspection.

Overall, the safety profile of maribavir is more favourable than that of alternative treatments.

**AEs of special interest (AESIs)**

*Taste disturbance*

Taste disturbance events, including dysgeusia occurred in approximately half of patients receiving 400 mg BID in the 3 clinical studies (Phase 3 study 303: 46.2%, Phase 2 study 202: 60% (dysgeusia), Phase 2 study 203: 45% (dysgeusia)). Most events were mild to moderate in severity and occurred early upon initiation of treatment. As described for Phase 2 studies 202 and 203, the majority of TEAEs of dysgeusia were reported as "metallic taste" or "bitter taste". While some evidence of dose dependence was observed in Phase 2 study 202 (60%, 63%, and 73% in the maribavir 400 mg BID, 800 mg BID, and 1200 mg BID groups), the proportion of patients with dysgeusia decreased as maribavir dose increased in Phase 2 study 203 (45.0%, 40.0%, and 35.9% in the maribavir 400 mg BID, 800 mg BID, and 1200 mg BID groups). Most events associated with taste disturbance were considered by the investigator to be related to maribavir. Dysgeusia led to treatment discontinuation for 2 (0.9%) patients in Phase 3 study 303 and 1 patient in Phase 2 study 202 (maribavir 1200 mg BID). No patients in Phase 2 study 203 discontinued because of events of dysgeusia. The Applicant analysed if cases of dysgeusia reported in Phase 3 study 303 and in Phase 2 studies 202 and 203 were related to any changes in vital signs, body weight or caloric intake. Overall, cases of dysgeusia reported in Phase 3 Study 303 and in Phase 2 studies 202 and 203 were not related to changes in vital signs and body weight. Data on caloric intake were not collected in Phase 3 and 2 Studies.

For Phase 3 study 303 time to event analyses were performed. From the 119 patients who had dysgeusia (or similar terms) while on maribavir treatment, the event(s) resolved during treatment for 44 (37.0%) patients, with an observed median duration of dysgeusia while on treatment of 43 days (range: 7 to 59 days). The Kaplan-Meier estimate of time to resolution of dysgeusia while on treatment was 58 days. From the 75 patients who had dysgeusia (or similar terms) that was ongoing at the time of the last dose of maribavir, the event(s) resolved for 67 (89.3%) patients, with an observed median duration of dysgeusia off treatment of 6 days. The median Kaplan-Meier estimate of time to resolution of dysgeusia following discontinuation of study drug was 7 days (95% CI: 4 to 8 days). According to the analyses provided, in 63% of the reported cases dysgeusia (or similar terms) was detectable until the end of treatment with maribavir. Of these, in 89.3% the event(s) of dysgeusia resolved. Overall, of the 119 patients who had dysgeusia (or similar terms) while on maribavir treatment, in 111 patients (93.3%) the symptoms of taste disturbance resolved during or the days after treatment. In 8 patients (10.7%) the symptoms remained. The Applicant further clarified that only 4 events were indeed ongoing at the end of the study. Of the 8 events one event of taste disturbance is considered as not applicable. In this case, the subject had a prior history of dysgeusia and this event occurred 30 days after the treatment was ended. For 3 events, the outcome could not be assessed because the subjects had a fatal outcome. In the remaining 4 cases reported as not recovered subjects were receiving other concomitant medications such as valganciclovir and amlodipine, which are known to be associated with dysgeusia.

*Nausea/diarrhoea/vomiting*

In nonclinical investigations histologic change of mucosal cell hyperplasia in the intestinal tract associated with clinical observations of soft to liquid stool, electrolyte changes and dehydration was

observed. In Phase 3 study 303 the incidence of diarrhoea was comparable between maribavir group and IAT group (18.8% vs. 20.7%). Most of these patients had diarrhoea that were Grade 1 or 2 in severity. One (0.4%) maribavir-treated patient had a Grade 4 event of diarrhoea. In 3.8% of patients the event of diarrhoea was considered related to study-assigned treatment (IAT group 5.2%). In Phase 2 study diarrhoea occurred in 12.5% of the patients in the maribavir 400 mg BID group. Diarrhoea occurred more frequently in the 2 higher maribavir dose groups (32.5% of patients in the 800 mg BID group and 25.0% of patients in the 1200 mg BID group). In line with this, in Phase 2 study 203 the rate of diarrhoea increased with higher maribavir doses (17.5% of patients in the 400 mg and 800 mg BID groups and 25.6% of patients in the 1200 mg BID group (compared with 10.0% of patients in the valganciclovir group).

Diarrhoea was included as an adverse reaction with a frequency of very common in section 4.8 of the SmPC, which is supported. Furthermore, the Applicant analysed shifts from normal values of electrolytes in patients with diarrhoea during treatment with maribavir 400 mg BID reported in Phase 3 Study 303 and Phase 2 studies 202 and 203. In addition, shifts from normal values of electrolytes in patients with diarrhoea in the IAT group were provided and compared to results for maribavir. Overall, no significant differences between maribavir and comparator groups could be identified.

Nausea (maribavir: 50 (21.4%) patients; IAT: 25 (21.6%) patients) and vomiting (maribavir: 33 (14.1%) patients; IAT: 19 (16.4%) patients) were reported for a similar percentage of patients in the maribavir and IAT group in Phase 3 study 303. Most reported TEAEs were Grade 1 or 2 in severity. Cases of nausea and vomiting were considered related to study-assigned treatment in 8.5% and 7.7% of maribavir treated patients. In Phase 2 study 202, 37.5% and 27.5% of patients in the maribavir 400 mg BID group reported events of nausea and vomiting. In Phase 2 study 203, the percentage of patients reporting events of nausea was higher in the maribavir 400 mg BID group (22.5%) compared with the valganciclovir group (15%), while similar proportions of patients in the 2 groups (10.0%) reported vomiting. Overall, there was no evidence that the occurrence of nausea and vomiting was related to maribavir dose.

*Immunosuppressant drug level increased*

During Phase 3 study 303 a higher rate of immunosuppressant drug concentration level increased was reported in maribavir-treated patients (9.0%) compared to patients treated with IAT (0.9%). In 6% of patients increased drug level of immunosuppressant was considered related to maribavir. In one patient the increased drug level of immunosuppressant was reported as a TESAE.

The rates of immunosuppressant drug concentration level increased were in general comparable in Phase 2 studies 202 and 203. The occurrence of TEAEs of increased immunosuppressant drug levels appeared to be dose related, with the highest proportion of patients with increased immunosuppressant drug level events in the 1200 mg BID dose groups (Phase 2 study 202 15%, Phase 2 study 203 15.4%).

The Applicant was requested to further analyse if immunosuppressant drug concentration level increased in maribavir 400 mg BID treated patients resulted in a reporting of adverse events related to the immunosuppressant drug (including cases of graft rejection). As expected, in a part of the patients with immunosuppressant drug concentration level increased additional TEAEs were reported that could be related to the increased immunosuppressant drug level, such as cases of acute kidney injury and blood creatinine increased. Furthermore, one case of worsening of graft vs host disease is described.

The Applicant included a warning in section 4.4 of the SmPC in addition to the information in section 4.5 to inform about the risk of immunosuppressant drug concentration level increased, which is supported taking into account that immunosuppressants are given frequently in the target population. Furthermore, immunosuppressant drug level increased was defined as important identified risks in the

RMP. Further evaluation is suggested in the context of an ongoing study (SHP-620-302) and post-marketing by means of follow-up questionnaire. As sufficient scientific evidence is recognised for the increase in immunosuppressant levels, but there is currently insufficient evidence for the risk of increased SAEs due to increased immunosuppressant levels, this risk is renamed to "Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level" and included as important potential risk in the RMP.

*Rash*

In the Phase 3 study 303 AEs related to rash were reported more frequently in the maribavir group (7.3%) than in the IAT group (2.6%). However, none of these events were considered as related to treatment with maribavir. In the Phase 2 study 202 TEAE related to rash was reported for 7 (17.5%) maribavir 400 mg BID patients, 6 (15.0%) 800 mg BID patients, and 3 (7.5%) 1200 mg BID patients. In 8 of the 16 patients the event of rash was considered to be related to maribavir. In Phase 2 study 203 TEAE related to rash was reported in 2 (5.0%) maribavir 400 mg BID treated patients, 4 (10.0%) maribavir 800 mg treated patients, 1 (2.6%) maribavir 1200 mg treated patient, and 3 (7.5%) valganciclovir-treated patients. In none of the maribavir 400 mg BID treated patients the TEAE related to rash was considered related to maribavir. Overall, TEAEs related to rash were of mild or moderate severity and no treatment discontinuations were described.

*Neutropenia*

Neutropenia occurred less common in maribavir-treated patients than in IAT group during Phase 3 study 303 (maribavir: 24 [10.3%] patients; IAT: 30 [25.9%] patients - ganciclovir/valganciclovir-treated patients: 22 [39.3%], foscarnet-treated patients: 8 [17.0%]). In 32.1% of patients treated with ganciclovir/valganciclovir the event of neutropenia was considered related to treatment, whereas the rate of treatment related events of neutropenia was 4.3% in foscarnet-treated patients and 1.7% in maribavir-treated patients.

Neutropenia is a known very common side effect of ganciclovir/valganciclovir. Furthermore, neutropenia is labelled as an adverse reaction in section 4.8 of the SmPC of foscarnet with frequency common. Overall, regarding the risk of neutropenia there seems to be a significant advantage of maribavir over ganciclovir/valganciclovir as well as an advantage over foscarnet.

*Tissue-invasive CMV disease/syndrome*

In the Phase 3 study 303 TEAEs in the AESI class of tissue-invasive CMV disease/syndrome were reported for 3.4% of patients in each treatment group. Overall, no safety signal could be identified based on the data presented.

*Invasive fungal or bacterial or viral infections*

In Phase 3 study 303 (on-treatment period) a higher proportion of maribavir-treated patients had TEAEs related to invasive fungal or bacterial or viral infections compared to IAT-treated patients (23.5% vs. 19.0%). Furthermore, in 9.8% of patients in the maribavir group and 5.2% of patients in the IAT group the infections were reported as TESAEs. However, none of the infections in the maribavir group were considered related to treatment. The applicant justifies the higher rates of maribavir with the longer duration of exposure to maribavir compared to IAT which is acceptable taking the high risk of infections in the target population into account.

*GVHD*

In the Phase 3 study 303, at baseline, the rate of patients with acute GVHD was numerically higher for patients in the maribavir group versus the IAT group (9.8% vs 6.8%). This could be a reason why the rate of a TEAE of new or worsening GVHD during the on-treatment observation period was higher in

maribavir-treated patients (9.0%) compared to patients in the IAT group (4.3%). When comparing TEAEs of a new onset of treatment-emergent GVHD the difference between treatment groups is less pronounced (6% vs. 3.4%).

Two cases of GVHD reported during Phase 3 Study 303 were considered related to treatment with maribavir. One of these patients with a nonserious AE of GVHD in the intestine had a GVHD at baseline, the other patient experienced a non-serious AE of graft versus host disease, which was reported as "cutaneous GVHD". No safety signal could be identified based on these single cases.

*Graft rejection*

In the Phase 3 study 303 the rate of graft rejection was comparable between treatment groups (maribavir 3.4%, IAT 2.6%). None of these TEAEs were considered related to study-assigned treatment.

**Serious adverse events**

**Phase 3 study 303**

The rate of reported treatment-emergent SAEs was similar in the maribavir and IAT groups during the Phase 3 study 303 (38.5% vs. 37.1%). As expected in a post-transplant population, most SAEs were detectable in the infections and infestations SOC. For the assessment of these cases, please see section AESIs above.

Overall, more cases of SAEs neutropenia were reported in the IAT group compared to the maribavir group (3 [2.6%] vs. 0). Regarding other SAEs no differences between treatment groups could be identified.

Treatment-emergent SAEs considered related to study-assigned treatment were reported less frequently in the maribavir group than in the IAT group (5.1% and 14.7%) which was partly caused by more cases of neutropenia and febrile neutropenia in the IAT group.

**Phase 2 study 202**

In the maribavir 400 mg BID group of the Phase 2 study 202 the rate of patients with TESAEs were higher compared to the rate in the Phase 3 study 303 (70% vs. 38.5%). Anaemia was the most frequently occurring SAE in the 400 mg BID group (10% [n=4]). Except reported cases of cytomegalovirus infection (8%), other SAEs occurred in the 400 mg BID group in 2 or fewer patients. In the 400 mg BID group 8 patients (20%) had treatment-emergent SAEs that were considered to be related to maribavir therapy. No safety signal could be identified based on these cases.

**Phase 2 study 203**

In the Phase 2 study 203 in 40% of patients in the maribavir 400 mg BID group and 32.5% in the valganciclovir group SAEs were reported. The difference was justified by the longer treatment duration of maribavir compared to valganciclovir. All SAEs in the maribavir 400 mg BID group occurred in 2 or less cases. SAEs considered related to the study drug were reported in 3 maribavir 400 mg BID patients. No safety signal could be identified based on these cases.

**Deaths**

**Phase 3 study 303**

In the Phase 3 study 303 the rate of deaths (maribavir group 11.5%, IAT group 11.2%) as well as the timing of deaths were comparable between treatment groups. The only fatal TESAEs reported for more than 1 patient were respiratory failure (maribavir: 2 patients; IAT: 1 patient), acute myeloid leukaemia (recurrent) (maribavir: 1 patient; IAT:1 patient) and leukaemia (recurrent) (maribavir: 1 patient; IAT:

1 patient). The reported post-treatment fatal SAEs were consistent with progression of disease in the population under study. Overall, no safety signal could be identified based on the information of death cases provided.

In 1 (0.4%) maribavir-treated patient and 1 (0.9%) valganciclovir-treated patient (febrile neutropenia and resulting pneumonia and tuberculosis) fatal treatment-emergent SAEs were considered related to study-assigned treatment. In the maribavir group 1 case of sudden death was reported . Maribavir was administered for at least 4 days. However, on day 7 the patient was found dead at home. The investigator interpreted this event as sudden cardiac death due to arrhythmia, and reported it as related to maribavir based on the possibility of drug-drug interaction, with posaconazole cited as the particular agent of concern causing the arrhythmia. The Applicant stated that while there was potential for drug-drug interactions resulting in fatal arrhythmia, those interactions do not reasonably include the investigational product (maribavir). Rather, the most likely agents involved were domperidone (for anorexia) and posaconazole, both started during hospitalisation and continued at discharge. This is supported by the information in the product information of domperidone where it is stated that domperidone is associated with QTc prolongation and increased risk of sudden cardiac death and that concurrent use of domperidone with potent CYP3A4 inhibitors (such as posaconazole) is contraindicated. Overall, the argumentation of the Applicant is agreed and the concomitant administration of domperidone and posaconazole represents the more likely cause of sudden death.

**Phase 2 study 202**

In 25% of patients in the maribavir 400 mg BID group death was reported. The higher rate compared to Phase 3 study 303 could be explained by the longer study period. Overall, no particular AE resulted in more than 2 deaths. In one patient in the 800 mg BID group the death due to multi-organ failure was considered to be possibly related to maribavir therapy. However, due to pronounced medical history (non-Hodgkin's lymphoma, chronic renal failure, and graft pancreatitis after receiving a pancreas transplant) no further conclusion is possible based on this case.

**Phase 2 study 203**

In the Phase 2 study 203 in 5% (2 cases) of patients in the maribavir 400 mg BID group death was reported and none of the SAEs resulting in death were considered to be treatment related. No signal could be identified based in the cases provided.

**Laboratory findings**

In Phase 3 study 303 the rates of potentially clinically significant creatinine values were comparable between treatment groups. Median change from baseline in liver function parameters, cholesterol, triglycerides, albumin, glucose, and creatine kinase were minimal at the last on-treatment assessment and the last on-study observation. According to the documentation, at the last on-treatment assessment, shifts from a lower NCI CTCAE grade to Grade 3 or 4 occurred in 4.4% of maribavir-treated patients for glucose (IAT: 0%), in 3.2% of maribavir-treated patients for ALT (IAT: 0%) and 4.1% of maribavir-treated patients for triglycerides (IAT: 1.0%). Therefore, the Applicant was requested to provide further information about these shifts in laboratory parameters and to justify the differences in treatment groups. Overall, no correlation to treatment with maribavir can be established based on the information of cases with shifts from a lower NCI CTCAE grade to Grade 3 or 4.

No safety signal could be identified based on the data from Phase 2 studies 202 and 203.

**Safety in special populations**

Age, Sex, and Race

Regarding age, sex and race no significant differences in safety data were identified.

Renally Impaired Patients

The Applicant was requested to compare safety data in patients with different degrees of renal impairment from Phase 3 study 303. Overall, 81 patients with normal renal function, 71 patients with mild renal impairment and 68 patients with moderate or severe renal impairment received maribavir during Phase 3 study 303. Based on the data provided, the safety profile was in general comparable between patient groups. As expected, the rate of blood creatinine increased was higher the worse the renal function was (mild renal impairment 5.6%, moderate/severe 10.3%).

Hepatically Impaired Patients

The Applicant was requested to compare safety data in patients with different degrees of hepatic impairment from Phase 3 study 303. Overall, only a very limited number of patients with hepatic impairment received maribavir during Phase 3 study 303 (9 patients with grade 1 and 4 patients with grade 2 hepatic impairment). Therefore, a meaningful comparison of the safety profile between patients with different degrees of hepatic impairment is not possible.

**Safety related to drug-drug interactions and other interactions**

Pharmacokinetic-based DDI risk is low, and dose adjustment of maribavir is only needed when maribavir is coadministered with a strong or moderate CYP3A4 inducer. With the exception of selected immunosuppressants and rosuvastatin, coadministration with maribavir does not impact the use or outcomes of a wide range of other drugs commonly used in the target patient population.

Regarding cases of immunosuppressant drug level increased, please see section AESIs above.

**Discontinuation due to AEs**

**Phase 3 study 303**

In the Phase 3 study 303 the rate of TEAEs leading to discontinuation of study-assigned treatment was significantly less in the maribavir group (13.2%) compared to the IAT group (31.9%). This difference was mainly driven by TEAEs in the SOCs of blood and lymphatic system disorders and renal and urinary disorders that led to treatment discontinuation in the IAT group.

The most frequently reported on-treatment TEAE in the maribavir group dysgeusia led to treatment discontinuation for only 2 (0.9%) maribavir-treated patients.

**Phase 2 study 202**

In the Phase 2 study 202, 28% of patients in the maribavir 400 mg BID group were discontinued due to an AE. The rate was comparable in the maribavir 1200 mg BID group (33%) and higher in the maribavir 800 mg BID group (43%). When comparing to the Phase 3 study 303 the rate in the Phase 2 study 202 was higher which could be explained by the significant longer treatment period (up to 24 weeks). Furthermore, it should be noted that only a limited number of patients received maribavir 400 mg BID (n=40). Except cases of CMV infection, no other particular TEAE led to discontinuation of maribavir in more than 1 patient in each treatment group.

**Phase 2 study 203**

In the Phase 2 study 203, 30% of patients in the maribavir 400 mg BID group were discontinued due to an AE compared to 12.5% of valganciclovir patients. The rates in the maribavir 800 mg BID and 1200 mg BID groups were 12.5% and 25.6%. Compared to the Phase 3 study 303 the rate in the maribavir 400 mg BID group of the Phase 2 study 203 was higher which could be explained by the longer treatment period (up to 12 weeks). Furthermore, only a limited number of patients received maribavir 400 mg BID (n=40). Except cases of CMV infection, no other particular TEAE led to discontinuation of maribavir in more than 1 patient in each treatment group.

**Determination of labelling of section 4.8 of the SmPC**

The Applicant sufficiently justified, which adverse reactions should be labelled in section 4.8 of the SmPC considering the recommendations in the SmPC-Guideline and the related TEAEs reported during Phase 3 Study 303. Furthermore, the Applicant carefully evaluated if further adverse reactions reported during Phase 1 and Phase 2 studies need to be included into section 4.8. The following adverse reactions are included in section 4.8 of the SmPC:

| System Organ Class | Frequency | Adverse reactions |
|---|---|---|
| **Nervous system disorders** | Very common | Taste disturbance* |
| | Common | Headache |
| **Gastrointestinal disorders** | Very Common | Diarrhoea, Nausea, Vomiting |
| | Common | Abdominal pain upper |
| **General disorders and administration site conditions** | Very common | Fatigue |
| | Common | Decreased appetite |
| **Investigations** | Common | Immunosuppressant drug level increased*, Weight decreased |

For the determination of the frequency of adverse reactions the Applicant used the frequencies of adverse events reported during Phase 3 Study 303. Taking the concerns regarding a potentially biased relatedness assessment identified during the GCP inspection into account this is agreed.

## 2.6.10. Conclusions on the clinical safety

Overall, the safety profile of maribavir appears favourable and manageable in the treatment context, with dysgeusia and abdominal complaints as the main side effects.

# *2.7. Risk Management Plan*

## 2.7.1. Safety concerns

Summary of safety concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • None |
| Important potential risks | • Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level |
| Missing information | • Use in patients with end stage renal disease (ESRD) including peritoneal dialysis or haemodialysis |

## 2.7.2. Pharmacovigilance plan

The Applicant proposes routine and additional pharmacovigilance activities to monitor the safety concerns. Routine PhV activities are supplemented with FUQ to further characterised the important potential risk use in "Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level".

### *Summary of planned additional PhV activities from RMP*

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation | | | | |
| Not applicable | | | | |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances | | | | |
| Not applicable | | | | |
| **Category 3** - Required additional pharmacovigilance activities | | | | |
| SHP620-302: A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients<br><br>Ongoing | Primary Objective<br><br>The primary objective of the study is to compare the efficacy of maribavir to valganciclovir in CMV viraemia clearance at the end of Study Week 8 in asymptomatic CMV infection in HSCT recipients<br><br>A list of secondary objectives can be found in Annex 2. | Important potential risk: Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level | Final study report | February 2023 |
| Study number TBD<br><br>Retrospective chart review study on safety outcomes associated with use of maribavir in patients with post-transplant | Evaluate the known and potential safety risks for patients treated with maribavir who also have end-stage renal disease including patients on peritoneal dialysis or haemodialysis | Missing information: Use in patients with end stage renal disease (ESDR) including peritoneal dialysis or haemodialysis | Protocol submission | Q2 2023 |

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| refractory or resistant cytomegalovirus (CMV) infection and having end-stage renal disease (ESDR) including patients on peritoneal dialysis or haemodialysis<br><br>Planned | | | | |

## 2.7.3. Risk minimisation measures

**Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concerns**

| Safety concern | Risk minimisation measure | Pharmacovigilance activities |
|---|---|---|
| Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level | **Routine risk minimisation measures:**<br>SmPC Section 4.4, Section 4.5, Section 4.8 and PL Section 2.<br>The prescribers are informed of the potential for increased immunosuppressant drug level while patients are on maribavir therapy. The prescribers are advised to frequently monitor level of these immunosuppressant drugs (sirolimus, tacrolimus, everolimus, and cyclosporine) throughout treatment, especially following initiation and after discontinuation of Livtencity and adjust the dose, as required.<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Immunosuppressant drug level increased (IDLI) Questionnaire<br><br>**Additional pharmacovigilance activities:**<br>Clinical study SHP620-302 |
| Use in patients with end stage renal disease (ESRD) including peritoneal dialysis or haemodialysis | **Routine risk minimisation measures:**<br>SmPC Section 4.2<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None |

| | | |
|---|---|---|
| | | **Additional pharmacovigilance activities:**<br><br>Planned Retrospective chart review study (Study number TBD) |

### 2.7.4. Conclusion

The routine risk minimisation measures as proposed in version 0.7 of the RMP is acceptable.

## *2.8. Pharmacovigilance*

### 2.8.1. 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.

### 2.8.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the IBD to determine the forthcoming Data Lock Points. 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 an alignment of the PSUR cycle with the international birth date IBD. The IBD is 23 Nov 2021.

## *2.9. Product information*

### 2.9.1. 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.*

### 2.9.2. Additional monitoring

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

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 indication applied for by the Applicant is for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT).

The aim of treatment is to prevent post-transplant progression of CMV infection and disease and the development of complications (i.e., CMV end-organ disease, graft loss and mortality) during the period of intense immunosuppression. The application rests on the surrogacy of impact on CMV viraemia to protect against symptomatic disease. This principle is broadly accepted, as illustrated by prophylactic and pre-emptive therapies.

### 3.1.2. Available therapies and unmet medical need

Prior to the advent of antiviral therapies, CMV infection was a major cause of death post transplantation. The current standard of care involves empiric use of available anti-CMV agents such as ganciclovir, valganciclovir, foscarnet, and cidofovir. The dose and duration of treatment with these agents, relative to the period in which a transplant recipient is immunosuppressed and at risk of breakthrough CMV infection/reactivation, is limited due to their respective toxicities and due to the development of resistance.

Patients whose disease is resistant/refractory after treatment with first line anti-CMV agents, have limited treatment options and may ultimately lose their graft or die because of CMV infection or disease.

### 3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single phase 3 multi-centre, randomised, open-label, active-controlled study SHP-620-303 to assess the efficacy and safety of maribavir (MBV) treatment compared to Investigator-assigned treatment (IAT) in haematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) with CMV infections that are refractory or resistant to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir.

To be eligible for the study, patients had to have a documented CMV infection and had to have a current CMV infection that was refractory to the most recently administered of the four anti-CMV treatment agents building the IAT arm in this study, and may, in addition, had one or more resistance-associated amino acid substitutions (RASs) known to confer resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir at baseline. The definition of refractory used in study 303 was documented failure to achieve $\geq$1 log10 decrease in CMV DNA levels after 14 days or longer treatment. The definition of resistance in study 303 was defined as refractory CMV infection AND documentation of one or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir.

Patients (N=352) were randomised in a 2:1 allocation ratio to receive open label maribavir 400 mg BID or IAT for 8 weeks. Within the IAT group, the investigator selected the actual study treatment. The

primary endpoint was CMV viraemia clearance at the end of study week eight, regardless of whether study-assigned treatment was discontinued before the end of stipulated 8 weeks of therapy. Patients who initiated alternative anti-CMV therapy or rescue treatment before Week 8 were counted as non-responders.

An alpha-protected secondary endpoint was CMV viraemia clearance and symptom control at the end of Study Week 8, followed by maintenance of this treatment effect for an additional 8 weeks off treatment (i.e., Follow-up Week 16) regardless of whether study-assigned treatment was discontinued before the end of stipulated 8 weeks of therapy.

Supportive data of the antiviral efficacy of maribavir is derived from the -203 study. This was a Phase 2, randomised, dose-ranging study to assess the safety and anti-CMV activity of 400 mg, 800 mg and 1200 mg twice daily maribavir versus valganciclovir for the pre-emptive treatment of SOT or HSCT recipients with CMV infection without CMV organ disease or resistant/refractory CMV infection. 161 patients were randomised equally to the four treatment arms. The primary endpoint was confirmed undetectable plasma CMV DNA (central laboratory) within 3 weeks and within 6 weeks, defined as 2 consecutive post-baseline, on-treatment undetectable results (<200 copies/mL) separated by at least 5 days.

## *3.2. Favourable effects*

The analyses for the primary endpoint in study 303 showed that the proportion of patients achieving confirmed CMV viraemia clearance at week 8 without a need for alternative anti-CMV therapy or rescue treatment was higher in the maribavir group compared to the IAT group (56% compared to 24%, adjusted difference in proportion of responders: 32.8 % (95%CI: 22.80, 42.74, p=<0.001).

The treatment effect was consistent across transplant type, age group, and the presence of CMV syndrome/disease at baseline. Maribavir was numerically less effective against subjects with increased CMV DNA levels (≥ 50,000 IU/mL) and patients with absence of genotypic resistance to IAT. Moreover, the results on the primary endpoint were robust to several conservative sensitivity analyses.

Efficacy results for the key secondary endpoint demonstrate that more patients in the maribavir achieved CMV viraemia clearance and CMV infection symptom control at Week 8, with maintenance of this treatment effect through Week 16 compared with patients in the IAT group (19% vs. 10%, respectively). The adjusted treatment difference (95% CI) in proportion of responders between the treatment groups was 9.5 (2.02, 16.88), p=0.013.

Recurrence requiring anti-CMV treatment after Week 8 was reported for 34/131 (26.0%) of patients randomised to maribavir patients compared to 10/28 (35.7%) randomised to IAT.

The antiviral effects of maribavir are further supported by the results of the -202 study. This confirmed a flat dose-response from 400-1200 mg maribavir, with 77% of patients reaching the primary endpoint of viraemia clearance at week 3 and 6, versus 65% in the active control arm. Moreover, the antiviral drug pressure of maribavir is mechanistically supported by the in vivo selection of resistant variants, as well as the frequency of viraemia recurrence on scheduled discontinuation.

## *3.3. Uncertainties and limitations about favourable effects*

The standard of care for relapsed or refractory CMV post-transplant, is the re-use of valganciclovir or the use of highly toxic alternative agents. The need for a control treatment of physician's choice, the i.v. administration of some agents, and the need for specific monitoring with specific therapies

necessitated an open-label trial design. The open-label nature of the study poses a risk of investigator bias.

The management of control therapies might have been impacted by the availability of maribavir in case of discontinuation. However, there is no indication of bias sufficient to question the overall positive study results.

Through the study design and given that viraemia control may occur without the resort of an antiviral agent (due to the restoration of immune competence), the pivotal study does not completely isolate the antiviral effects of maribavir. Based on the biology of CMV infection and the immune status of the patients, it is very unlikely that the week 8 results would have been achieved without effective antiviral therapy. This assertion is illustrated by the relapse frequency post scheduled discontinuation.

The barrier to resistance of maribavir is slim. In many cases this results in a limited durability of response Moreover, after a fixed duration of 8 weeks of therapy, the virological control rate at week 16 is low.  While the product information recommends a treatment duration of 8 weeks, treatment duration may need to be individualised based on the clinical characteristics of each patient.

## *3.4. Unfavourable effects*

The overall safety population consists of 1,555 patients which have been exposed to maribavir across a broad range of doses and treatment durations. Overall, the size of the presented safety database is sufficient to characterise the safety profile of maribavir.

Maribavir was in general well tolerated. The most frequently reported TEAE during the Phase 3 study 303 was dysgeusia, which occurred predominantly in maribavir-treated patients (maribavir: 37.2%; IAT: 3.4%). Maribavir was also associated with other gastrointestinal symptoms, such as diarrhoea, nausea, vomiting and abdominal pain. Most events were mild to moderate in severity, occurred early upon initiation of treatment and were considered by the investigator to be related to maribavir. Dysgeusia led to treatment discontinuation for only 2 (0.9%) patients in Phase 3 study 303.

Maribavir was shown to increase the whole blood trough concentration of tacrolimus by 57% in a drug interaction study. Accordingly, drug levels of immunosuppressants were monitored during Phase 3 study 303. As expected, the TEAE of immunosuppressant drug level increased was reported in a higher proportion of patients in the maribavir group (9.0%) compared to the IAT group (0.9%).

Compared to the IAT group maribavir showed an advantage in terms of the rate of neutropenia (maribavir group 9.4% vs IAT group 22.4%) reported during Phase 3 study 303. Furthermore, maribavir-treated patients had a lower incidence of TEAEs than foscarnet-treated patients for the TEAE acute kidney injury (8.5% and 21.3%).

Discontinuation of treatment due to related TEAEs occurred in 4.7% of patients in the maribavir group and in 23.3% of patients in the IAT group.

The rate of deaths in the Phase 3 study 303 (maribavir group 11.5%, IAT group 11.2%) was comparable between treatment groups.

## *3.5. Uncertainties and limitations about unfavourable effects*

The side effect profile of the comparator IAT drugs are complex and different between drugs, including haematological and renal toxicity. This leads to a potential lack of sensitivity to fully isolate and describe the safety profile of maribavir.

In the Phase 3 study 303, at baseline, the rate of patients with acute GVHD was numerically higher for patients in the maribavir group versus the IAT group (9.8% vs 6.8%). This could be a reason why the rate of a TEAE of new or worsening GVHD during the on-treatment observation period was higher in maribavir-treated patients (9.0%) compared to patients in the IAT group (4.3%). When comparing TEAEs of a new onset of treatment-emergent GVHD the difference between treatment groups is less pronounced (6% vs. 3.4%).

## *3.6. Effects Table*

Table 65 Effects table for maribavir

| Effect | Short Description | Unit | MBV | IAT | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| CMV viraemia clearance at week 8<br><br>(regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy). | CMV DNA <137 IU/mL or undetectable | % | 56 | 24 | **RR:** 32% (CI: 22.80, 42.74, p<0.001)<br><br>**S:** Sensitivity analyses to isolate the antiviral effect of maribavir from the effect of the favourable safety profile compared to IAT.<br>**U:** Open-label design | Study 303 CSR |
| CMV viraemia clearance and symptom control at week 8 and maintenance trough week 16<br><br>(regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy). | CMV DNA <137 IU/mL or undetectable and CMV symptom assessment (worsening, no change, improvement) | % | 19 | 10 | RR: 9.5% (CI: 2.02, 16.88, p=0.013)<br><br>**U:** Treatment duration in patients in viral suppression at high risk for CMV recurrence at end of the recommended treatment. | Study 303 CSR |
| CMV recurrence requiring anti-CMV treatment after Week 8 | Plasma CMV DNA concentration ⩾ LLOQ in 2 consecutive plasma samples at least 5 days apart, after achieving confirmed viraemia clearance. | % | 26 | 36 | | Study 303 CSR |
| All-cause mortality | Secondary EP | % | 12 | 11 | No effect. | Study 303 |

| Effect | Short Description | Unit | MBV | IAT | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Unfavourable Effects** | | | | | | |
| Dysgeusia | Phase 3 study 303 – adverse reaction | % | 35.9 | 0.9 | | CSR |
| Immunosuppressant drug level increased | Phase 3 study 303 - adverse reaction | % | 6.0 | 0 | **U:** Risk of increased rates of adverse reactions of the immunosuppressant drug | CSR |
| Neutropenia | Phase 3 study 303 - adverse reaction | % | 1.7 | 13.8 | **S:** Advantage over IAT | CSR |
| Acute kidney injury | Phase 3 study 303 - adverse reaction | % | 1.7 | 7.8 | **S:** Advantage over foscarnet | CSR |

Abbreviations: CSR= Clinical study report. IAT= investigator-assigned treatment, U= uncertainties, RR= Response Rates, LLOQ = Lower Limit of quantification

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The purpose of antiviral therapy post transplantation is to suppress viraemia and prevent disease during the stage where the patient is profoundly immunosuppressed. Once immune function somewhat recovers, antiviral protection against CMV is no longer needed.

The antiviral effect of maribavir may be inferred from the -303 study, supported by the -203 study. Methodological concerns raised regarding the pivotal study have been sufficiently addressed through sensitivity analyses and clarification of study conduct.

The safety profile of maribavir is clearly superior to available treatments, with dysgeusia and abdominal complaints as the main side effects. There is no evident haematological or renal toxicity.

The rate of viral suppression at week 8 indicates that the antiviral effect of maribavir results in clinical utility. The barrier to resistance of maribavir, however, is low. A cautionary statement to inform the prescriber that virologic failure can occur during and after treatment with maribavir was included in the SmPC.

In summary, clinically relevant antiviral activity has been demonstrated, along with a favourable safety profile. It can be concluded that maribavir has clinical utility as part of the treatment armamentarium for patients that do not achieve virological control with first line agents such as ganciclovir.

### 3.7.2. Balance of benefits and risks

Clinically relevant benefits in the claimed indication were shown for maribavir. The risks associated with maribavir use are adequately addressed in the product particulars. The B/R balance is positive.

### 3.7.3. Additional considerations on the benefit-risk balance

N/A

## *3.8. Conclusions*

The overall benefit/risk balance of Livtencity is positive.

# 4. Recommendations

***Similarity with authorised orphan medicinal products***

The CHMP by consensus is of the opinion Livtencity (maribavir) is not similar to Prevymis (letermovir) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

See Appendix on Similarity

***Outcome***

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

LIVTENCITY is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT).

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

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new

information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

Not applicable.

These conditions fully reflect the advice received from the PRAC.

***New Active Substance Status***

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