MARIBAVIR

SPONSOR BRIEFING DOCUMENT

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation/Term	Definition
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration vs time curve from time 0 to infinity
AUC_{day}	area under the plasma concentration-time curve from 0 to 24 hours on the day of the adverse event
AUC_{ss}	area under the plasma concentration-time curve at steady state
BID	twice daily
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
BSEP	bile salt export pump
C_{avg}	average concentration on each study day
CI	confidence interval
C_{max}	maximum observed plasma drug concentration
C_{maxday}	maximum concentration from 0 to 24 hours on the day of the adverse event
$C_{max, ss}$	steady-state maximum observed plasma drug concentration
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
CSR	clinical study report
C_{trough}	plasma concentration at the end of a dosing interval
CYP	cytochrome P450
DDI	drug-drug interaction
EAC	Endpoint Adjudication Committee
EC_{50}	half maximal effective concentration
FDA	Food and Drug Administration
f_m	fraction of systemic clearance
GI	gastrointestinal
GvHD	graft vs host disease
HIV	human immunodeficiency virus
HMG-CoA	β-Hydroxy β-methylglutaryl-CoA
HSCT	hematopoietic stem cell transplant
HSV	herpes simplex virus
IAT	investigator-assigned anti-CMV treatment
ICH	International Council for Harmonisation
IR	immediate release
IV	intravenous
K_a	the absorption rate constant
LLOQ	lower limit of quantification
LOAEL	lowest observed adverse effect level
LOCF	last observation carried forward
MoA	mechanism of action
mTOR	mechanistic target of rapamycin
NDA	New Drug Application
NG	nasogastric
NOAEL	no observed adverse effect level
OCT	organic ion transporter

Abbreviation/Term	Definition
on-treatment observation period	In Study 303, the combined 8-week treatment period and 12 weeks of follow-up
OR	odds ratio
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic
P-gp	P-glycoprotein
PK	pharmacokinetic
PPI	proton pump inhibitor
pUL97	designation of the human cytomegalovirus protein kinase targeted by maribavir
QD	once daily
qPCR	quantitative polymerase chain reaction
RAS	resistance-associated amino acid substitution
Refractory	In reference to cytomegalovirus (CMV), per inclusion criteria for the Study 303 clinical trial: documented failure to achieve >1 log10 decrease in CMV DNA level in whole blood or plasma after a 14-day or longer treatment period with anti-CMV agent.
Resistant	In reference to cytomegalovirus (CMV), per inclusion criteria for the Study 303 clinical trial: Refractory CMV infection (as defined above) AND documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir.
R/R	resistant and/or refractory
SAE	serious adverse event
SD	Standard deviation
SOC	system organ class
SOT	solid organ transplant
$t_{1/2}$	terminal half-life
UGT	uridine diphosphate-glucuronosyltransferase
UL97	designation of the gene encoding the human cytomegalovirus protein kinase targeted by maribavir
ULN	upper limit of normal
US	United States

1 EXECUTIVE SUMMARY

1.1 Introduction

Takeda Pharmaceuticals is seeking approval of maribavir, an oral benzimidazole riboside cytomegalovirus (CMV) pUL97 protein kinase inhibitor, for the treatment of adults with post-transplant CMV infection and/or disease that are resistant and/or refractory (R/R) to ganciclovir, valganciclovir, cidofovir or foscarnet. Post-transplant R/R CMV is a rare and serious condition for which maribavir has been granted Breakthrough Therapy Designation (December 2017) and Orphan Drug Designation (June 2011) by the United States (US) Food and Drug Administration (FDA).

This briefing document summarizes the collective data from the maribavir clinical development program demonstrating that maribavir delivers consistent treatment of R/R CMV infection and disease in solid organ (SOT) and hematopoietic stem cell transplant (HSCT) recipients, with an acceptable safety and tolerability profile in the context of benefit:risk in this population. The clinical studies consist of a randomized, active-controlled, pivotal Phase 3 clinical trial (Study 303; N=352), as well as 2 supportive Phase 2 clinical trials (Study 202 [N=120] and Study 203 [N=159]), which provided data relevant to dose-ranging and safety (Additional details on these studies are provided in Table 1).

The favorable maribavir safety profile lacks the dose-limiting toxicities of available CMV antivirals, none of which are FDA-approved for this indication. This safety benefit confers an important advantage over available therapy which translates to improved efficacy. Maribavir has a novel mechanism of action, is orally bioavailable and does not require dose adjustments based on transplant type, age, sex, race/ethnicity, mild-moderate hepatic impairment, or mild-severe renal impairment. The benefit:risk profile of maribavir does not differ by transplant type (HSCT vs SOT), or SOT type. Thus, maribavir has the potential to fill a significant unmet medical need, providing both efficacy against CMV infection and disease while avoiding complicating safety issues in these medically complex patients.

1.2 Background and Unmet Need

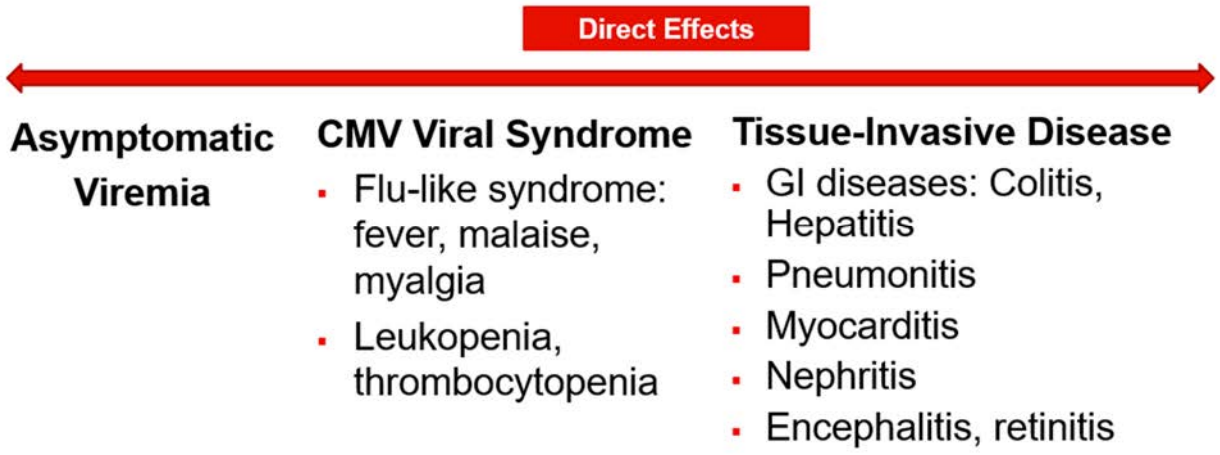
Human CMV is a beta herpesvirus that commonly infects people of all ages. Data suggest that about half of American adults have been infected with CMV (Bate, Dollard, & Cannon, 2010). Like all human herpes viruses, CMV persists after initial infection, a phenomenon termed latency. Most people with prior latent infection from CMV show no signs or symptoms, since infection is well-controlled by an intact immune system.

In recipients of an HSCT or SOT, the ability of the immune system to control the latent CMV infection can be inhibited as a result of receiving powerful immunosuppressants to prevent graft rejection, and this immune system inhibition often results in CMV reactivation. The immune status and degree of immunosuppression of patients affects

their probability of experiencing CMV reactivation post-transplant (Fishman, 2017; Katabathina, Menias, Pickhardt, Lubner, & Prasad, 2016; Ono, Medina Pestana, & Aranha Camargo, 2019).

Though post-transplant CMV is an orphan condition, it is one of the most common opportunistic infections experienced by transplant recipients, with an estimated incidence rate of around 8%–75% in SOT recipients and 5%–60% in HSCT recipients (Azevedo et al., 2015; Marty et al., 2017). CMV infection (CMV viremia) is a significant post-transplant complication that, if left untreated, may progress to clinically severe, even life-threatening tissue-invasive disease (Figure 1). Transplant recipients with CMV infection have a higher risk of complications and poor outcomes, such as graft failure and mortality (Azevedo et al., 2015). These complications may occur not only after symptomatic CMV disease, but also after asymptomatic viremia (Martin-Gandul, Mueller, Pascual, & Manuel, 2015). Thus, asymptomatic CMV viremia is clinically consequential, not only because it may progress to symptomatic CMV disease, but also because it may portend adverse consequences.

Figure 1: CMV Infection: A Spectrum of Disease



(Kotton, 2013; Torres-Madriz & Boucher, 2008)

To avoid these serious consequences, prompt and effective treatment of post-transplant CMV infection is required to prevent progression to symptomatic CMV disease by clearing CMV viremia to undetectable levels (Kotton et al., 2018).

To date, the FDA has not approved any antivirals for the treatment of post-transplant CMV infection in any population. The antivirals currently used to treat CMV infection include CMV DNA polymerase inhibitors (ganciclovir, valganciclovir, foscarnet, and cidofovir), which are all used off-label in this indication, and thus, lack safety and efficacy data from controlled clinical trials in this condition typical of FDA-approved therapies. Each of these currently used DNA polymerase inhibitors share the same viral target, pUL54. Maribavir's viral target, pUL97 (a serine/threonine protein kinase), is different, and confers an efficacy advantage by reducing maribavir's susceptibility to the

development of cross-resistance following use of the other agents (Avery, 2007; Limaye, Corey, Koelle, Davis, & Boeckh, 2000).

Beyond their shared mechanism of action and susceptibility to resistance development, there are several challenges associated with treatment using these conventional CMV antivirals in the setting of prolonged immunosuppression. For example, their effectiveness is limited by the toxicities associated with their use; specifically, bone marrow suppression caused by ganciclovir/valganciclovir and renal impairment caused by foscarnet or cidofovir (Boeckh et al., 2003; Kotton et al., 2018; Ljungman et al., 2001; Reusser et al., 2002; Salzberger, Bowden, Hackman, Davis, & Boeckh, 1997). Neutropenia has been reported to occur in approximately 30% of patients who received ganciclovir or valganciclovir (Maffini et al., 2016; Takahata et al., 2015) and is an independent risk factor for higher mortality in HSCT recipients (Salzberger et al., 1997). Foscarnet-associated renal impairment can lead to electrolyte imbalances, which in turn may lead to cardiac or neurologic disorders (Huycke et al., 2000; Pierce, Richardson, Lacloche, Allen, & Ison, 2018). The risk of nephrotoxicity, which is increased with foscarnet and cidofovir, may necessitate discontinuation or dose adjustment (Bonatti et al., 2017; Foscavir (foscarnet), 2019; Minces et al., 2014; Pierce et al., 2018).

These treatment-limiting toxicities, in the setting of pre-existing bone marrow suppression and renal insufficiency commonly seen in the transplant population, can dramatically impact clinical care. Both treatment-related neutropenia and acute kidney injury have been reported as independent predictors of mortality in this patient population (Kemmner, Verbeek, & Heemann, 2017; Salzberger et al., 1997). These toxicities make it challenging to provide sustained anti-CMV treatment and can potentially lead to treatment failure of post-transplant CMV infection. As a consequence, transplant care providers are often faced with risky tradeoffs: balancing the risk of graft rejection if immunosuppression is reduced to control CMV infection against the risk of causing myelosuppression and renal toxicity when CMV is treated with one of these agents.

Drug delivery is also a major clinical issue with the currently used anti-CMV treatments, since ganciclovir, foscarnet, and cidofovir require intravenous (IV) administration, the latter two, obligatorily. Intravenous administration often requires additional time in the hospital or other specialized facility, or through a home IV infusion program with additional complexities associated with the need for careful monitoring for toxicity. The need for frequent IV hydration in patients receiving foscarnet or cidofovir, and electrolyte repletion in patients receiving foscarnet, also complicate outpatient administration.

1.3 Product Overview

Maribavir is a novel, orally bioavailable benzimidazole riboside antiviral with a mechanism of action that is differentiated from current CMV antivirals. Unlike currently utilized agents that all inhibit CMV DNA polymerase, maribavir attaches to the pUL97 encoded serine/threonine kinase at the adenosine triphosphate (ATP) binding site,

abolishing phosphotransferase required for a variety of essential viral processes such as DNA replication, encapsidation, and nuclear egress (Biron et al., 2002; Shannon-Lowe & Emery, 2010; Wolf, Courcelle, Prichard, & Mocarski, 2001). This mechanism enables activity against strains of CMV with viral DNA polymerase mutations. Strains of human CMV resistant to ganciclovir, foscarnet, cidofovir, or combinations of these drugs, remained sensitive to maribavir in both in vitro and clinical studies (see Section 4.4 and Section 5.6 for additional information on the mechanism of action and viral resistance, respectively).

Maribavir has the benefit of a development lifespan of over 2 decades, which has enabled the accumulation of extensive safety data from more than 1500 patients treated to date in clinical trials across a range of doses. Of these, 495 transplant patients have been treated at a maribavir dose of 400 mg BID (the dose currently proposed for approval) or higher (up to 1200mg BID) for durations of up to 24 weeks.

Additional information on the product, the mechanism of action, and clinical pharmacology is provided in Section 3, Section 4, and Section 5 of this document, respectively.

1.4 Efficacy Findings

As shown in the pivotal Phase 3 Study 303, maribavir is an efficacious treatment for patients with post-transplant R/R CMV infection and disease compared with currently available (but not FDA approved) CMV antivirals. Maribavir demonstrated consistent confirmed CMV viremia clearance; an objective, precise, and reproducible endpoint validated for use in registrational studies in this patient population:

- The presence of CMV viremia is predictive of CMV disease and mortality in transplant recipients (Emery, Cope, Bowen, Gor, & Griffiths, 1999; Emery et al., 2000; Gor et al., 1998; Green et al., 2016; Jang et al., 2012; Natori et al., 2018).
- CMV viremia clearance has been identified in FDA Guidance as a validated surrogate efficacy endpoint in post-transplant CMV registration trials (U.S. Food and Drug Administration, 2020).

Additional details on the endpoint selection are provided in Section 4.2.

For Study 303, definitions for refractory and resistant CMV infections were as follows:

- All patients enrolled in Study 303 were required to have a current CMV infection that was **refractory** to anti-CMV agents as shown by a documented failure to achieve a >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 one or a combination of IV ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir.
- Patients whose CMV infection was **resistant** to anti-CMV agents were also allowed to enroll in Study 303. In addition to meeting the definition for refractory

CMV infection described above, resistant infections were documented as having 1 or more CMV genetic mutations associated with resistance to one or more of ganciclovir/valganciclovir, foscarnet, and/or cidofovir.

Summary descriptions of the pivotal Phase 3 study for treatment of post-transplant CMV infection and the supportive Phase 2 studies of maribavir are provided in Table 1.

Table 1: Description of CMV Treatment Efficacy Studies

Clinical Study Phase, Dates, and Reference (if applicable)	Study Title/Design	Study Population and Sample Size	Dosing Regimen and Duration
Phase 3 Study303 (officially designated as SHP620-303) 22 Dec 2016 – 17 Aug 2020	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 CMV infections that are refractory or resistant to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir	Population: Patients ≥12 years old, recipients of HSCT or SOT, with CMV infection refractory (with or without resistance) to treatment with ganciclovir/ valganciclovir/ foscarnet/ or cidofovir Enrolled: 352; treated 350: 234 maribavir, 116 investigator-assigned anti-CMV treatment (IAT); 1 patient in each treatment was not treated; 22 IAT patients received maribavir rescue	Maribavir 400 mg BID or IAT for 8 weeks Up to 2-week screening phase; 8-week study treatment phase; and 12-week follow-up phase Eligible patients in the IAT arm with clear evidence of virologic failure after a minimum of 3 weeks of treatment could be evaluated for rescue treatment with maribavir. The rescue arm also included an 8-week study treatment phase and 12-week follow-up phase.
Phase 2 Study 202 (officially designated as SHP620-202) 17 Jul 2012 – 05 Dec 2014 Maertens et al., 2019	Maribavir for treatment of resistant or refractory CMV infections in transplant recipients (Randomized in parallel groups to different doses of maribavir; no control)	Population: Patients ≥12 years who were recipients of HSCT or SOT CMV infection that was refractory, with or without resistance, to treatment with ganciclovir/ valganciclovir/ or foscarnet Enrolled: 120 maribavir	Maribavir 400, 800, or 1200 mg BID up to 24 weeks Treatment duration up to 24 weeks per investigator judgment; post-treatment follow-up duration of 12 weeks

Table 1: Description of CMV Treatment Efficacy Studies

Clinical Study Phase, Dates, and Reference (if applicable)	Study Title/Design	Study Population and Sample Size	Dosing Regimen and Duration
Phase 2 Study 203 (officially designated as SHP620-203) 14 May 2012 – 25 Jul 2014 Papanicolaou et al., 2019	A Phase 2, randomized, dose-ranging study to assess the safety and anti-cytomegalovirus (CMV) activity of maribavir versus valganciclovir for treatment of CMV infections in transplant recipients who do not have CMV organ disease	Population: Adult recipients of HSCT or SOT with CMV infection No CMV organ disease or CMV infection genotypically resistant to other anti-CMV drugs Enrolled: 159; 119 maribavir, 40 valganciclovir	Maribavir 400, 800, or 1200 mg BID up to 12 weeks; or valganciclovir 900 mg BID for 3 weeks, then once daily (QD) up to 9 weeks Treatment duration was up to 12 weeks; post-treatment follow-up duration was 12 weeks

BID=twice daily; CMV=cytomegalovirus; HSCT=hematopoietic stem cell transplant; IAT=investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); QD=once daily; SOT=solid organ transplant

1.4.1 Rationale for Dose Selection

The maribavir dose selected for use in the Phase 3 Study 303 and proposed for marketing approval was identified based on findings from the clinical development program. Earlier studies evaluated maribavir as a potential CMV prophylactic agent at a lower 100 mg BID dose (Studies 1263-300 and 1263-301; see Table 7 for additional details). These studies showed that maribavir 100 mg BID was insufficient to prevent CMV disease in transplant recipients and thus, this dose was not evaluated in CMV treatment studies. Maribavir doses of 400, 800 and 1200 mg BID were evaluated in Phase 2 dose-ranging CMV treatment studies, since it was expected that a maribavir dose providing a C_{min} above the half maximal effective concentration (EC_{50}) would be necessary to demonstrate antiviral activity in the treatment setting. Further, maribavir 400 mg BID achieved mean C_{min} close to protein-binding adjusted C_{min} (4.1 ug/mL; see details in Section 4.4.1) suggesting that doses lower than 400mg were unlikely to be effective. Results from the dose-ranging Phase 2 CMV treatment studies (Studies 202 and 203) demonstrated comparable efficacy across the 400 mg BID, 800 mg BID, and 1200 mg BID maribavir dose groups in clearance of CMV viremia in patients with resistant and/or refractory as well as first-episode CMV infection.

Regarding dose-related safety findings, in both Phase 2 studies, a greater proportion of patients at the highest dose of maribavir were reported to have elevated immunosuppressant drug concentration levels, and in one of the studies (Study 202), dysgeusia (taste disturbance), which is known to be associated with maribavir use, was more common at higher doses. Otherwise, the safety findings in the Phase 2 studies

were generally similar across dose levels. (Additional details on safety findings are provided in Section 7.)

Based on the comparable efficacy with higher doses and the better safety profile shown in the Phase 2 studies, the 400 mg BID dose was selected for use in the Phase 3 pivotal study. Further details on the recommended dose and rationale are provided in Section 3.2.2.

1.4.2 Efficacy Findings for Pivotal Phase 3 Study 303

1.4.2.1 Study Design and Patient Baseline Characteristics

Study 303 was a multicenter, randomized (2:1 ratio) pivotal study rigorously designed to assess the efficacy and safety of maribavir in post-transplant patients with CMV infection or disease who were resistant/refractory to prior treatment (as defined in Section 1.4).

Study 303 was designed as an open-label study as study physicians had to individualize the selection of (an) effective comparator(s) in medically complex patients with many concomitant medications, and because the dosing adjustments of investigator-assigned anti-CMV treatment (IAT) agents needed to be made based on renal function. Allowing investigator choice for comparator treatment, rather than specifying a single agent control treatment, was guided by investigator feedback during protocol development and ensured accumulation of data on maribavir's efficacy in comparison to all of the CMV antivirals commonly used for treatment of post-transplant R/R CMV infection. In addition, 2 of the available comparator treatments could only be administered via IV whereas maribavir can only be given orally, a significant challenge to blinding the study without introducing an extreme burden to these vulnerable patients. Therefore, an open-label design was selected as a safe and practical way to conduct this study. The primary endpoint, CMV DNA clearance, was based on an objective central laboratory assessment. The FDA considered the overall design of Study 303, including patient population, treatment duration, and primary (confirmed CMV viremia clearance at a pre-specified timepoint) as well as secondary composite endpoints, to be acceptable.

Additional details on the open label design are provided in Section 6.4.1.1.3.

There were 3 phases in Study 303: Phase 1, a screening phase that could be up to 2-weeks; Phase 2, an 8-week treatment phase; and Phase 3, a 12-week follow-up phase. The 8-week treatment duration was chosen since it was assessed as the longest duration that could be safely studied due to the toxicities associated with the agents used in the IAT arm. In addition, the majority of patients in both Phase 2 studies achieved viremia clearance by 6 weeks. Consistent with clinical practice (where physicians typically treat beyond the point of viremia clearance, particularly for challenging transplant types such as lung transplants), an additional two weeks of therapy was added to the 6 weeks from the phase 2 data for a total treatment duration of 8 weeks. Importantly, in line with FDA guidance, the endpoint for the study was at a fixed time point (8 weeks) after the commencement of therapy.

In the active-controlled design, 352 eligible patients were enrolled and randomized in a 2:1 ratio to either maribavir (n=234 patients dosed) or to the best available therapy selected by the investigator (termed the IAT arm) (n=116 patients dosed).

For the IAT arm, investigators could select either one (monotherapy) or 2 (combination therapy) of the available anti-CMV agents to treat the CMV infection. As previously mentioned, all patients enrolled in the study were refractory to at least 1 anti-CMV agent (with or without resistance). Investigators, where possible, could select an anti-CMV drug to which the patient's CMV infection was not resistant or refractory or, if not feasible, increase the dose of the original agent where applicable or select combination anti-viral therapy. In addition, patients started on combination IAT could discontinue one of the drugs in the event of a safety or tolerability issue without resulting in an automatic treatment failure. Patients randomized to IAT who had an inadequate virologic response after a minimum of 3 weeks on IAT treatment could receive maribavir rescue treatment for 8 weeks. (See Section 6.4.1.1.2 for additional details regarding IAT parameters.)

The primary objective of Study 303 was to compare the efficacy of maribavir to IAT in achieving CMV viremia clearance at the end of Week 8. Patients who received alternative/rescue treatment in either arm were considered failures in the primary analysis. The key secondary efficacy objective was to compare the efficacy of the 2 study treatment groups in regard to the composite of CMV viremia clearance and symptom control, with maintenance of this treatment effect through Week 16.

The study population was consistent with the epidemiology of SOT and HSCT patients with CMV infection and disease, allowing for the results to be generalized to the target population.

Risk factors were generally balanced between the maribavir and IAT groups. Importantly, 60% of all randomized patients, at baseline, had documented resistance to 1 or more of the currently available agents, highlighting the unmet need in this patient population.

Patient demographic characteristics were also broadly similar between the 2 treatment groups, with 2 exceptions: the maribavir group had a higher proportion of patients ≥65 years of age compared with IAT (23.0% and 13.7%, respectively) and a higher proportion of male patients (63.0% and 55.6%, respectively). No patients under 18 years of age were enrolled in the study, even though the protocol had allowed enrollment of patients ≥12 years of age.

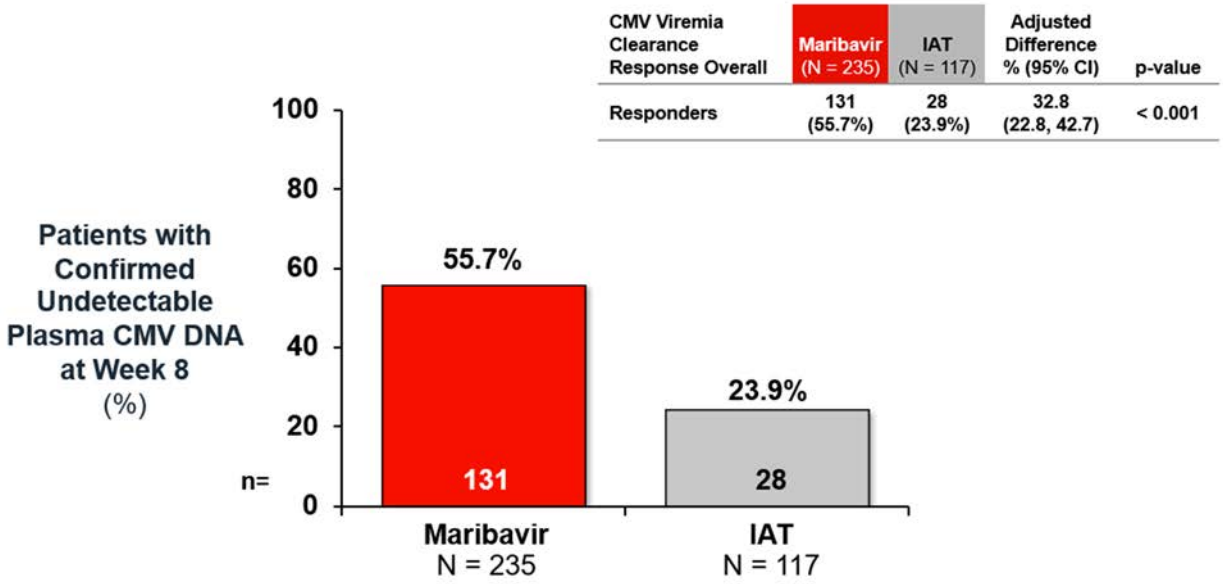
As expected, maribavir was more tolerable than IAT in this study. Overall, 220 (62.5%) of the 352 randomized patients completed 8 weeks of study-assigned treatment. The treatment completion rate was over twice as high for patients in the maribavir group compared to patients in the IAT group (77.9% [183/235] vs 31.6% [37/117], respectively).

1.4.2.2 Efficacy Results

1.4.2.2.1 Primary Efficacy Endpoint: Confirmed CMV Viremia Clearance at End of Study Week 8

Viremia clearance was defined as plasma CMV DNA concentration below the lower limit of quantification (LLOQ; ie, <137 IU/mL), per central laboratory result, in 2 consecutive post-baseline samples that were separated by at least 5 days. The proportion of maribavir-treated patients who achieved confirmed CMV viremia clearance at Week 8 was statistically superior, being more than 2-fold greater than among patients who received standard of care treatment with IAT (maribavir: 55.7% [131/235]; IAT: 23.9% [28/117]) (Figure 2). The adjusted difference using Cochran-Mantel-Haenszel weights across stratification factors was 32.8% (95% confidence interval [CI]: 22.80, 42.74; p<0.001).

Figure 2: Study 303 - Confirmed CMV Viremia Clearance at End of Study Week 8



CMV=cytomegalovirus; CI=confidence interval; IAT=investigator-assigned anti-CMV (ganciclovir, valganciclovir, foscarnet, or cidofovir) treatment

While there is an overall paucity of historical post-transplant CMV response rate data in clinical practice, outcomes are especially not well characterized in the R/R population. Available literature consists of mostly single-center, retrospective case series with a limited number of subjects, where outcome is generally assessed at variable time points from the initiation of therapy without consideration for changes/switches in therapy in the assignment of success (Avery et al., 2016; Mehta Steinke et al., 2021). The lower-than-expected response rates observed in the IAT arm underscore the unmet need in this patient population and illustrate the severity of the limitations of existing therapy when the analysis of outcome requires demonstrating durability of viral suppression, such as in Study 303.

1.4.2.2.2 Primary Efficacy Endpoint: Sensitivity Analyses

Multiple sensitivity analyses were performed to test the robustness of the results and address any potential concerns arising from the study design, including its open-label nature:

- A sensitivity analysis included patients in both treatment groups who met the criteria of confirmed clearance at the time of study discontinuation as responders, (ie, last observation carried forward [LOCF]). This analysis eliminated any beneficial effect accruing from early study discontinuations due to drug toxicity, withdrawal of consent, or other reasons. However, the analysis included only patients who met the criteria of confirmed CMV viremia clearance at the time of study discontinuation and did not receive alternative treatment. In this analysis, maribavir remained statistically significantly better at clearing CMV viremia compared to IAT (58.3% [137/235] vs 33.3% [39/117], respectively; p-value: <0.001).
- Another sensitivity analysis counted patients who had viremia clearance anytime within 8 weeks as responders. This analysis counted patients as responders regardless of when in the treatment period they achieved CMV viremia clearance. Thus, it assumed viremia clearance even if other factors, such as lack of tolerability, led to treatment switching or discontinuation after the initial viremia clearance was achieved. In this sensitivity analysis, maribavir maintained its superior CMV viremia clearance compared to IAT (74.0% [174/235] vs 52.1% [61/117], respectively; p-value: <0.001).
- Finally, a sensitivity analysis examined CMV viremia clearance regardless of the use of alternative anti-CMV treatment (including rescue). This analysis assessed efficacy at Week 8, even if alternative anti-CMV treatment (including rescue) was utilized. In essence, the tolerability benefit of maribavir enabling better efficacy was eliminated in this analysis, as IAT patients were not penalized for taking nonstudy anti-CMV agents after premature treatment discontinuation. The results of the analysis confirmed the true virologic effect of maribavir, which maintained its superior CMV clearance at Week 8 compared to the IAT group (59.1% [139/235] vs 42.7% [50/117], respectively; p-value: 0.002).

1.4.2.2.3 Primary Efficacy Endpoint: Subgroup Analyses

The results in the various subgroup analyses were generally consistent with the primary outcome of the study. These subgroups included IAT type chosen, transplant type, patients with symptomatic CMV infection, genotypic resistance to other anti-CMV agents at baseline, antilymphocyte use, and baseline viral load. The subgroup of patients who received more than 1 IAT type did not favor maribavir; however, the number of patients in that IAT subgroup was small. The overall consistency of the primary outcome and the subgroup analyses illustrate the robustness of the anti-CMV

efficacy study results. Further details showing maribavir's efficacy by subgroup are provided in Section 6.4.3.3.

1.4.2.2.4 Secondary Efficacy Endpoints

Key Secondary Endpoint: Viral Clearance and Symptom Control through Week 16

The key secondary endpoint in Study 303 was a composite endpoint incorporating viral clearance and CMV infection symptom control at Week 8, with maintenance through Week 16. After the 8 week treatment period, patients in Study 303 were followed for 12 additional weeks. At the Week 16 assessment, patients in the maribavir group showed a higher response rate compared to IAT for CMV viremia clearance and CMV infection symptom control (Table 2). Importantly, the outcome assessments at Week 16 were conducted while patients were off therapy, despite continuing immunosuppression. As a result, in both treatment arms, it is unsurprising that the virologic response rates during the off-treatment follow-up period were lower than at Week 8.

Table 2: Study 303 - Viral Clearance and Symptom Control at Week 16

Viral Clearance and Symptom Control at Week 16	**Maribavir 400 mg BID (N=235) n (%)**	**IAT (N=117) n (%)**
Week 16 (8 weeks post-treatment phase)		
Responders	44 (18.7%)	12 (10.3%)
Adjusted Difference (95% CI)	9.5% (2.02, 16.88)	
p-value	0.013	

BID=twice daily; CI=confidence interval; IAT=investigator-assigned anti-cytomegalovirus treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir)
Patients with response (both virological response and symptomatic CMV infection control) at Study 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 Study Week 16, as applicable, are considered as responders.
Note: Between-group difference, adjusted for baseline CMV viral load (low, intermediate/high), and transplant type (SOT, HCT) was compared with CMH test.

Symptomatic CMV Infections

The data from Study 303, in addition to demonstrating maribavir's efficacy in CMV viremia clearance, also showed a benefit in the improvement and resolution of symptomatic CMV infection (i.e. CMV tissue-invasive disease or CMV syndrome [SOT only]), albeit in a more limited sample size.

For the composite key secondary endpoint assessments, all investigator-assessed cases of symptomatic CMV infection were reviewed and adjudicated by an independent, blinded Endpoint Adjudication Committee (EAC).

In total, 29 patients (8.5%) were adjudicated by the EAC to have documented symptomatic CMV infection, a number consistent with the declining incidence of symptomatic CMV infection in this patient population (Griffiths & Reeves; 2021). Of the 21 patients in the maribavir group with EAC-confirmed tissue-invasive disease/CMV syndrome at baseline, the EAC-confirmed resolution or improvement of the baseline tissue-invasive disease/CMV syndrome occurred for 16/21 (76.2%) maribavir-treated patients; there

was no change for 5/21 (23.8%) maribavir-treated patients, and no worsening of symptoms for any maribavir-treated patients at the Week 8/end of treatment assessment. There were only 8 patients with symptomatic CMV infection in the IAT arm, limiting the interpretation of results in this treatment group. However, of the 8 patients in the IAT group with EAC-confirmed tissue-invasive disease/CMV syndrome at baseline, the EAC-confirmed resolution or improvement of the baseline tissue-invasive disease/CMV syndrome occurred for 5/8 (62.5%) patients; there was no change for 1/8 (12.5%) patients and worsening for 2/8 (25.0%) patients at the Week 8/end of treatment assessment.

The EAC confirmed 22 total cases of new onset (i.e., post-baseline) symptomatic CMV infection in 21 patients (maribavir: 14 [6.0%] patients; IAT: 7 [6.0%] patients).
One patient in the IAT group had 2 different episodes of new onset symptomatic CMV infection at 2 different times post-baseline. The development of new onset symptomatic CMV infection was predictive of a poor outcome. While the numbers are small and the response rates lower than the overall asymptomatic population, a higher proportion of maribavir patients in this high risk population were primary endpoint responders; 5/14 maribavir-treated patients vs 0/7 IAT-treated patients. Of these 5 maribavir-treated patients, the new onset symptomatic CMV infection developed at Week 12, four weeks after cessation of maribavir therapy.

Recurrence of CMV

Recurrence of CMV viremia in Study 303 was defined as plasma CMV DNA concentrations ≥LLOQ (137 IU/mL), when assessed by central specialty laboratory, in 2 consecutive plasma samples separated by at least 5 days after achieving confirmed viremia clearance.

On-treatment phase recurrence (i.e., through Week 8) was generally low and numerically higher in the maribavir arm, this despite a higher proportion of maribavir treated patients (78.3% [184/235]) vs. IAT (55.6% [65/117]) achieving CMV viremia clearance at any time on study and hence having a higher at risk population available to recur (Table 3).

Of these patients, 17.9% in the maribavir group and 12.3% in the IAT group had a recurrence of CMV viremia during the first 8 weeks of the study.

Post-treatment phase recurrence (i.e., after Week 8) was assessed from Week 9 through the end of the study, including rescue visits, if applicable. Patients in both arms were generally off treatment after Week 8 unless the investigator placed the patient on another therapy. In this analysis, 38.6% (71/184) of patients in the maribavir group and 21.5% (14/65) in the IAT group had a recurrence of CMV viremia during the follow-up weeks.

Of note, CMV recurrence while off therapy in the setting of continuing immunosuppression is not illustrative of lack of effect, but more likely is due to the ongoing immunocompromised state of the host, which renders them unable to mount an

adequate immune response to the virus. In addition, Study 303 included patients with multiple previous recurrences of CMV. These patients may have been phenotypically predisposed to recurrence upon discontinuation of CMV treatment. Furthermore, Study 303 did not allow for secondary prophylaxis, so recurrence may not be inherent to maribavir treatment itself but may reflect what occurs when CMV treatment is limited to a maximum of 8 weeks with no secondary prophylaxis given.

Table 3: Study 303 - Recurrence of CMV Following Confirmed Clearance

	Maribavir 400 mg BID (N=235) n (%)	**IAT (N=117) n (%)**
Number of patients who had CMV viremia clearance after study-assigned treatment at any time on study	184 (78.3%)	65 (55.6%)
Recurrence of CMV		
During the First 8 Weeks [1]	33 (17.9%)	8 (12.3%)
During the Follow-up Weeks [2]	71 (38.6%)	14 (21.5%)

BID=twice daily; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir)
[1] During first 8 weeks regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy.
[2] From Week 9 through end of study, including rescue visits if applicable.
Source: Study 303 CSR Table 14.2.3.4.1

Efficacy for Maribavir as Rescue Therapy

The maribavir rescue arm is described in Section 1.4.2.1 and Section 6.4.1.1.2. In Study 303, it included 22 IAT patients who received maribavir rescue therapy after documented worsening or failure to improve after 3 weeks on IAT. Following treatment with maribavir, half (50.0%) of these patients achieved confirmed CMV viremia clearance at Rescue Week 8.

1.4.2.2.5 Resistance

Resistance testing in this study was frequent, scheduled and more intensive than in clinical practice (where treatment is generally empiric and resistance testing only performed when there is a rapidly rising viral load and/or deterioration in clinical signs/symptoms despite treatment).

In addition, this was a study of 2nd line treatment of CMV infection, meaning that the 60% of patients with reported baseline resistance to IAT at the beginning of this study represents the frequency of treatment emergent resistance associated with use of IAT therapy prior to the infection being declared refractory.

Samples from patients were genotyped every 4 weeks if plasma CMV viral load was above 500 copies/mL during the study, and additional samples were genotyped at time of treatment discontinuation or CMV recurrence or rebound. As expected, baseline resistance to maribavir in Study 303 was rare, at approximately 1%.

Following its use for treatment, for the 1st time in these R/R patients, maribavir resistance associated mutations developed in 27.1% (58 out of 214 [with genotypic data available]) of patients post-baseline in the maribavir arm (all at pUL97). This number compares favorably with the 60% resistance associated with 1st time use of IAT.

Of these 58 patients, 11 met the primary endpoint despite the presence of resistance mutations whereas in 47/214 patients (21%), the maribavir resistance mutation resulted in failure to meet the primary endpoint.

High baseline viral load was the only identified risk factor that predisposed to maribavir resistance associated mutations. These resistance mutations mostly appeared after 6 weeks of treatment. For patients who developed post-baseline maribavir resistance associated mutations, including those cross-resistant to ganciclovir/valganciclovir at pUL97 (F342Y and C480F), treatment with foscarnet or ganciclovir/valganciclovir was generally effective in clearing the CMV viremia.

1.4.3 Supportive Phase 2 Studies

1.4.3.1 Phase 2 Study 202

Study 202 was an open-label, randomized dose-ranging trial that enrolled a population analogous to that of Study 303. The study did not have a comparator arm since study patients were already failing their conventional therapies and their participation was largely contingent on potentially receiving effective therapy with maribavir.

The primary efficacy outcome was the proportion of patients with confirmed undetectable plasma CMV DNA within 6 weeks. The 3 dose regimens of 400 mg BID, 800 mg BID and 1200 mg BID achieved comparable efficacy, with confirmed undetectable plasma CMV DNA in 70.0% (28/40), 62.5% (25/40), and 67.5% (27/40) of patients, respectively, within 6 weeks of treatment. Subgroup analysis for all doses showed that the proportion of patients who achieved the primary endpoint was similar regardless of the presence or absence of a baseline resistance mutation (61% [43/71] vs 76% [37/49], respectively).

Further details on Study 202 are provided in Section 6.1 and Section 6.2.

1.4.3.2 Phase 2 Study 203

Study 203 was a partially open-label, dose-ranging randomized comparator-controlled trial that assessed the safety and anti-CMV activity of maribavir (400, 800 and 1200 mg BID) vs valganciclovir (900 mg BID). Similar to Study 202, the primary endpoint was confirmed undetectable plasma CMV DNA within 3 and 6 weeks. However, the majority of enrolled patients were experiencing a first episode of post-transplant CMV infection (ie, they were treatment naïve), unlike the patients with R/R CMV who were included in Study 202 and Study 303.

In general, patients treated with maribavir across the 3 maribavir arms in Study 203 had similar CMV viremia clearance rates when compared to valganciclovir, and there was

no significant dose-response across the 3 maribavir dose groups. The 3 dose regimens of 400 mg BID, 800 mg BID, and 1200 mg BID achieved similar efficacy to valganciclovir; within 6 weeks of treatment, the treatment effect estimate for confirmed CMV viremia clearance in the maribavir dose groups (estimated rate: 400 mg BID, 79%; 800 mg BID, 83%; and 1200 mg BID, 74%) was comparable to the valganciclovir group (67%).

Further details on Study 203 are provided in Section 6.1 and Section 6.3.

1.5 Safety Findings

Transplant patients often have comorbidities and take multiple concomitant medications with accompanying side effects. This is reflected in the analysis of overall adverse events (AEs) in Study 303, where a high proportion of patients in both treatment arms had at least one adverse event. Overall, maribavir provides a favorable safety profile with respect to the treatment-limiting toxicities of currently used CMV antivirals, namely myelosuppression and acute kidney injury. This safety advantage of maribavir improves its tolerability relative to existing agents, enables patients to stay longer on maribavir treatment and translates to an efficacy benefit for patients.

Key safety findings from pivotal Study 303 are provided in this section, and additional details can be found in Section 7.

1.5.1 Extent of Exposure

To date, over 1,500 healthy subjects and patients have been exposed to maribavir in clinical trials, across different doses ranging from 100 mg BID to 1200 mg BID. These participants include 380 patients who received maribavir in Phase 1 dose-ranging studies, 680 treated in an earlier CMV prophylaxis program at a dose of 100 mg BID, and 495 transplant patients in the CMV treatment program (the focus of this document) at doses of 400 mg BID or higher for up to 24 weeks (see Section 7.1 for additional details on exposure to study drug).

Because of its better tolerability compared to IAT, in Study 303 the exposure based on the number of days of actual exposure to study-assigned treatment was 50% longer for the maribavir group compared to the IAT group: mean (SD) exposure of 48.6 (13.82) days in the maribavir group and 31.2 (16.91) days in the IAT group (Table 4).

Table 4: Study 303 - Exposure to Study-Assigned Treatment by Treatment Group (Safety Set)

Parameter	Maribavir 400 mg BID (N=234) n (%)	IAT (N=116) n (%)
Exposure duration (days)[a]		
n[b]	230	114
Mean (SD)	52.5 (11.81)	36.0 (18.06)
Median	57.0	34.0
Min, max	2, 64	4, 64
Actual exposure to study-assigned treatment (days)[c]		
n[b]	230	114
Mean (SD)	48.6 (13.82)	31.2 (16.91)
Median	55.0	28.0
Min, max	1, 60	3, 59

BID=twice daily; IAT=investigator-assigned anti-cytomegalovirus treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); max=maximum; min=minimum; N=number of patients; SD=standard deviation
[a] Exposure duration: Number of days between the date of the first exposure and the date of last exposure of the drug administered.
[b] Two patients in the IAT group (valganciclovir) and 4 patients in the maribavir group did not have any eDiary data collected for administration of oral study-assigned treatment. These patients are not included in this table.
[c] Actual exposure days to study-assigned treatment: Number of days in which at least 1 dose of study-assigned treatment was taken/administered.
Source: 303 CSR Section 14, Table 14.3.7.1.1.1

1.5.2 Overview of Adverse Events

A summary of AEs in Study 303 is provided in Table 5.

Table 5: Study 303 - Safety Overview (Adverse Events)

Parameter	Maribavir* 400 mg BID (N=234) n (%)	IAT (N=116) n (%)
Any AE	228 (97.4%)	106 (91.4%)
Any severe AE	75 (32.1%)	44 (37.9%)
Any AE leading to discontinuation of treatment	31 (13.2%)	37 (31.9%)
Any AE leading to study withdrawal	17 (7.3%)	9 (7.8%)
Any SAE	90 (38.5%)	43 (37.1%)

AE=adverse event; BID=twice daily; IAT=investigator-assigned anti-cytomegalovirus treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); SAE=serious adverse event.
* Patients remained on maribavir therapy 46% longer than IAT (ganciclovir, valganciclovir, foscarnet, cidofovir).
Source: Study 303 CSR, Table 14.3.1.1.1

Safety findings regarding AEs in pivotal Study 303 include the following:

- The majority of patients in both treatment groups had at least 1 AE (maribavir: 97.4%; IAT: 91.4%).
- The percentage of patients with SAEs was comparable; 38.5% in the maribavir group and 37.1% in the IAT group.

- A total of 40 patients had AEs leading to death; fatal events were reported for 11.5% (27/235) of patients in the maribavir group and 11.2% (13/116) of patients in the IAT group. (Details on patient deaths in Study 303 are provided in Section 7.2.5.)
- Treatment discontinuation due to AEs was more than twice as common among patients in IAT vs. maribavir arm (maribavir: 13.2%; IAT: 31.9%).
- Taste disturbance (dysgeusia) as an AE of special interest (AESI) class included events with the preferred terms ageusia, dysgeusia, hypogeusia, and taste disorder. In Study 303, these events occurred more frequently for patients in the maribavir group compared to patients in the IAT group (maribavir: 108 [46.2%] patients; IAT: 5 [4.3%] patients). However, these events led to treatment discontinuation for only 2 (0.9%) maribavir-treated patients and no patients in the IAT group. Most events were mild to moderate in severity and none were assessed as serious. Dysgeusia generally resolved either during treatment with maribavir or shortly after discontinuation of treatment. A post-hoc analysis showed that the AEs of dysgeusia were not associated with weight loss.
- During the on-treatment observation period, 21 (9.0%) maribavir-treated patients had an AE of new or worsening graft vs host disease (GvHD) compared with 5 (4.3%) patients in the IAT group. Of note, at baseline the percentage of patients with acute GvHD was numerically higher in the maribavir group compared to the IAT group (9.8% [23 patients] vs 6.8% [8 patients]). This imbalance may have contributed to the difference in the incidence rates of acute GvHD between treatment groups during the study.

1.5.3 Investigation of Known AEs Associated with Available CMV Antivirals

Renal impairment is a recognized treatment-limiting adverse reaction associated with foscarnet/cidofovir use. In Study 303, maribavir-treated patients had a lower incidence of severe renal and urinary disorders compared with IAT (0.9% vs 4.3%; in patients who received foscarnet as the IAT, 8.5%).

Similarly, neutropenia is the most important treatment-limiting side effect of valganciclovir/ganciclovir. In Study 303, maribavir-treated patients had a lower incidence of neutropenia as an AESI class, ie, febrile neutropenia, neutropenia, and neutrophil count decreased combined (maribavir 10.3% vs IAT 25.9% of patients; patients who received ganciclovir/valganciclovir as the IAT, 39.3%). Neutropenia was reported as an SAE for no maribavir-treated patients, compared with 3 (5.4%) ganciclovir/valganciclovir-treated patients.

1.5.4 Drug-Drug Interactions

Maribavir may increase the concentration of certain immunosuppressants (eg, tacrolimus) as well as rosuvastatin and digoxin when used concomitantly. Data shows that maribavir use does not impact the use or outcomes of a wide range of other drugs

commonly used in the target patient population. Due to a potential for maribavir to antagonize the MOA of val/ganciclovir, co-administration is not recommended. Precautions regarding coadministration are addressed in the proposed labeling.

Additional information on drug-drug interactions is provided in Section 5.5.

1.6 Benefit-Risk Summary

Post-transplant patients with CMV infection are faced with significant morbidity and mortality. They have a need for efficacious and less toxic therapeutic options with a mechanism of action that may overcome resistant/refractory CMV, as well as a safety profile that enables sustained and uninterrupted treatment, a critical deficiency of existing therapies.

Maribavir's attributes and observed results from the various clinical trials meet this important unmet medical need:

- Maribavir demonstrated clearance of CMV infection in pivotal Study 303; maribavir was statistically superior to IAT in achieving confirmed CMV viremia clearance at Study Week 8 in SOT and HSCT recipients with resistant/refractory CMV infection and/or disease.
- Maribavir provides a favorable safety profile with a significant safety advantage over currently available CMV antivirals with respect to the critical treatment-limiting toxicities, neutropenia and acute kidney injury, commonly seen with these agents. Maribavir does not possess these critical treatment-limiting toxicities, which cause premature discontinuation of therapy and treatment failure, and may also predispose to development of resistance.
- In addition to being orally bioavailable, maribavir, unlike other therapies, does not need dose adjustments based on transplant type, age, sex, race/ethnicity, mild-moderate hepatic impairment, or for mild-severe renal impairment, and food effect.

Maribavir presents an important option for care providers who manage patients with post-transplant CMV infection and/or disease which is R/R to prior antiviral treatment. Its novel mechanism of action, proven efficacy in this condition, favorable safety and tolerability profile, lack of known treatment-limiting toxicities, wide therapeutic window, and oral dosing render it an important advance in the therapeutic armamentarium for these vulnerable patients.

2 BACKGROUND ON POST-TRANSPLANT CYTOMEGALOVIRUS (CMV) INFECTION

Human cytomegalovirus (CMV) is a common betaherpesvirus. Evidence suggests that the majority of adults and many children in the Americas have latent CMV infection (Lanzieri et al., 2015; Zuhair et al., 2019).

Like all human herpes viruses, CMV persists after initial infection, a phenomenon termed latency. Most people with prior latent infection from CMV show no signs or symptoms, since infection is well-controlled by an intact immune system.

In recipients of an HSCT or SOT, who receive powerful immunosuppressants to prevent graft rejection, the ability of the immune system to control the latent CMV infection is inhibited, often resulting in CMV reactivation. In these patients, CMV infection becomes a significant post-transplant complication and is often associated with substantial morbidity and reduced long-term survival (Falagas et al., 1998; San Juan et al., 2008; Yoo, Trinh, Lim, Wims, & Morrison, 2011). In 2019, approximately 60,000 transplant patients required a long period of immunosuppression after SOT or HSCT to protect their graft
(Center for International Blood & Marrow Transplant Research (CIBMTR), 2020; US Department of Health and Human Services, 2021).

Though post-transplant CMV is an orphan disease, it is one of the most common opportunistic infections experienced by transplant recipients, with an estimated incidence rate of around 8%–75% in SOT recipients and 5%–60% in HSCT recipients (Azevedo et al., 2015; Marty et al., 2017). CMV infection (CMV viremia) is a significant post-transplant complication that, if left untreated, may progress to clinically severe, even life-threatening tissue-invasive disease. Transplant recipients with CMV infection have a higher risk of complications and poor outcomes, such as graft failure and mortality (Azevedo et al., 2015). These complications may occur not only after symptomatic CMV disease, but also after asymptomatic viremia (Martin-Gandul et al., 2015). Thus, asymptomatic CMV viremia is clinically consequential, not only because it may progress to symptomatic CMV disease, but also because it may portend adverse consequences.

The effects caused by CMV infection are believed to be mediated by the virus' ability to modulate the host's immune system:

- The direct effects include development of CMV single or multi-organ disease, including pneumonia, hepatitis, gastroenteritis, retinitis, and encephalitis.
- The indirect effects include increased incidence of other opportunistic infections, a greater risk of GvHD in HSCT recipients, and reduced survival (Boeckh & Ljungman, 2009), and adverse impact on allograft function in some SOT recipients (Martin-Gandul et al., 2015), particularly lung transplant recipients (Paraskeva et al., 2011).

- Untreated CMV pneumonia, when present, has a mortality rate of >50% among HSCT recipients (Boeckh et al., 1996; Konoplev et al., 2001). In addition, CMV infection results in a higher risk of other infections (viral, fungal, bacterial), post-transplant lymphoproliferative disorder, rejection, post-transplant diabetes, and overall mortality (Kotton, 2013).

Management of post-transplant CMV infection focuses on preventing disease progression and development of complications during the period of immunosuppression by reducing CMV viremia to undetectable levels. To date, the FDA has not approved any antivirals for the treatment of post-transplant CMV infection in any population. The antivirals currently used to treat CMV infection include CMV DNA polymerase inhibitors (ganciclovir, valganciclovir, foscarnet, and cidofovir), which are all used off-label in this indication, and thus, lack safety and efficacy data from controlled clinical trials in this condition typical of FDA-approved therapies. Adjunctive therapies may also be used, such as a reduction of immunosuppression, use of CMV immunoglobulin, and adoptive T-cell therapies (Kotton et al., 2018).

The duration of treatment with the available anti-CMV agents is limited by their respective toxicities. Reviews of the use of foscarnet and cidofovir show high rates of toxicity, morbidity, and mortality (Avery et al., 2016; Bonatti et al., 2017; Mehta Steinke et al., 2021; Minces et al., 2014; Stern et al., 2021). Bone marrow suppression is associated with ganciclovir/valganciclovir and renal impairment is associated with foscarnet or cidofovir (Boeckh et al., 2003; Ljungman et al., 2001; Reusser et al., 2002; Salzberger et al., 1997).

The shared mechanism of action (ie, inhibition of viral DNA polymerase activity at gene locus UL54) among these agents makes them susceptible to the development of resistance and cross-resistance (Avery, 2007; Limaye et al., 2000).

Drug delivery can also be a major clinical issue with the currently used antiviral treatments, since ganciclovir, foscarnet, and cidofovir all require IV administration. At present, valganciclovir is the only oral option for CMV treatment. Intravenous administration often requires additional time in the hospital or other specialized facility, or through a home IV infusion program with additional complexities associated with the need for careful monitoring for toxicity. The need for frequent IV hydration in patients receiving foscarnet or cidofovir, and electrolyte repletion in patients receiving foscarnet, also complicate outpatient administration. Having additional options for an effective oral therapy would provide significant clinical flexibility for patients and clinicians.

The combination of drug resistance, IV administration and potentially severe treatment-limiting toxicities with existing agents highlights the unmet need for therapies with a novel mechanism of action and a more favorable safety profile (Avery et al., 2016).

3 PRODUCT DESCRIPTION

Summary

- Maribavir is a potent and selective, orally bioavailable benzimidazole riboside antiviral drug with a novel mechanism of action against human CMV.
- Maribavir attaches to the pUL97 encoded kinase at the adenosine triphosphate (ATP) binding site, abolishing phosphotransferase needed in processes such as DNA replication, encapsidation, and nuclear egress (Biron et al., 2002; Shannon-Lowe & Emery, 2010; Wolf et al., 2001).
- The proposed indication for maribavir is for the treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease that are resistant and/or refractory to ganciclovir, valganciclovir, cidofovir or foscarnet.
- The recommended therapeutic dose of maribavir is 400 mg twice daily (BID).

3.1 Product Overview

Maribavir is a potent, selective, and orally bioavailable benzimidazole riboside antiviral drug with a novel mechanism of action against human CMV.

Maribavir drug product is provided as an immediate release tablet dosage form for oral administration, available in a single strength of 200 mg of maribavir.

3.2 Proposed Indication and Dosing

3.2.1 Indication

Maribavir is indicated for the treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease that are resistant and/or refractory to ganciclovir, valganciclovir, cidofovir or foscarnet

3.2.2 Overview of Dose Recommendation and Rationale

The dose recommendation of 400 mg BID is primarily supported by the efficacy and safety data from 2 Phase 2 dose-ranging studies, Study 202 and Study 203, which demonstrated a flat dose-response curve for antiviral activity from 400 mg BID to 1200 mg BID and better safety/tolerability at 400 mg BID. This was confirmed by the pivotal Phase 3 study, Study 303, evaluating 400 mg BID. Further, 2 previous Phase 3 studies of maribavir for post-transplant CMV prophylaxis demonstrated that a low dose of 100 mg BID did not show sufficient activity to prevent CMV disease. Clinical pharmacology data (exposure-response analysis, drug-drug interactions, and special populations), as well as nonclinical and clinical virology data, further support the dose recommendation (see Section 3.2.2.1 for additional details on exposure-response relationship and Section 5 for additional information on clinical pharmacology).

In Study 303, maribavir 400 mg BID demonstrated a statistically significant higher rate of CMV viremia clearance compared to IAT in post-transplant patients with CMV

infections which are R/R to currently available CMV antivirals. Maribavir, at this dose, met both its primary and secondary endpoints, demonstrating benefit over IAT in clearance of CMV viremia and CMV infection symptom control (see Section 6.4.3 and Section 6.4.4 for details). Moreover, maribavir 400 mg BID had a more favorable safety profile than IAT with respect to treatment-limiting toxicities (see Section 7.2 for additional details on safety findings in Study 303).

Based on these findings, the recommended therapeutic dose of maribavir is 400 mg BID. No dose adjustments are needed, regardless of transplant type, age, gender, race, or body weight, mild or moderate hepatic impairment, and in patients with mild, moderate, or severe renal impairment.

3.2.2.1 Exposure-Response Relationship

3.2.2.1.1 Phase 2 Studies (Study 202 and Study 203)

Exposure-response analyses from the Phase 2 dose-ranging studies for CMV treatment demonstrated that lower and higher maribavir exposures achieved using the clinical doses of 400, 800, and 1200 mg BID were associated with similar antiviral effects. Thus, the 400 mg BID regimen is expected to result in similar antiviral activity in comparison with the 2 higher doses that were studied (see Appendix 10.1 for additional details). The types of reported AEs were similar across the 3 tested doses of maribavir. The occurrence of AEs at increased immunosuppressant drug levels appeared to be dose-related, with the highest incidence observed in the 1200 mg BID dose group (~15%), compared with the 2 lower dose groups (5-10%). The majority of these AEs were mild to moderate in severity. In one of the Phase 2 studies (Study 202), the incidence of dysgeusia increased at higher dose levels; see Section 7.3 for additional details.

3.2.2.1.2 Phase 3 Study 303

The exposure-efficacy analysis based on data from Study 303 showed statistically significant, negative correlations between maribavir AUC_{ss} and the primary or key secondary efficacy endpoints. However, these exposure-efficacy relationships were not considered clinically meaningful since the odds ratios (ORs) were close to 1 (Table 6). Similar trends were observed for $C_{max,ss}$ and $C_{trough,ss}$.

Table 6: Logistic Regression Parameters for Primary and Key Secondary Efficacy Endpoints Based on the Exposure-Efficacy Analysis for Study 303[a]

Parameters	Estimate	SE	OR	95% CI OR	p-value
Primary Efficacy Endpoint - Confirmed CMV Clearance of Plasma CMV DNA at Week 8[b]					
Intercept	1.50	0.393	-	-	<0.001
AUC_{ss} of maribavir – increment of 10 µg*h/mL	-0.0259	0.0112	0.974	(0.953, 0.996)	0.0202
Treatment-emergent CMV mutation conferring resistance to maribavir [N=60]	-2.28	0.383	0.102	(0.0481, 0.216)	<0.001
CD8+CD69+ cell count at baseline					
≥ 0.5 - < 2 [N=42]	-0.251	0.470	0.778	(0.310, 1.95)	0.5934
≥2 [N=12]	1.16	0.552	3.20	(1.09, 9.46)	0.0349
Not reported [N=46]	-0.177	0.397	0.838	(0.385, 1.82)	0.6557
Key Secondary Efficacy Endpoint - Confirmed CMV Viremia Clearance and Symptom Control Followed by Maintenance Through Study Week 16[c]					
Intercept	0.725	0.544	-	-	0.1830
AUC_{ss} of Maribavir – increment of 10 µg*h/mL	-0.0680	0.0182	0.934	(0.902, 0.968)	<0.001
CD8+CD69+ cell count at baseline					
≥ 0.5 - < 2 [N=28]	-0.363	0.633	0.696	(0.201, 2.41)	0.5664
≥2 [N=29]	1.94	0.537	6.99	(2.44, 20.0)	<0.001
Not reported [N=46]	0.0515	0.499	1.05	(0.396, 2.80)	0.9178
CMV DNA level at baseline Intermediate/High [N=80]	-1.28	0.498	0.279	(0.105, 0.741)	0.0105
Solid Organ Transplant (SOT) [N=140]	-0.849	0.394	0.428	(0.198, 0.925)	0.0310

AUC_{ss}=area under the plasma concentration-time curve on the last day of exposure; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; N=number of patients; OR=odds ratio; PK=pharmacokinetics; TE=treatment-emergent; SE=standard error

[a]. Based on updated exposure-efficacy analysis using Study 303 20 May 2021 STDM datasets

[b]. Reference patient had no Treatment-emergent CMV mutation genes conferring resistance to maribavir and had CD8+CD69+ cell count of <0.5 at baseline.

[c]. Reference patient had CD8+CD69+ cell count <0.5, low CMV DNA level at baseline; and hematopoietic stem cell transplant (HSCT)

There were no clinically meaningful exposure-safety relationships observed between AEs or AESIs and maribavir exposure (area under the plasma concentration-time curve from 0 to 24 hours on the day of the AE [AUC_{day}], maximum concentration from 0 to 24 hours on the day of the AE [C_{maxday}], average concentration on each study day [C_{avg}], AUC_{ss}, or $C_{max,ss}$). No correlation exists between maribavir drug exposure and immunosuppressant drug concentration increase.

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- Maribavir was granted Orphan Drug Designation (2011) and Breakthrough Therapy Designation (2017) by the US FDA.
- The FDA considered the overall design of pivotal Study 303, including patient population, treatment duration, and the primary (CMV viral clearance) and secondary endpoints, to be acceptable.
- To date, in the completed studies a total of 1,555 individuals (healthy subjects and patients) have been exposed to maribavir across both the prophylaxis and treatment programs, covering a broad range of doses (50 mg to 2400 mg per day) and a range of treatment durations up to 24 weeks. A total of 337 patients have received at least 1 dose of maribavir 400 mg BID, the proposed dose.

4.1 Key Regulatory Milestones

Maribavir was granted Orphan Drug Designation by the US FDA in June 2011 for the "treatment of clinically significant CMV viremia and disease in at-risk patients" (designation #10-3322). On 15 December 2017, the FDA granted Breakthrough Therapy Designation for maribavir for "treatment of CMV infection in transplant patients resistant or refractory to prior therapy," in recognition of maribavir's potential to demonstrate substantial improvement in this rare and serious condition.

4.2 Phase 3 Study Design and Use of CMV Viremia Clearance as a Surrogate Endpoint

Takeda developed maribavir as a treatment of post-transplant CMV infection in close consultation with the FDA. The Agency considered the overall design of open-label Study 303, including patient population, treatment duration, and the primary and secondary endpoints, to be acceptable.

Selection of CMV viremia clearance as a validated surrogate efficacy endpoint in post-transplant CMV registration trials was made in accordance with the FDA Guidance for Industry document on "Cytomegalovirus in Transplantation: Developing Drugs to Treat or Prevent Disease" (revised May 2020), which described the justification for this endpoint as follows:

> The accumulated clinical literature supports the premise that CMV viremia predicts development of CMV disease in transplant recipients (Emery et al., 1999; Emery et al., 2000; Gor et al., 1998; Green et al., 2016; Jang et al., 2012; Natori et al., 2018). Prophylaxis or preemptive therapy for CMV viremia prevents CMV disease (Green et al., 2016), the suppression of viremia is associated with clinical resolution of CMV disease (Asberg et al., 2007), and

> CMV prophylaxis in HSCT recipients is associated with decreased mortality (Marty et al., 2017).
>
> These observations have prompted the FDA to consider CMV viremia (DNAemia) as a validated surrogate endpoint to be used as a part of a composite endpoint to support traditional approval.
> (U.S. Food and Drug Administration, 2020)

As described in Section 6 of this briefing document, CMV viremia clearance was used for the primary endpoint in the pivotal Phase 3 Study 303 as well as in supportive Phase 2 Studies 202 and 203.

It was also agreed, in consultation with the FDA, that Study 303 should enroll as many patients with symptomatic CMV (Tissue-Invasive Disease or CMV Syndrome) as possible to evaluate CMV viremia clearance and symptom control as a composite key secondary endpoint, also in line with FDA's guidance.

4.3 Nonclinical Development Program

A comprehensive package of nonclinical studies has been conducted with maribavir to support oral clinical use in the treatment of post-transplant CMV. The program consisted of nonclinical pharmacology, safety pharmacology, pharmacokinetics and drug metabolism, and toxicology studies conforming to contemporaneous international regulatory guidance.

Information on the mechanism of action and nonclinical pharmacology for maribavir is provided in Section 4.4 and cell culture models of viral resistance are described in Section 5.6.1.

In safety pharmacology studies, maribavir had no major effects on the central nervous system, cardiovascular, or respiratory systems, nor on autonomic functions. In vivo studies demonstrated that maribavir is primarily metabolized in the liver after systemic absorption in mice, rats, and monkeys, where it is biotransformed predominantly by CYP3A-catalyzed oxidative metabolism via primary pathways of oxidation, N-dealkylation, N-glycosidic bond hydrolysis, and glucuronidation. VP 44469 (N-dealkylation of the isopropyl group) has been shown to be a metabolite in mice, rats, monkeys, and humans, but with much weaker anti-CMV activity than maribavir.

In vitro data indicate maribavir is a weak time-dependent inhibitor for CYP3A and weak inducer of CYP3A4. Physiologically based pharmacokinetic (PBPK) modeling predicted a less than 2-fold increase in systemic exposure to maribavir following coadministration of CYP3A4 inhibitors such as ketoconazole, ritonavir, erythromycin, and diltiazem. Hence, maribavir can be dosed with CYP3A inhibitors without dose adjustment. However, CYP3A inducers significantly reduce maribavir exposure; therefore, to ensure antiviral efficacy (using the BID trough concentration at 12 hours as the marker), a maribavir dose increase is necessary when co-administered with CYP3A inducers.

Toxicities, including regenerative anemia, electrolyte changes, clinical observations of soft to liquid stool, and dehydration, were observed in the pivotal repeat-dose toxicity studies in rats (26 weeks) and monkeys (52 weeks). These events were common across species, and were representative of human gastrointestinal-related AEs seen clinically. While the no observed adverse effect levels (NOAELs)/lowest observed adverse effect levels (LOAELs) were in general at sub-therapeutic exposures in rats, small margins exist (unbound AUC approximately twice as high compared to unbound clinical AUC values) in monkeys. Furthermore, findings were reversible or showed progression to recovery after cessation of dosing and can be monitored clinically. Exposure to maribavir was greater than to the metabolite VP 44469 in both rats and monkeys.

Comprehensive evidence from the in vitro and in vivo genotoxicity studies indicates that maribavir does not exhibit genotoxic potential.

Maribavir was not carcinogenic in the 2-year study in rats at up to 100 mg/kg/day. However, in the 2-year study in CD-1 mice, an equivocal increase (12.9%) in incidence of hemangioma, hemangiosarcoma, and combined hemangioma/ hemangiosarcoma across multiple tissues was noted in males only at 150 mg/kg/day (high dose) that marginally exceeded the incidence rate in control mice (12% Charles River Laboratories, 8.3% Covance) of the same strain. These findings were not observed in females at 150 mg/kg/day and at doses ≤75 mg/kg/day, at which unbound AUC values were approximately 2x higher than unbound clinical exposure.

Maribavir did not affect fertility or reproductive performance in rats, nor was it teratogenic in rats (up to 400 mg/kg/day) or rabbits (up to 100 mg/kg/day). However, a decrease in the number of viable fetuses and increase in pre- and post-implantation losses were observed at doses ≥100 mg/kg/day in pregnant rats, likely due to maternal toxicity observed at these doses. In a pre- and post-natal developmental toxicity study in rats, decreased pup survival due to poor maternal care and reduced body weight gain associated with a delay in developmental milestones were observed at doses ≥150 mg/kg/day. However, the subsequent fertility and mating performance of these offspring, and their ability to maintain pregnancy and to deliver live offspring, were unaffected by maribavir.

These findings from the nonclinical assessment of maribavir, together with supporting literature, were supportive of the clinical development and registration of maribavir.

4.4 Mechanism of Action

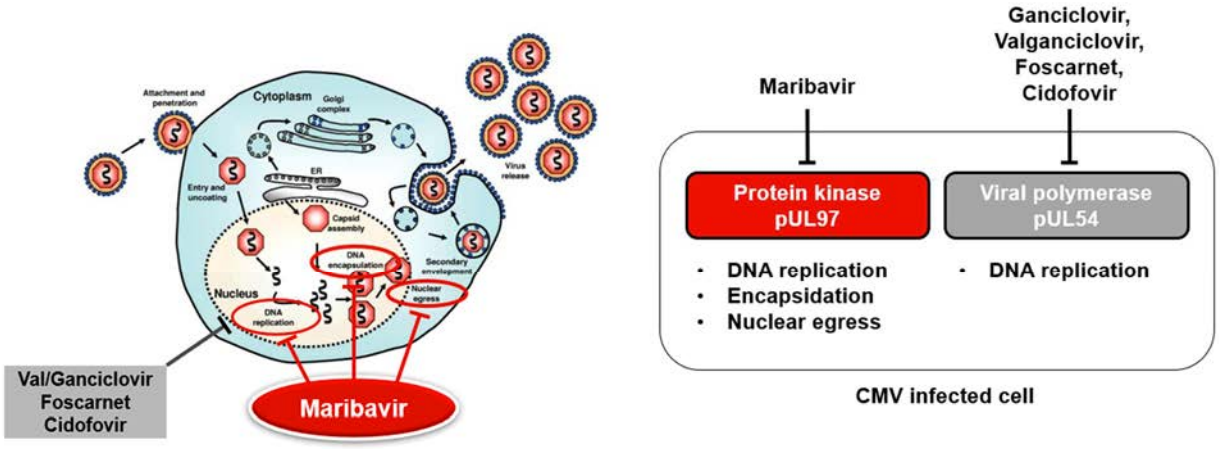
A schematic of the CMV lifecycle, showing points at which CMV antivirals work, is provided in Figure 3. All existing agents used to treat CMV infection are DNA polymerase inhibitors, which target the virus at UL54, a specific location on the viral genome controlling viral DNA replication. In contrast, maribavir is the only antiviral that targets CMV at pUL97, which not only results in inhibition of viral DNA replication, but

also encapsidation and nuclear egress (Biron et al., 2002; Shannon-Lowe & Emery, 2010; Wolf et al., 2001).

This unique and multi-modal mechanism of action confers an efficacy advantage, enabling maribavir to treat CMV infections resistant to currently available therapies while reducing susceptibility to cross-resistance. Strains of human CMV resistant to ganciclovir, foscarnet, cidofovir, or combinations of these drugs, remained sensitive to maribavir in both in vitro and clinical studies.

Additional details on the antiviral activity of maribavir are provided below.

Figure 3: Maribavir Mechanism of Action (MoA)



- Maribavir MoA Works at 3 Points in Viral Lifecycle, Unlike Existing Therapies
- Novel MoA enables efficacy against drug resistant CMV

4.4.1 In Vitro Antiviral Activity

Maribavir selectively inhibited in vitro human CMV replication in yield reduction, DNA hybridization, and plaque reduction assays in human embryonic lung fibroblast and human foreskin fibroblast cells at noncytotoxic submicromolar concentrations with a mean EC_{50} of 0.11 µM, and a EC_{50} range of 0.03 to 0.31 µM. Maribavir is highly selective for human CMV. There is no significant difference in baseline maribavir EC_{50} values across the 4 human CMV glycoprotein B genotypes. At the recommended therapeutic dose of 400 mg BID, maribavir C_{trough} (plasma concentration at the end of a dosing interval) is estimated at 4.9 µg/mL, which is greater than the in vitro EC_{50} adjusted for plasma protein binding (0.11 µM * 376 [molecular weight] /0.01 [free fraction] = 4.1 µg/mL).

4.4.2 Combination Antiviral Activity

When maribavir was tested in combination with other antiviral compounds, it showed strong synergy with the mechanistic target of rapamycin (mTOR) inhibitor sirolimus,

additive interactions with letermovir, foscarnet, and cidofovir against wild-type and mutant human CMV, and strong antagonism with ganciclovir.

4.5 Clinical Development Program

4.5.1 Development History

4.5.1.1 Early Clinical Development: CMV Retinitis and Prevention of CMV Disease

The clinical development history of maribavir spans 24 years. GlaxoSmithKline initiated maribavir clinical evaluation in 1996 as a treatment for CMV retinitis in patients with human immunodeficiency virus (HIV) infection. Because of the decreasing incidence of CMV retinitis in HIV patients (associated with the advent of highly active antiretroviral therapy), clinical development efforts were discontinued in August 2001.

In 2004, clinical development of maribavir for the prevention of CMV disease in transplant recipients was initiated. Based on encouraging results from a Phase 2 prevention study (1263-200), maribavir 100 mg BID was evaluated in 2 Phase 3 CMV prophylaxis studies (1263-300, initiated in 2006, and 1263-301; initiated in 2007). Maribavir 100 mg BID was safe and well-tolerated in these studies but failed to reduce the incidence of CMV disease. Thus, 100 mg BID (25% of the current proposed treatment dose) was determined to be a sub-therapeutic.

4.5.1.2 Treatment of Post-Transplant CMV Infection and Disease

After the CMV prevention program was stopped, data from transplant recipients with CMV infection treated with maribavir under individual Emergency Investigational New Drug applications in the US (N=6), and under a named patient program in France (N=12), were reviewed. The data suggested that maribavir treatment at higher doses was associated with a reduction in CMV DNA in the blood in most patients with post-transplant CMV infection. As a result, development of maribavir as a treatment of post-transplant CMV infection and disease, using significantly higher doses, ie 400 mg BID to 1200 mg BID, was initiated in 2012.

Based on positive data from two Phase 2 treatment studies (Study 202 and Study 203), two Phase 3 studies (Study 302 [ongoing; see description in Section 4.5.2] and Study 303) to assess the efficacy and safety of maribavir for the treatment of CMV infection and disease were initiated. The recently completed Study 303 provides the primary evidence supporting the NDA.

4.5.2 Description of Clinical Studies

The pivotal Phase 3 Study 303 demonstrated the efficacy and safety of maribavir in the treatment of CMV infection that is resistant/refractory to prior therapy. Across clinical trials, maribavir treatment was associated with consistent CMV viremia clearance in patients with post-transplant CMV.

In total, the maribavir clinical development program consists of 23 completed studies: Seventeen Phase 1 studies, two Phase 2 studies, and one Phase 3 study of maribavir

as a CMV treatment in transplant recipients, and three Phase 2 and 3 studies of maribavir for CMV prevention in transplant recipients.

Completed studies for treatment of CMV are described in Table 1 (in Section 1.4 above). Studies for prevention of CMV, as well as the currently ongoing treatment study (Study 302, which is investigating maribavir compared to valganciclovir in HSCT recipients with treatment naïve CMV infection), are described in Table 7.

To date, in the completed studies a total of 1,555 individuals (healthy subjects and patients) have been exposed to maribavir across both the prophylaxis and treatment programs, covering a broad range of doses (50 mg to 2400 mg per day) and a range of treatment durations up to 24 weeks (see Section 7.1 for additional details on exposure to study drug). A total of 337 patients have received at least 1 dose of maribavir 400 mg BID, the proposed dose.

All studies with maribavir were conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice, the principles of the Declaration of Helsinki, the US Code of Federal Regulations, and the European Union Clinical Trials Directive, as well as any other applicable local/regional regulations and guidelines regarding the conduct of clinical studies.

Table 7: CMV Studies in the Maribavir Clinical Development Program

Study, Dose, Regimen, Reference (if applicable)	Title	Patient Populations, Start/Completion Dates
CMV Prevention Studies		
Phase 3 Prevention Studies		
1263-300[a] Maribavir 100 mg BID for up to 12 weeks, or placebo (Marty et al., 2011)	A Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Prophylactic Use of Maribavir for the Prevention of Cytomegalovirus Disease in Recipients of Allogeneic Stem Cell Transplants	Adult allogeneic HSCT recipients (donor or recipient CMV seropositive) (674: 451 maribavir, 223 placebo) Study start: 13 Dec 2006 Study completion: 23 May 2009
1263-301[a,b] Placebo or maribavir 100 mg BID and placebo or ganciclovir 1000 mg TID×14 weeks	A Randomized, Double-blind Study To Assess The Efficacy And Safety Of Prophylactic Use Of Maribavir Versus Oral Ganciclovir For The Prevention Of Cytomegalovirus Disease In Recipients Of Orthotopic Liver Transplants	Adults undergoing first orthotopic liver transplantation (donor CMV seropositive/ recipient negative) (303: 147 maribavir, 156 ganciclovir) Study start: 23 Jul 2007 Study completion: 14 Sep 2009
Phase 2 Prevention Study		
1263-200[b] Placebo, 100 mg BID, 400 mg QD, 400 mg BID for up to 12 weeks (Winston et al., 2008)	A Randomized, Double-blind, Placebo-controlled, Dose-ranging Study to Assess the Safety, Tolerability, and Prophylactic Anti-cytomegalovirus Activity of Maribavir in Recipients of Allogeneic Stem Cell Transplant	Adult allogeneic HSCT recipients (recipient CMV seropositive) (110: 82 maribavir, 28 placebo) Study start: 28 Oct 2004 Study completion: 05 Apr 2006

Table 7: CMV Studies in the Maribavir Clinical Development Program

Study, Dose, Regimen, Reference (if applicable)	Title	Patient Populations, Start/Completion Dates
Ongoing CMV Treatment Study		
Phase 3 Treatment Study		
Study 302 (officially designated SHP620-302) Maribavir 400 mg BID or valganciclovir 900 mg BID for 8 weeks	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	Patients 16 years of age or older who are recipients of HSCT with a documented asymptomatic CMV infection; projected enrollment is 550 participants. Study start: 14 Apr 2017 Estimated study completion: 22 May 2022

BID=twice daily; CMV=cytomegalovirus; HSCT=hematopoietic stem cell transplant; QD=once daily; SOT=solid organ transplant; TID=3 times daily

[a] Conducted by ViroPharma

[b] Study discontinued on recommendation of Data Monitoring Committee due to imbalance in the incidence of CMV infections between the maribavir and ganciclovir groups.

5 CLINICAL PHARMACOLOGY

Summary

- Maribavir is a potent, selective, and orally bioavailable antiviral drug.
- Extensive data on clinical pharmacology have been collected across the clinical program including 17 Phase 1 studies, 3 Phase 2 studies, and 1 Phase 3 study.
- Due to novel mechanism of action, maribavir can be used to treat human CMV that is resistant to other, conventional anti-CMV therapies. There is clinical evidence of a low level of cross-resistance to maribavir and ganciclovir/valganciclovir.
- Coadministration of maribavir with ganciclovir or valganciclovir is not recommended, since maribavir may antagonize their antiviral effects by inhibiting human CMV pUL97 serine/threonine kinase, which is required for activation/phosphorylation of ganciclovir.
- Maribavir can be taken with or without food.
- No dose adjustment is needed based on transplant type, age, gender, race, or body weight, in patients with mild or moderate hepatic impairment, or in patients with mild, moderate, or severe renal impairment.
- Drug-drug interaction (DDI) risk is limited, and a dose adjustment of maribavir is only needed when maribavir is co-administered with a strong or moderate CYP3A4 inducer. With the exceptions 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.

5.1 Overview of Clinical Pharmacology

The clinical pharmacology of maribavir has been characterized for pharmacokinetics (PK) and pharmacodynamic (PD) in 17 Phase 1 studies, 3 Phase 2 studies, 1 Phase 3 study, as well as 30 human biomaterial (in vitro and ex vivo) studies.

5.2 Pharmacokinetics

The summary of the absorption, distribution, metabolism, and elimination (ADME) properties and the key characteristics of clinical pharmacology of maribavir are summarized in Table 8 and the sections below.

Table 8: Summary of the ADME Properties of Maribavir

Pharmacokinetics in Transplant Patients	
Steady-state exposure[a,b]	Maribavir: C_{max}: 17.2 (39.3%) µg/mL $AUC_{0-\tau}$: 128 (50.7%) µg*h/mL C_{trough}: 4.90 (89.7%) µg/mL
Pharmacokinetics in Healthy Subjects	
Steady-state exposure[a,b]	Maribavir: C_{max}: 16.4 (28.6%) µg/mL $AUC_{0-\tau}$: 101 (37.0%) µg*h/mL

Table 8: Summary of the ADME Properties of Maribavir

	C_{trough}: 2.89 (71.7%) µg/mL
	VP 44469[c]: C_{max}: 1.55 (22.4%) µg/mL $AUC_{0-\tau}$: 13.1 (16.9%) µg*h/mL C_{trough}: 0.66 (19.4%) µg/mL
Dose proportionality	Approximately dose-proportional following a single dose from 50 to 1600 mg and multiple doses up to 2400 mg per day
Accumulation ratio	AUC: 1.24-1.49 based on NCA C_{max}: 1.37; AUC: 1.47 based on population PK analysis
Time to steady-state	2 days
Time dependence	No
Absorption	
Median T_{max}	1.0 to 3.0 h
Effect of food (relative to fasting)[d]	AUC: 0.864 (0.804, 0.929) C_{max}: 0.722 (0.656, 0.793)
Distribution	
Mean apparent steady-state volume of distribution	27.3 L
% In vitro bound to human plasma proteins	Maribavir: 98.0% mean across the concentration range of 0.05-200 µg/mL VP 44469: 89.7% and 92.4% following single doses of 200 mg and 800 mg, respectively
In vitro blood-to plasma ratio	1.37 across the concentration range of 0.005-10 µg/mL
Metabolism	
Metabolic pathways	CYP3A4 (primary, fm = 0.35) and CYP1A2
Drug-related components in plasma	88% unchanged parent drug and 12% VP 44469 during the first 24 hours
Metabolic ratio for VP 44469[e]	0.15 - 0.20
Elimination	
Route of elimination	Hepatic metabolism
Mean terminal $t_{1/2}$ in transplant patients	4.32 h
Mean terminal $t_{1/2}$ in healthy subjects	3.87 h
Oral clearance CL/F in transplant patients	2.85 L/h
Oral clearance CL/F in healthy subjects	3.77 L/h
% of dose excreted in feces[f]	14%
% of unchanged drug excreted in feces[f]	5.7%
% of dose excreted in urine[f]	61%
% of unchanged drug excreted in urine[f]	<2%

Table 8: Summary of the ADME Properties of Maribavir

AUC=area under the plasma concentration-time curve; $AUC_{0-\tau}$=area under the plasma concentration-time curve during a dosing interval; C_{max}=maximum observed plasma concentration; C_{trough}=observed plasma concentration at the end of a dosing interval; CYP=cytochrome P450; fm=fraction of systemic clearance of the substrate mediated by the CYP enzyme; NCA=noncompartmental analysis; PK=pharmacokinetic; $t_{1/2}$=terminal half-life; T_{max}=time to maximum observed plasma concentration

[a] Maribavir 400 mg twice daily (BID).

[b] Presented as geometric mean (% coefficient of variation for geometric mean).

[c] VP 44469 is the N-dealkylated metabolite of maribavir. Molecular weight (MW) for maribavir and VP 44469 are 376.24 and 334.2, respectively.

[d] Values refer to geometric mean ratio (fed/fasted) and (90% confidence interval). Fed condition = ingestion of a standard, moderately high fat meal immediately prior to dosing.

[e] Calculated as the ratio of $AUC_{0-\infty}$ of VP 44469/MW of VP 44469 to $AUC_{0-\infty}$ of maribavir/MW of maribavir.

[f] Single oral administration of radiolabeled maribavir in mass balance study.

Note: Values were obtained in studies with healthy subjects unless otherwise indicated.

Absorption: Maribavir is rapidly absorbed following oral administration with peak plasma concentrations (C_{max}) observed 1 to 3 hours post-dose and the fraction of dose absorbed is estimated to be 61 to 94%. Coadministration with a moderately high fat meal did not change maribavir area under the plasma concentration-time curve (AUC) while reduced C_{max} by 28%. Given lack of significant food effects, maribavir was allowed to be taken with or without food in Phase 2 and Phase 3 studies. Bioavailability of maribavir is unaffected by crushing the tablet, and crushed tablets can be administered via a nasogastric/orogastric tube with negligible drug loss. Maribavir can be co-administered with antacid, histamine H2 receptor antagonists (H2 blockers), or proton pump inhibitors (PPIs) without dose adjustment or staggering.

Distribution: Maribavir is highly bound to plasma proteins (98.0% in vitro and 98.5% to 99.0% ex vivo), independent of maribavir plasma concentrations up to 200 µg/mL. Maribavir can penetrate the blood-retinal barrier but is not expected to cross the blood-brain barrier in humans based on the animal tissue distribution data.

Metabolism: Maribavir is primarily eliminated by hepatic metabolism via cytochrome P450 (CYP)3A4 (primary metabolic pathway; fraction of systemic clearance [f_m], through CYP3A4 estimated at 35%), with secondary contribution from CYP1A2 (f_m estimated ≤25%). VP 44469 (through N-dealkylation) is the primary metabolite, accounting for 34.0% and 7.2% of the oral dose recovered in urine and feces, respectively, based on a human mass balance study. In plasma, maribavir and VP 44469 concentrations represent 88% and 12% of total drug-related material over 24 hours post-dose.

Elimination: Maribavir PK is time-independent. Oral clearance is estimated to be 3.77 L/h in healthy subjects and 2.85 L/h in transplant patients. Renal clearance of maribavir is negligible (<2%). The terminal half-life ($t_{1/2}$) of maribavir is estimated to be 3.87 h in healthy subjects and 4.32 h in transplant patients. Due to relatively short half-life, steady state was reached within 2 days of dosing with accumulation ratio ranging from 1.24 to 1.49 for AUC after BID dosing.

Plasma exposure to maribavir increases approximately dose proportionally following a single dose from 50 to 1600 mg or multiple doses from 300 to 2400 mg per day.

5.3 Pharmacodynamics

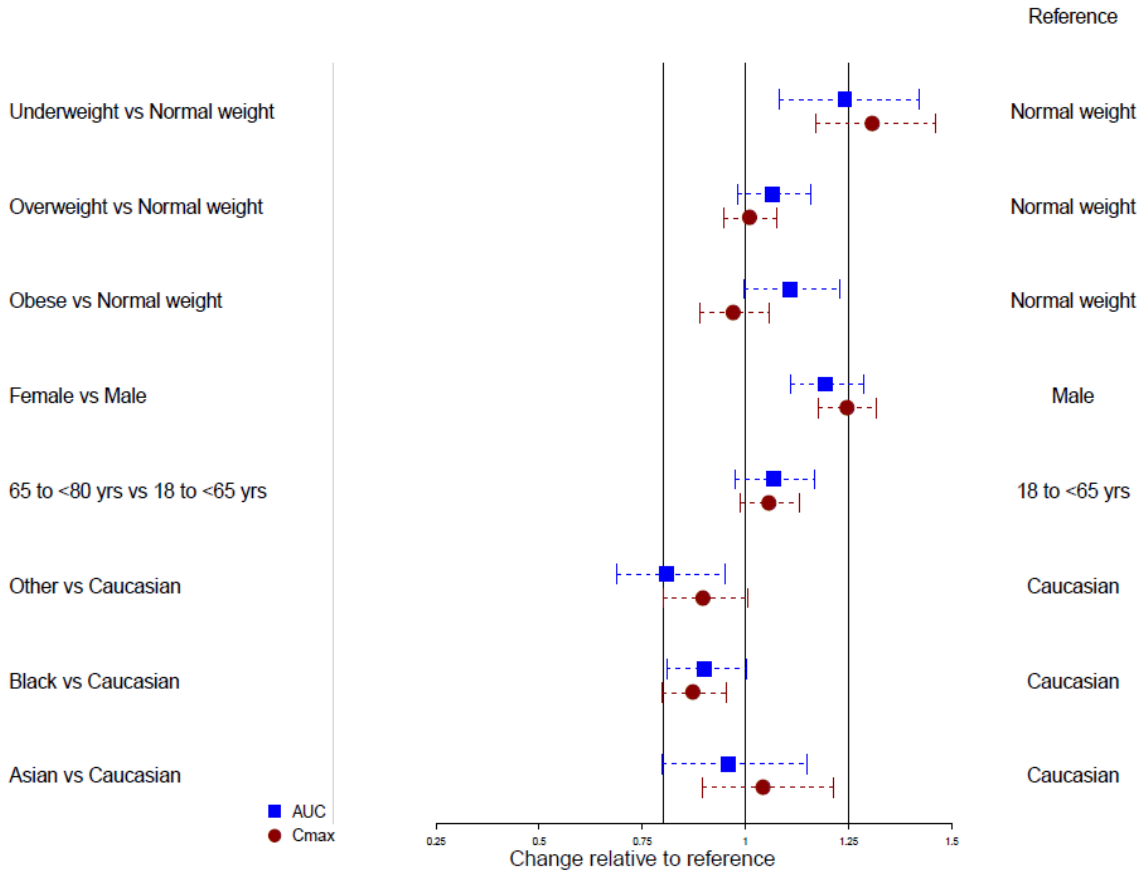
Based on the large differences in the in vitro anti-CMV activity and the plasma exposure between maribavir and its main metabolite, VP 44469, maribavir pharmacological effects are due to the parent drug.

At a maribavir dose of 100 mg and 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, maribavir does not prolong the QT interval to any clinically relevant extent.

5.4 Special Populations

- No clinically relevant impact on maribavir PK related to age (18-79 years), gender, race (Caucasian, Black, Asian or others), ethnicity (Hispanic/Latino, or non-Hispanic/Latino), or weight (36 to 141 kg) were identified based on population PK analysis (Figure 4).
- No dose adjustment is needed for geriatric patients. Exposure in patients aged 65 or older showed no more than 7% higher exposure compared to patients aged less than 65 in the final population PK analysis.
- No dose adjustment is needed based on gender, as gender was not a significant covariate for any PK parameter in the final population PK analysis.
- No dose adjustment is needed based on race (Caucasian, Black, Asian, or others) or ethnicity (Hispanic/Latino vs non-Hispanic/Latino). Race or ethnicity was not a significant covariate for any PK parameter in the final population PK analysis.
- Transplant types (HSCT vs SOT), between SOT types (liver, lung, kidney, or heart) or presence of gastrointestinal (GI) GvHD do not impact the PK of maribavir (Figure 5).
- No dose adjustment is required for patients with mild, moderate, or severe renal impairment (Figure 6). PK of maribavir in patients with end-stage renal disease (creatinine clearance less than 10 mL/min), including patients on dialysis, is unknown.
- No dose adjustment is required for patients with mild or moderate hepatic impairment (Figure 6). PK of maribavir in patients with severe hepatic impairment is unknown.

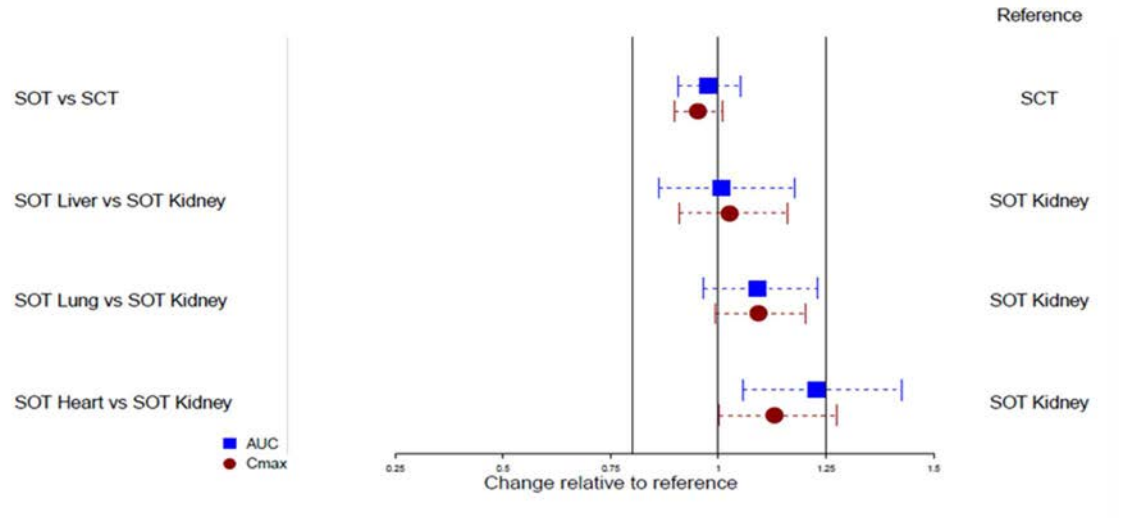
Figure 4: Geometric Mean Ratios and 95% CIs for Comparisons of Steady State $AUC_{0-\tau}$ and C_{max} in Transplant Patients with CMV Infections for Weight, Gender, Age and Race



$AUC_{0-\tau}$=area under the concentration-time curve during a dosing interval; C_{max}=maximum observed plasma concentration.

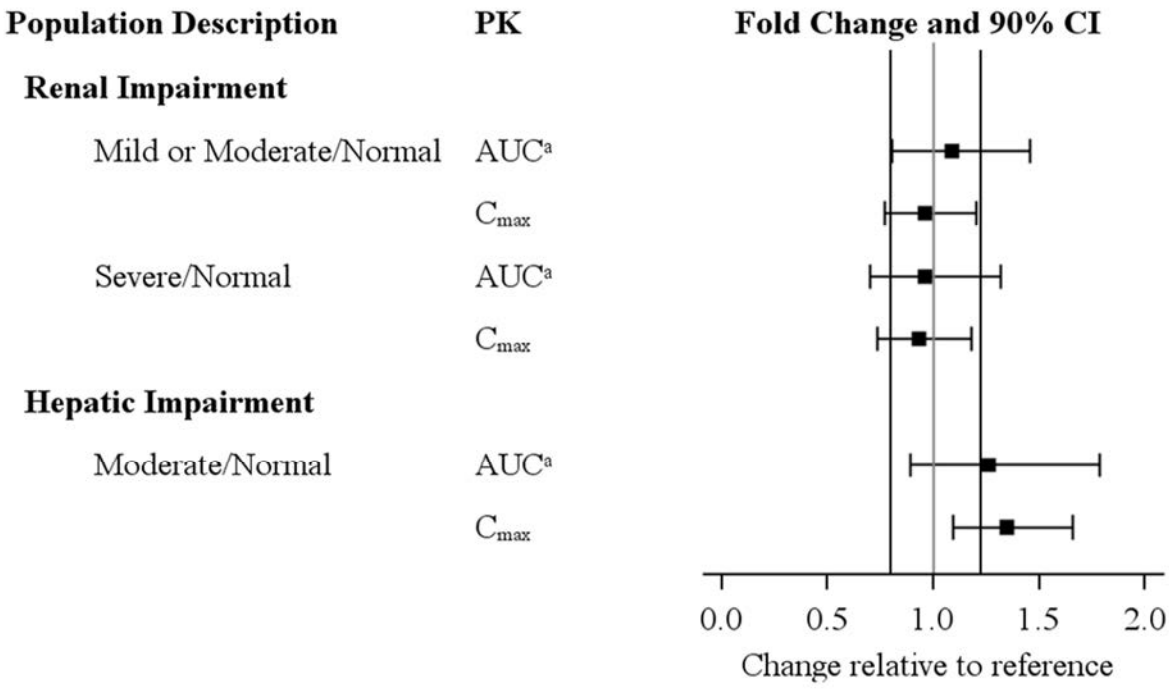
Under-weight=BMI<18.5 kg/m^2, normal weight=18.5≤BMI<25 kg/m^2, over-weight =25≤BMI<30 kg/m^2, obese=BMI≥30 kg/m^2

Figure 5: Geometric Mean Ratios and 95% CIs for Comparisons of Steady State $AUC_{0-\tau}$ and C_{max} in Transplant Patients with CMV Infections and Different Transplant Types



$AUC_{0-\tau}$=area under the plasma concentration-time curve during a dosing interval; C_{max}=maximum observed plasma concentration; SCT=stem cell transplant; SOT=single organ transplant.

Figure 6: Impact of Renal or Hepatic Impairment on the Single-dose Pharmacokinetics of Maribavir



CI=confidence interval; C_{max}=maximum observed plasma concentration; PK=pharmacokinetics

[a] $AUC_{0-\infty}$

5.5 Drug-Drug Interactions

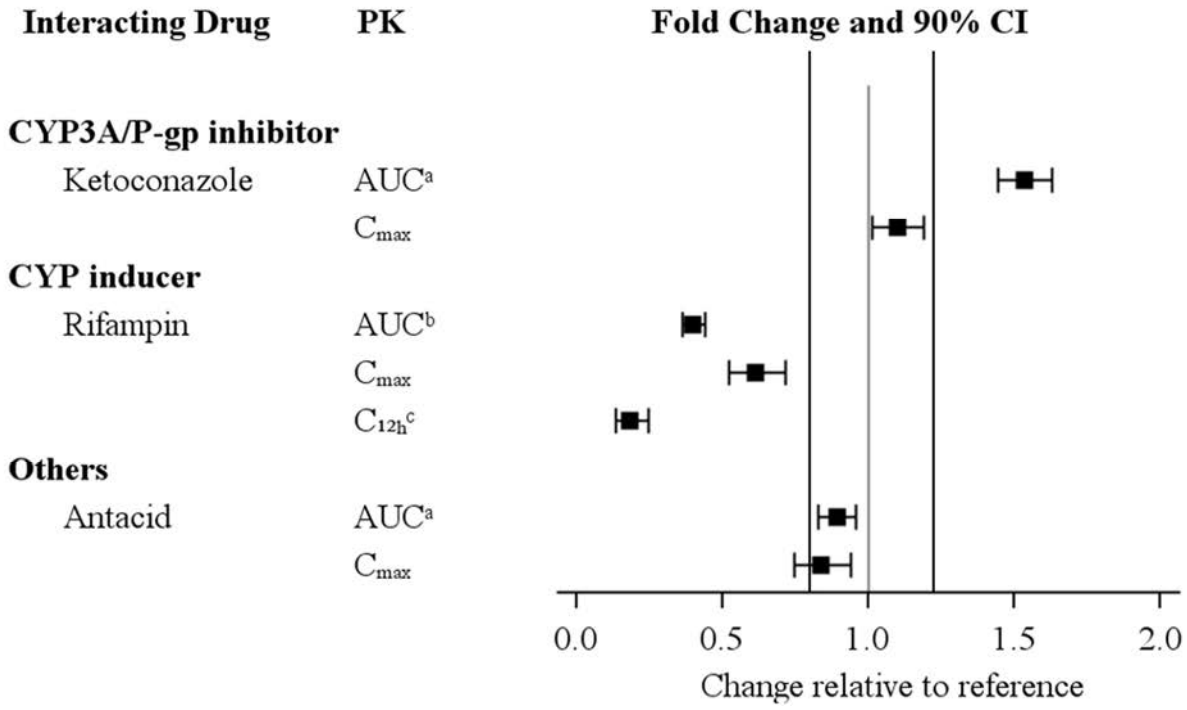
Maribavir is not recommended with valganciclovir/ganciclovir, since it may antagonize ganciclovir's antiviral effects due to maribavir's inhibitory effect on pUL97 serine/threonine kinase, which is required for activation/phosphorylation of ganciclovir. Maribavir can be administered with other anti-CMV drugs, including letermovir, foscarnet, and cidofovir as clinically significant PK- or PD-based DDIs are not expected.

PK-based DDI risk is low, and dose adjustment of maribavir is only needed when maribavir is co-administered with a strong or moderate CYP3A4 inducer. With the exceptions of selected immunosuppressants, rosuvastatin, and digoxin, coadministration with maribavir does not impact the use or outcomes of a wide range of other drugs commonly used in the target patient population (Figure 7 and Figure 8).

Effect of Other Drugs on PK of Maribavir

- Based on in vitro studies, the metabolism of maribavir is not mediated by CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A5, UGT1A4, UGT1A6, UGT1A10, or UGT2B15. The transport of maribavir is not mediated by OATP1B1, OATP1B3, or BSEP.
- Strong or moderate CYP3A inducers may significantly decrease the plasma exposure to maribavir. Coadministration with rifampin (strong inducer of CYP3A and moderate inducer of CYP1A2) decreased C_{max}, AUC and C_{trough} by 39%, 60% and 82%, respectively (Figure 7), and therefore, is not recommended due to the potential for a decrease in efficacy of maribavir based on the magnitude of the reduction in maribavir C_{trough}. Alternative antimicrobial or anti-tuberculosis therapy with a lower CYP3A induction potential, eg, pyrazinamide, ethionamide, should be considered. When maribavir is co-administered with other strong or moderate CYP3A inducers, a dose increase is recommended (800 mg BID for carbamazepine and phenobarbital and 1200 mg BID for phenytoin) based on PBPK modeling.
- Strong CYP3A4 inhibitors may increase the plasma exposure to maribavir. Coadministration with ketoconazole (strong CYP3A and P-gp inhibitor) increased C_{max} and AUC by 10% and 53%, respectively (Figure 7). Based on the less than 3-fold increase in maribavir exposure expected, lack of dose-limiting toxicity and a wide therapeutic window, maribavir can be co-administered with a strong CYP3A4 inhibitor (eg, ketoconazole, itraconazole, posaconazole, and voriconazole, clarithromycin) without dose adjustment.

Figure 7: Impact of Co-administered Drugs on the Pharmacokinetics of Maribavir



AUC=area under the plasma concentration-time curve; C_{max}=maximum observed plasma concentration; C_{trough}=observed plasma concentration at the end of a dosing interval; CYP=cytochrome P450; PK=pharmacokinetics; P-gp=P-glycoprotein

[a] $AUC_{0-\infty}$.

[b] AUC_{0-t}.

[c] C_{trough} at 12 hours post-dose.

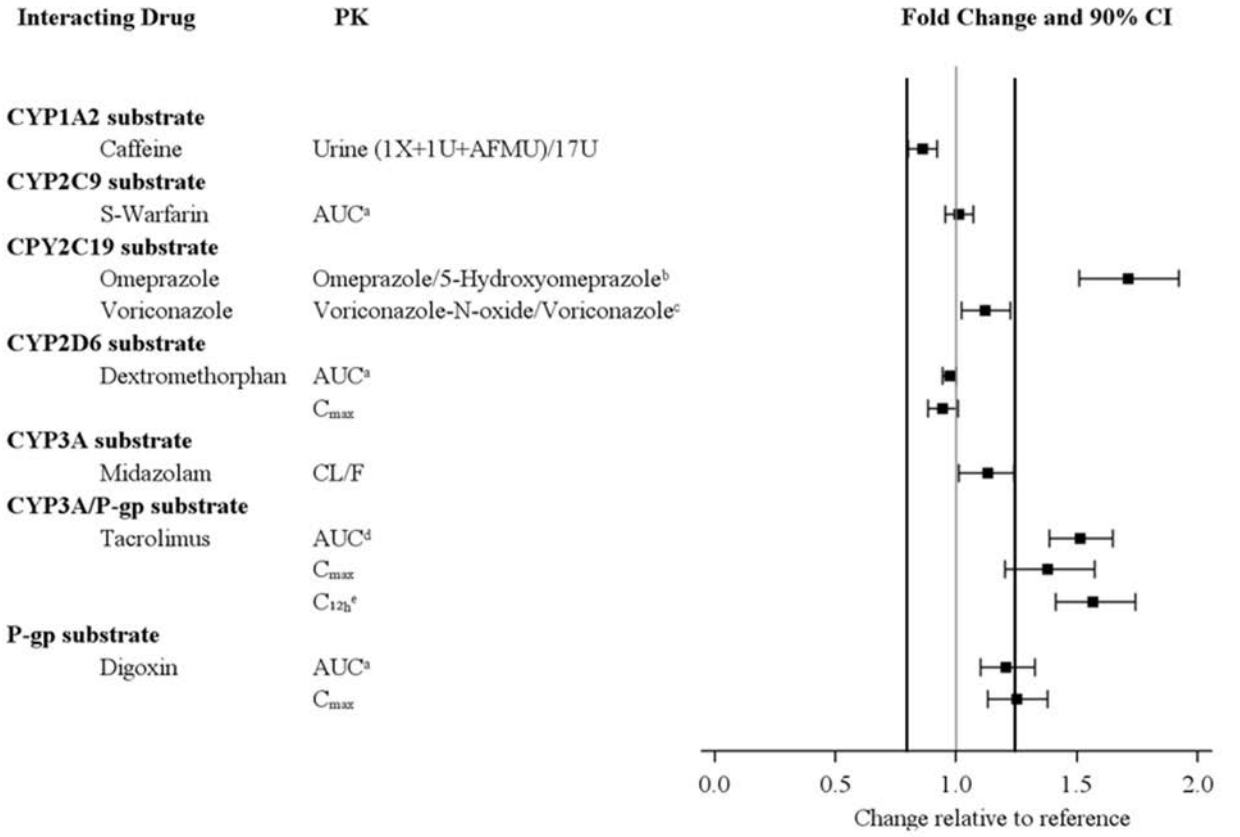
Effect of Maribavir on PK of Other Drugs

- In vitro, maribavir is not an inhibitor of CYP2A6, CYP2B6, CYP2C8, CYP2D6, CYP2E1, UGT1A4 or UGT1A6 and is not an inducer of CYP1A2 or CYP2B6; maribavir is not an inhibitor of OCT2, OAT1 or multidrug and toxin extrusion transporter (MATE)2K and VP 44469 is not an inhibitor of OAT1, OAT3, OCT2, MATE1, or MATE2K. In vitro, maribavir is a weak time-dependent inhibitor for CYP3A4 and inducer of CYP3A4. In vitro, maribavir is a weak inhibitor of CYP1A2, CYP2C9, CYP2C19, UGT1A1, UGT1A3, UGT1A9, UGT2B7, P-glycoprotein (P-gp), OATP1B1, OATP1B3, OCT1, OAT3, MATE1, Breast Cancer Resistance Protein (BCRP), and bile salt export pump (BSEP). However, no clinically significant inhibitory or inducing effects of maribavir were observed in the drug-drug interaction studies with substrates of various CYP isozymes or transporter: CYP1A2 (caffeine), CYP2C9 (S-warfarin), CYP2C19 (voriconazole), CYP2D6 (dextromethorphan), or CYP3A4/5 (midazolam) (Figure 8). Based on

the estimated R values, maribavir is not expected to cause clinically significant DDI with substrates of OATPs, OAT3, MATE1.

- Coadministration of 400 mg BID maribavir with tacrolimus, an immunosuppressant and a CYP3A4 and P-gp substrate, increased the tacrolimus whole blood C_{max}, AUC, and C_{trough} by 38%, 51%, and 57%, respectively (Figure 8). Although no clinical DDI study has been conducted with other immunosuppressant agents, including cyclosporine, everolimus and sirolimus, blood concentrations of these immunosuppressants were monitored prior to and during treatment with maribavir and in the follow-up period. Among the 234 patients in the maribavir treatment group, 21 out of 216 patients on concomitant immunosuppressants (9.7%) had an AE of immunosuppressant drug level increase during maribavir treatment period; 19 out of these 21 patients (90.5%) were on treatment with tacrolimus. These AEs of immunosuppressant drug level increase were reported as mild, moderate, and severe in 13, 6, and 2 patients, respectively, and all moderate and severe AEs were associated with the use of tacrolimus. Based on the available PK and safety data, the impact of coadministration of maribavir on other immunosuppressants is expected to be lower compared to what was observed for tacrolimus. When immunosuppressants tacrolimus, cyclosporine, everolimus, or sirolimus are co-administered with maribavir, their whole blood concentrations should be frequently monitored throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir, and immunosuppressant dose should be adjusted, as needed.
- Based on PBPK modeling results, coadministration of 400 mg BID maribavir with rosuvastatin, a sensitive BCRP substrate, is expected to increase rosuvastatin AUC by 2.15- to 2.94-fold, and C_{max} by 3.40- to 4.97-fold. However, in Phase 2 and Phase 3 studies, there was no increased risk of musculoskeletal disorder when maribavir was co-administered with rosuvastatin or other commonly used statins in transplant patients with CMV infections. To be cautious, it is recommended that when initiating maribavir dosing in patients who are taking rosuvastatin, patients should be closely monitored for rosuvastatin-related events, especially the occurrence of myopathy and rhabdomyolysis.
- Coadministration of 400 mg BID maribavir with digoxin, a sensitive P-gp with a narrow therapeutic index, increased digoxin AUC and C_{max} by approximately 21% and 25%, respectively. Caution should be exercised when maribavir and digoxin are co-administered; serum digoxin concentrations should be monitored and the dose of digoxin may need to be reduced when co-administered with maribavir.

Figure 8: Impact of Maribavir on the Pharmacokinetics of Co-administered Drugs



AUC=area under the plasma concentration-time curve; CI=confidence interval; CL/F=oral clearance; C_{max}=maximum observed plasma concentration; C_{trough}=plasma concentration at the end of a dosing interval; CYP=cytochrome P450; PK=pharmacokinetics; P-gp=P-glycoprotein

[a] $AUC_{0-\infty}$.

[b] Plasma Omeprazole/5-Hydroxyomeprazole ratio at 2 hours post-dose.

[c] Voriconazole-N-Oxide/Voriconazole AUC_{0-t} ratio.

[d] AUC_{0-t}.

[e] C_{trough} at 12 hours post-dose.

Table 9 provides a listing of established or potentially clinically significant DDIs which are included in the proposed product label. The drug interactions described are based on the clinical studies conducted with maribavir or are predicted drug interactions that may occur with maribavir due to the expected magnitude of interaction and potential for SAEs or decrease in efficacy.

Table 9: Established and Other Potentially Significant Drug Interactions[a]

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
Antiarithmics		
Digoxin[b]	↑ Digoxin	Caution should be exercised when maribavir and digoxin are co-administered; serum digoxin concentrations should be monitored and the dose of digoxin may need to be reduced when co-administered with maribavir[c].
Anticonvulsants		
Carbamazepine	↓ Maribavir	A dose adjustment of maribavir to 800 mg twice daily is recommended when co-administered with carbamazepine.
Phenobarbital	↓ Maribavir	A dose adjustment of maribavir to 800 mg twice daily is recommended when coadministration with phenobarbital.
Phenytoin	↓ Maribavir	A dose adjustment of maribavir to 1200 mg twice daily is recommended when coadministration with phenytoin.
Antimycobacterials		
Rifabutin	↓ Maribavir	A dose adjustment of maribavir up to 1200 mg twice daily is recommended when co-administered with rifabutin.
Rifampin[b]	↓ Maribavir	Coadministration of maribavir and rifampin is not recommended due to potential for a decrease in efficacy of maribavir.
Herbal Products		
St. John's wort	↓ Maribavir	Coadministration of maribavir and St. John's wort is not recommended due to potential for a decrease in efficacy of maribavir.
HMG-CoA Reductase Inhibitors		
Rosuvastatin[c]	↑ Rosuvastatin	The patient should be closely monitored for rosuvastatin-related events, especially the occurrence of myopathy and rhabdomyolysis.
Immunosuppressants		
Cyclosporine	↑ Cyclosporine	Frequently monitor cyclosporine levels throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir and adjust dose, as needed[c].
Everolimus	↑ Everolimus	Frequently monitor everolimus levels throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir and adjust dose, as needed[c].
Sirolimus	↑ Sirolimus	Frequently monitor sirolimus levels throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir and adjust dose, as needed[c].
Tacrolimus[b]	↑ Tacrolimus	Frequently monitor tacrolimus levels throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir and adjust dose, as needed[c].

Table 9: Established and Other Potentially Significant Drug Interactions[a]

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
Antiarithmics		

↓=decrease; ↑ =increase; HMG-CoA=β-Hydroxy β-methylglutaryl-CoA
[a] This table is not all inclusive.
[b] The interaction between maribavir and the concomitant drug was evaluated in a clinical study.
[c] Refer to the respective prescribing information.

5.6 Viral Resistance

5.6.1 Viral Resistance to Maribavir

Cell Culture: Maribavir does not affect the viral polymerase encoded on gene *UL54* that when presenting certain mutations, confers resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir. However, specific amino acid substitutions in human CMV pUL97 or pUL27 gene products do confer resistance to maribavir. Common pUL97 mutations in the kinase ATP-binding and phosphotransfer domains of pUL97: L337M, F342Y, V353A, L397R, T409M, H411L/N/Y, and C480F conferred wide ranging (3.5-fold to >200-fold increase in EC_{50}) levels of maribavir resistance (Chou, 2008; Chou, Hakki, & Villano, 2012; Chou, Song, Wu, Bo, & Crumpacker, 2020; Chou, Wechel, & Marousek, 2007; Chou, Wu, Song, & Bo, 2019). pUL27 gene variants (R233S, W362R, W153R, L193F, A269T, V353E, L426F, E22stop, W362stop, 218delC, and 301-311del) conferred only mild maribavir resistance (<5-fold increase in EC_{50}) (Chou, 2009; Chou, Marousek, Senters, Davis, & Biron, 2004; Komazin, Ptak, Emmer, Townsend, & Drach, 2003; Lurain & Chou, 2010). In vitro strains of human CMV resistant to ganciclovir, foscarnet, or cidofovir, or resistant to combinations of these drugs, remained sensitive to maribavir, suggesting its utility in transplant patients whose CMV infection is resistant to these drugs (Drew, Miner, Marousek, & Chou, 2006; Schubert et al., 2013; Strasfeld, Lee, Tatarowicz, Villano, & Chou, 2010).

Clinical Trials: In Phase 3 Study 303, 58/214 patients (27.1%) were identified with treatment-emergent mutations in pUL97 that confer resistance to maribavir: T409M, H411N, H411L, H411Y, F342Y and C480F.

In Phase 2 Study 202 and Study 203 evaluating maribavir in 279 HSCT or SOT recipients, post-treatment pUL97 genotyping data from 23 of 29 patients who initially achieved viremia clearance and later experienced recurrent CMV infection while on maribavir showed 17 patients with mutations T409M or H411Y and 6 patients with mutation C480F. Among 25 patients who did not respond to >14 days of maribavir therapy, 9 had mutations T409M or H411Y, and 5 patients had mutation C480F. Additional pUL27 genotyping was performed on 39 patients in Study 202 and 43 patients in Study 203. The only resistance-associated amino acid substitution in pUL27 that was not detected at baseline was G344D. Phenotypic analysis of pUL27

and pUL97 recombinants showed that pUL97 mutations T409M, H411Y, and C480F conferred 78-fold, 15-fold, and 224-fold increases, respectively, in maribavir EC_{50} compared with the wild-type strain. The pUL27 mutation G344D was not shown to confer maribavir resistance.

In Phase 3 Study 1263-300 and Study 1263-301, no mutations conferring resistance to maribavir were observed.

5.6.2 Cross-Resistance to Maribavir and Ganciclovir/Valganciclovir

There is clinical evidence of cross-resistance to maribavir and ganciclovir/valganciclovir at pUL97: F342Y- 4.5-fold and 6.0-fold increase in EC_{50} to maribavir and ganciclovir, respectively; and C480F- 224-fold and 2.3-fold increase in EC_{50} to maribavir and ganciclovir, respectively. The prevalence of F342Y, which was the only cross-resistant mutation present in Study 303 patients prior to investigator-assigned or maribavir treatment, was low (3/309 patients with baseline pUL97 genotyping). T409M confers resistance to maribavir but not ganciclovir (Chou et al., 2007). H411L, H411Y, H411N confer resistance to maribavir but not ganciclovir (Chou & Marousek, 2008).

6 CLINICAL EFFICACY

Summary

- The efficacy of maribavir as a treatment of R/R CMV infection and disease in transplant recipients was demonstrated in pivotal Phase 3 Study 303.
- Efficacy results for pivotal Phase 3 Study 303 include the following:
  - The proportion of maribavir-treated patients who achieved confirmed CMV viremia clearance at Week 8 was statistically superior to and more than 2-fold greater than that of patients who received standard of care treatment with IAT (maribavir: 55.7%; IAT: 23.9%).
  - The virologic effect of maribavir compared to IAT was consistent in various pre-specified sensitivity analyses and supplementary analyses of the primary endpoint.
  - The proportions of responders at Week 8 were consistent across key subgroups, including transplant type (SOT vs HSCT), subpopulations of SOT, patients with symptomatic CMV infection, and patients with genotypic resistance to other anti-CMV agents.
  - Viremia clearance at Week 8 was achieved regardless of whether the patients had high/intermediate or low baseline viral loads.
  - Maribavir showed a higher response compared to IAT on the composite key secondary endpoint of achieving clearance of CMV viremia and symptom control, with maintenance through Week 16.
  - Maribavir's efficacy in the subset of patients who received rescue treatment after failing to respond to IAT was similar to the results in patients randomized to maribavir.

6.1 Overview of Efficacy

The proposed indication (the treatment of adults with post-transplant CMV infection and/or disease which are R/R to ganciclovir, valganciclovir, cidofovir or foscarnet) is supported by the pivotal Phase 3 (Study 303), with additional data especially relevant to dose-ranging and safety provided by the 2 Phase 2 studies (Study 202 and Study 203). Across the 3 treatment studies, 495 transplant recipients with CMV infection have been treated with maribavir 400 mg to 1200 mg BID for up to 24 weeks. A summary and comparison of key design features for the 3 treatment studies are provided in Table 10.

Table 10: Key Design Features of Studies Supporting the Efficacy of Maribavir in Treatment of CMV Infection

Design Feature	Study 202 N=120	Study 203 N=161	Study 303 N=352
Comparator	None	Valganciclovir	Investigator-assigned anti-CMV treatment (IAT) utilizing a single available agent (ganciclovir, valganciclovir, foscarnet, or cidofovir), or combination of 2 agents (ganciclovir or valganciclovir plus either foscarnet or cidofovir)
Disease Characteristics	Current CMV infection that was resistant or refractory to treatment	Current CMV infection that was not resistant to ganciclovir/valganciclovir, foscarnet, or cidofovir based on genotypic evidence and not refractory to available agents	Current CMV infection refractory to the most recently administered of the 4 anti-CMV treatment agents. Also, patients with refractory CMV infection plus documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir
Prior Therapy	When study drug was initiated, could not have received ganciclovir, valganciclovir, foscarnet, artesunate, or any investigational agent with known anti-CMV activity. Cidofovir, CMV immune globulin, and leflunomide must have been discontinued at least 14 days prior to first dose of study drug.	Could not have received ganciclovir, valganciclovir, foscarnet, cidofovir, CMV immune globulin, leflunomide, artesunate, or any investigational agent with known anti-CMV activity with a washout period of ≥24 hours between last dose and receipt of first dose of study treatment.	At study entry, could have been receiving ganciclovir, valganciclovir, cidofovir, or foscarnet. Could not have received leflunomide or artesunate at the time of study initiation. Washout periods were 14 days for leflunomide, 3 days for letermovir, and prior to the first dose for artesunate.
Refractory to Prior Therapy **Definition**	Yes Documented failure to achieve >1 $\log_{10}$ 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).	No Not applicable	Yes Documented failure to achieve >1 $\log_{10}$ 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.

Table 10: Key Design Features of Studies Supporting the Efficacy of Maribavir in Treatment of CMV Infection

Design Feature	Study 202 N=120	Study 203 N=161	Study 303 N=352
Includes Patients Resistant to Prior Therapy?	Yes	No	Yes
Definition	Documentation of 1 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 combination thereof)	Not applicable	Patients were refractory to at least 1 CMV agent AND had 1 or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir
Primary Efficacy Endpoint	CMV viremia clearance by central laboratory within 6 weeks	CMV viremia clearance by central laboratory within 3 and 6 weeks	Confirmed clearance of plasma CMV DNA (CMV viremia clearance) by central laboratory at the end of Week 8

CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IV=intravenous

6.2 Supportive Study 202

6.2.1 Investigational Plan

The multicenter Phase 2 Study 202 was a randomized, dose-ranging, parallel-group study that evaluated 3 doses of maribavir in post-transplant recipients of either HSCT or SOT with CMV infection who were refractory, with or without resistance, to treatment with ganciclovir/valganciclovir or foscarnet. All enrolled patients received maribavir, but patients, investigators, and study staff were blinded to dose strength.

The primary study objective was to evaluate the safety of maribavir. The secondary objective was to assess the comparative antiviral activity of the different doses of maribavir as measured by the proportion of patients who had achieved confirmed CMV viremia clearance by Week 6. This endpoint was defined as 2 consecutive post-baseline, on-treatment undetectable results (<200 copies/mL) separated by at least 5 days.

Patients were eligible to participate in the study if they had documented CMV infection in blood or plasma with a screening value of ≥1000 DNA copies/mL and their CMV infection was refractory and/or resistant to prior anti-CMV therapy (as defined in Table 10).

Patients were randomized in a 1:1:1 allocation ratio to receive oral maribavir at 400 mg BID, 800 mg BID, or 1200 mg BID for up to 24 weeks. Randomization of eligible

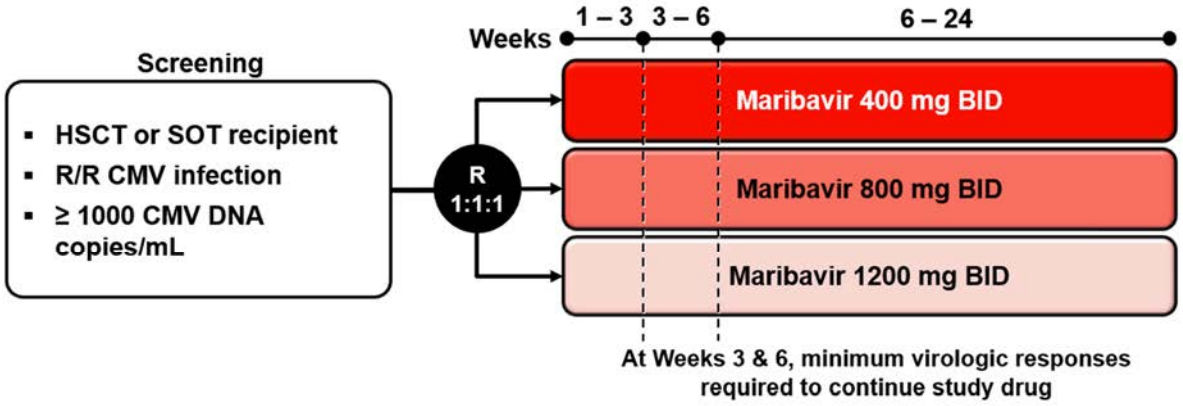
patients was stratified by transplant type (HSCT or SOT). After the 24-week treatment period (or premature discontinuation of study drug), patients were assessed during a 12-week follow-up period. A diagram providing a summary of the study design through the treatment period is presented in Figure 9.

The study was not powered to detect differences in efficacy between treatment groups; thus, no statistical comparisons of differences were performed among the 3 maribavir dose groups.

Other secondary endpoints that were common to Study 303, and presented in this document, were:

- Proportion of patients with undetectable plasma CMV DNA (central laboratory) at specified visits; results of the analysis are presented in Section 6.2.4.
- Proportion of patients with CMV recurrence during the study participation period, defined as achievement of undetectable plasma CMV DNA (central laboratory) at any time after Day 1 in at least 2 consecutive samples separated by at least 5 days, followed by detectable plasma CMV DNA (central laboratory) in at least 2 consecutive samples separated by at least 5 days; central laboratory plasma CMV DNA PCR values of ≥200 copies/mL were considered detectable. Results of this analysis are presented in Section 6.2.5.

Figure 9: Study 202 - Overview of Design for Study to Evaluate Maribavir in CMV Infections Refractory and/or Resistant to Prior Treatment



BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; HSCT=hematopoietic stem cell transplant; SOT=solid organ transplant

6.2.2 Study Patients

Study 202 randomized 120 patients into 3 dose groups with 40 patients in each group. The percentage of patients completing the protocol-specified maximum treatment

duration of 24 weeks was similar in the 400 mg BID (22.5%; 9/40), 800 mg BID (17.5%; 7/40), and 1200 mg BID (27.5%; 11/40) dose groups. (It should be noted that duration of treatment was determined primarily by investigator discretion, based on a demonstrated minimum virologic response at Weeks 3 and 6.) Similar proportions of patients across treatment groups discontinued treatment due to lack of efficacy (approximately 15% to 20%) or due to recovery from CMV infection (18% to 23%). Patients who discontinued study drug prematurely for reasons other than withdrawal of consent, lost to follow-up, or AE with an outcome of death, or who continued participation in the study and had end of treatment and follow-up assessments performed were considered to have completed the study. Approximately 60% of patients in each treatment group completed the study, whether or not treatment had been discontinued early. The most common reason for early discontinuation from the study was death (approximately 25% to 30% of patients across the treatment groups), followed by physician decision (3% to 13% across treatment groups) and withdrawal by patient (0% to 10% across treatment groups).

6.2.2.1 Baseline Demographics

More than half of patients in each treatment group were male (approximately 53% to 60%) and most were White (approximately 78% to 80%). The median age of all patients was 55.0 (range: 18 to 74) years.

6.2.2.2 Baseline Characteristics

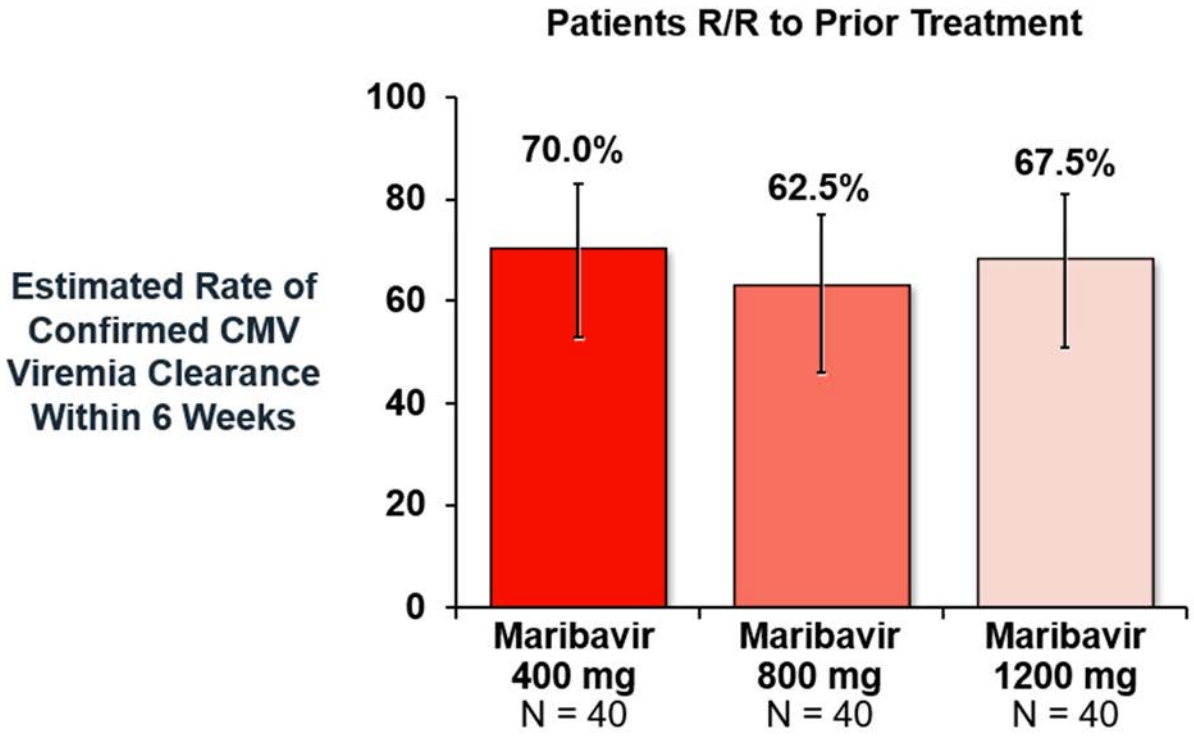
Stratification by transplant type controlled the proportion of HSCT and SOT recipients within each treatment group (overall maribavir: 39% and 61%, respectively). Among patients with SOTs, the most frequent transplant types were kidney (41%), lung (27%), pancreas (15%), and liver (14%).

Additional details on baseline characteristics of patients in Study 202 are provided in Appendix 10.2.

6.2.3 Primary Efficacy Endpoint: Confirmed Undetectable Plasma CMV DNA

Confirmed CMV viremia clearance (per the central laboratory) was generally similar across the treatment groups in Study 202, with no evidence of a dose-related response: 70.0% (28/40), 62.5% (25/40), and 67.5% (27/40) of patients in the 3 dose groups (400 mg BID, 800 mg BID and 1200 mg BID) achieved confirmed undetectable plasma CMV DNA (per the central laboratory) within 6 weeks (Figure 10).

Figure 10: Study 202 - CMV Viremia Clearance Within 6 Weeks in Patients Resistant/Refractory to Prior Treatment



6.2.4 Secondary Efficacy Endpoint: Confirmed CMV Viremia Clearance (Central Laboratory) at Specified Visits

The proportion of patients with confirmed CMV viremia clearance increased weekly to a plateau across the dose cohorts at Week 6. Therapy beyond 6 weeks did not appear to increase the proportion of confirmed undetectable CMV in study patients' plasma. As previously described, patients could receive treatment for up to 24 weeks at the discretion of the investigator. Median exposure was similar across the dose groups (72, 81, and 73 days in the 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively). At Week 12, the estimated rate of confirmed CMV viremia clearance for the 400 mg BID, 800 mg BID, and 1200 mg BID groups was 63% (95%CI: 0.46, 0.77), 50% (95%CI: 0.34, 0.66), and 55% (95%CI: 0.38, 0.71), respectively. After 20 weeks of maribavir treatment, at least half of patients in all dose cohorts maintained confirmed undetectable plasma CMV DNA.

6.2.5 Secondary Efficacy Endpoint: CMV Recurrence

Cytomegalovirus recurrence during the study was defined as undetectable plasma CMV DNA (per the central laboratory) at any time after Day 1 in at least 2 consecutive samples separated by at least 5 days, followed by detectable plasma CMV DNA (per the central laboratory).

Among the 86 patients (of 120 enrolled) who achieved confirmed CMV viremia clearance, 30 had CMV recurrence during the study. The 400 mg BID maribavir group (estimated rate [95% CI]: 0.24 [0.10, 0.44]) had a numerically lower proportion of patients with CMV recurrence than the 800 mg BID (0.41 [0.22, 0.61]) and 1200 mg BID (0.40 [0.23, 0.59]) groups. (Table 11).

Table 11: Study 202 - CMV Recurrence at any Time During the Study

Parameter	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 patients achieving confirmed undetectable CMV DNA [a]	29	27	30	86
Patients 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; N=number of patients
[a] Number of patients with at least 2 consecutive undetectable plasma CMV DNA results separated by at least 5 days, including
early withdrawn qualified patients.
[b] Any recurrence during the study, including early withdrawn patients who had recurrence before withdrawal from study.
[c] Did not have recurrence during the study, including early withdrawn patients who did not have recurrence before withdrawal from study.
[d] Numerator is all recurrences. Denominator is the number of patients achieving confirmed undetectable CMV DNA.
[e] Calculated using the exact (Clopper-Pearson) confidence limits for the binomial proportion.
Note: Results from central laboratory.
Source: Study 202 CSR, Table 11.2.9.1

6.3 Supportive Study 203

6.3.1 Investigational Plan

Study 203 was a Phase 2, partially open-label, randomized, dose-ranging, parallel-group study to assess the safety and anti-CMV activity of maribavir vs valganciclovir for treatment of CMV infections in transplant recipients with a first episode of CMV infection.

The primary efficacy endpoint was confirmed undetectable plasma CMV DNA (per 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; results of the analysis are presented in Section 6.3.3.

Patients were randomized in a 1:1:1:1 ratio to receive 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 once daily; with dose adjustment for renal function) for up to 12 weeks. Randomization of eligible patients was stratified by transplant type (HSCT or

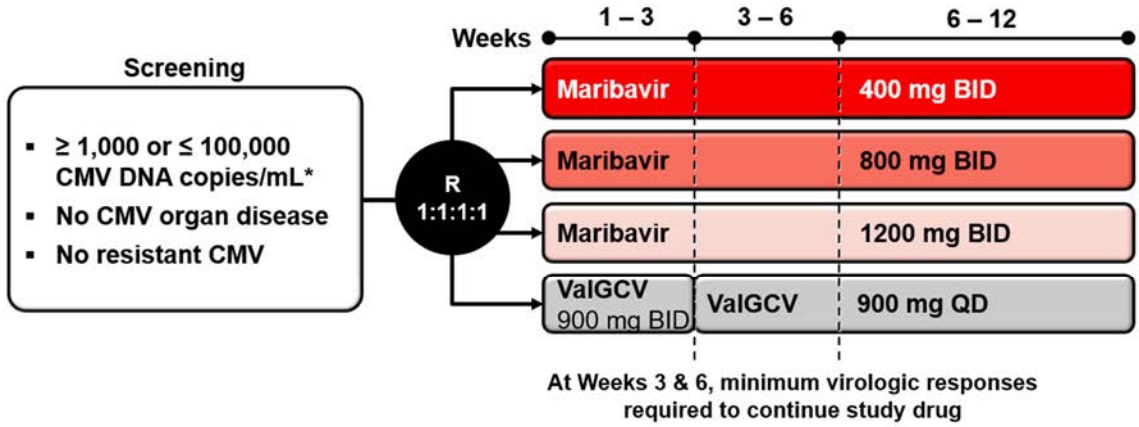
SOT). The study was partially open-label in that assignment to maribavir vs valganciclovir was known, but patients, investigators, and study staff were blinded to maribavir dose strength. An open-label design was necessary because the dosage of valganciclovir required modification for impaired renal function. After the treatment period (or premature discontinuation of study drug), patients were assessed during a 12-week follow-up period. A summary diagram of Study 203 through the treatment period is provided in Figure 11.

The study excluded patients with known CMV organ disease, and patients with CMV infections that were known to be genotypically resistant to ganciclovir/valganciclovir, foscarnet, or cidofovir,

For the primary efficacy endpoint, the primary comparison was maribavir (all dose groups combined) vs valganciclovir. The second comparison estimated the treatment effect by maribavir dose group vs valganciclovir.

All statistical tests were 2-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.

Figure 11: Study 203 - Overview of Design for Study to Evaluate Maribavir vs Valganciclovir for Treatment of CMV Infections



- Primary endpoint: proportion of patients with confirmed undetectable plasma CMV DNA (CMV viremia clearance) within 6 weeks of treatment

*Target of approximately 25% of all randomized patients were to have ≥ 10,000 CMV DNA copies/mL in plasma at baseline

BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; QD=once daily; ValGCV=valganciclovir.

6.3.2 Study Patients

Study 203 randomized 161 patients. One patient in the maribavir 1200 mg BID group and one patient in the valganciclovir 900 mg BID group were randomized but did not receive study drug. The remaining 159 patients received at least 1 dose of study drug

(maribavir 400 mg BID: 40 patients; maribavir 800 mg BID: 40 patients; maribavir 1200 mg BID: 39 patients; valganciclovir 900 mg BID: 40 patients). The percentage of patients completing the protocol-specified maximum treatment duration of 12 weeks was similar in the overall maribavir (28.3%; 34/120) and valganciclovir groups (31.7%; 13/41). (It should be noted that duration of treatment was determined primarily by investigator discretion, based on a demonstrated minimum virologic response at Weeks 3 and 6.) The most common reason for not completing treatment was recovery from CMV infection as judged by the investigator (overall maribavir, 39.2% [47/120]; valganciclovir, 34.1% [14/41]). Adverse event (overall maribavir, 19.2% [23/120]; valganciclovir, 14.6% [6/41]) and lack of efficacy (overall maribavir, 6.7% [8/120]; valganciclovir, 7.3% [3/41]) were the second and third most common reasons for not completing treatment.

6.3.2.1 Baseline Demographics

The median age of patients was 58.0 (range: 18 to 76) years, and the majority of all patients were White (91.2%) and male (61.6%). Overall, the distribution of demographic data was similar across the treatment groups.

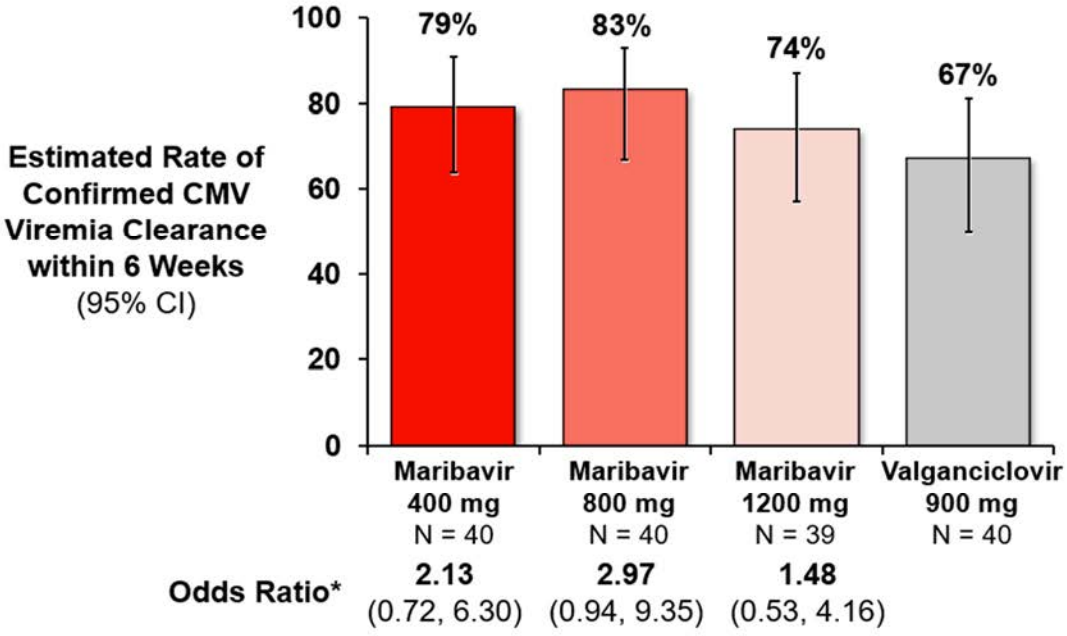
6.3.2.2 Baseline Characteristics

Stratification by transplant type resulted in comparable percentages of HSCT and SOT recipients within each treatment group (overall maribavir: 51.3% [61/119] and 48.7% [58/119], respectively; valganciclovir: 52.5% [21/40] and 47.5% [19/40], respectively). For all patients, acute myeloid leukemia was the most frequently reported primary underlying disease (19.5%), followed by myelodysplastic syndrome (8.2%), non-Hodgkin's lymphoma (5.0%), plasma cell myeloma (4.4%), and alcoholic cirrhosis, hepatitis C, and chronic renal failure (3.8% each). Other conditions reported for >2% of patients included acute lymphocytic leukemia, chronic obstructive pulmonary disease, glomerulonephritis, chronic lymphocytic leukemia, and chronic myeloid leukemia (approximately 3% each).

6.3.3 Primary Efficacy Endpoint: Confirmed Undetectable Plasma CMV DNA

Within 6 weeks of treatment, the treatment effect estimate for confirmed CMV viremia clearance in the maribavir dose groups (estimated rate: 400 mg BID, 79%; 800 mg BID, 83%; and 1200 mg BID, 74%) was comparable to the valganciclovir group (67%) (Figure 12).

Figure 12: Study 203 - Confirmed CMV Viremia Clearance for Maribavir vs Valganciclovir



*Treatment comparison with control; logistic regression model for maribavir vs valganciclovir (SAS PROC LOGISTIC): y = treatment + baseline plasma CMV DNA + transplant type

CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid

6.4 Pivotal Study 303

6.4.1 Investigational Plan

6.4.1.1 Overall Design

Study 303 was a Phase 3, multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir compared to IAT in HSCT and 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. The study was conducted at 94 sites in North America, Europe, and Asia Pacific. FDA considered the overall design of Study 303, including patient population, treatment duration, and endpoints, to be acceptable.

The following definitions were used for “refractory” and “resistant,” per the inclusion criteria for the maribavir clinical trials (Chemaly et al., 2019):

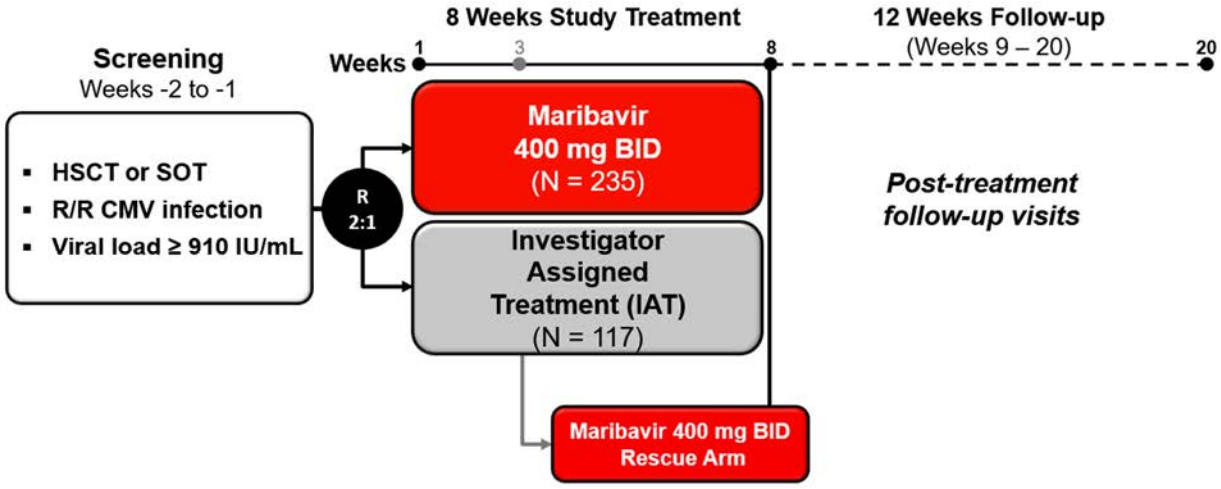
- Refractory: Documented failure to achieve >1 $\log_{10}$ decrease in CMV DNA level in whole blood or plasma after a 14-day or longer treatment period with anti-CMV agent.

- Resistant: Refractory CMV infection (per above definition) AND documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir.

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. In the follow-up phase, study-specific evaluations including CMV testing and safety assessments occurred weekly for the first 4 weeks, then every 2 weeks for the final 8 weeks of the 12-week follow-up phase.

A diagram summarizing the study design is provided in Figure 13.

Figure 13: Study 303 - Overview of Design for Randomized Controlled Study in Patients Refractory/Resistant to CMV Therapy



BID=twice daily; CMV=cytomegalovirus; IAT=investigator-assigned anti CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); R/R=resistant and/or refractory; HSCT=hematopoietic stem cell transplant; R=randomization; SOT=solid organ transplant

6.4.1.1.1 Stratification, Randomization, and Treatments

Eligible patients were stratified by transplant type (HSCT and SOT) and by the most recent screening CMV DNA viral load (quantitative polymerase chain reaction [qPCR] result) on study entry. Viral load measurements were determined by the most recent local or central specialty laboratory qPCR results and the stratification categories for viral load were as follows:

- High viral load: CMV DNA ≥273000 IU/mL in whole blood or ≥91000 IU/mL in plasma.
- Intermediate viral load: CMV DNA ≥27300 and <273000 IU/mL in whole blood or ≥9100 and <91000 IU/mL in plasma.
- Low viral load: CMV DNA <27300 and ≥2730 IU/mL in whole blood or CMV DNA <9100 and ≥910 IU/mL in plasma.

After stratification, patients were randomized in a 2:1 ratio to open-label maribavir 400 mg twice daily (BID) or IAT (ganciclovir, valganciclovir, foscarnet, or cidofovir) for 8 weeks.

6.4.1.1.2 Investigator-Assigned Anti-CMV Treatment (IAT) Description

While patients had to be refractory and potentially resistant per the protocol definition to at least 1 of the specified anti-CMV agents to be eligible for the study, the principal investigator individualized the IAT for patients randomized to the IAT arm, selecting 1 or 2 of the 4 available anti-CMV agents with knowledge of the patient's past medical history and clinical course with treatment of the current CMV infection, and after considering the risk/benefit of potential treatment options for the patient (ie, the best available therapy).

The protocol allowed study investigators flexibility to select the best monotherapy or combination therapy from the available standard of care choices for their patients, including choosing a combination of 2 antiviral drugs, cycling between oral valganciclovir and IV ganciclovir during the study, and modifying the dose of any drug as necessary. In addition, patients started on dual-agent IAT could discontinue one of the drugs in the event of a safety or tolerability issue, without resulting in an automatic treatment failure. Combination therapy of cidofovir with foscarnet was prohibited due to toxicity considerations per the prescribing information.

Patients with clear evidence of virologic failure (ie, not merely intolerance) after a minimum of 3 weeks of treatment could be evaluated by the medical monitor for entry into the rescue arm, starting at Visit 5/Week 3. Rescue treatment was with maribavir 400 mg BID for 8 weeks.

6.4.1.1.3 Discussion of Open Label Design

While an open-label design has the potential for bias, in this study physicians had to individualize the selection of (an) effective comparator(s) in medically complex patients with many concomitant drugs. Dosing adjustment is needed for the IAT agents based on renal function. In addition, 2 of the available comparator treatments can only be administered IV, and maribavir can only be given orally, posing challenges to blinding the study. Therefore, an open-label design was chosen as a safe and practical way to conduct this study. To allow for a robust comparison of maribavir vs IAT, the primary efficacy analysis was assessed at a fixed timepoint. Additionally, multiple sensitivity analyses were conducted to address the potential bias due to the different rate of early treatment discontinuation, which was 3-fold higher for IAT than for maribavir. To establish the consistency of treatment effect as well as the generalizability of the study outcomes, the primary efficacy endpoint was evaluated in clinically meaningful subgroups, including assessment of outcomes by HSCT vs SOT, presence or absence of baseline CMV resistance-associated amino acid substitutions (RASs), tissue-invasive disease/CMV syndrome, and by varying levels of viral load.

6.4.1.2 Endpoints

6.4.1.2.1 Primary Endpoint

The primary evaluation of efficacy was based on assessment of CMV viremia clearance at a fixed time point (8 weeks) for both study arms using an FDA-approved assay (COBAS® AmpliPrep/COBAS® TaqMan® CMV Test) performed by a central virology laboratory to control variability.

Confirmed CMV viremia clearance at the end of Study Week 8 was defined as plasma CMV DNA concentration <LLOQ (ie, <137 IU/mL) per central laboratory result in 2 consecutive post-baseline samples, separated by at least 5 days.

- This endpoint was assessed regardless of whether patients completed the stipulated 8 weeks of study-assigned treatment.
- Patients who initiated alternative (nonstudy) anti-CMV therapy or rescue treatment before Week 8 were counted as nonresponders.

6.4.1.2.2 Key Secondary Endpoint and the Endpoint Adjudication Committee (EAC)

For the key secondary endpoint assessment, all investigator-assessed cases of tissue-invasive CMV disease or CMV syndrome were reviewed and adjudicated by an independent, blinded EAC. The committee adjudicated the diagnosis at baseline, new symptomatic CMV infection and potential changes at Week 8/end of treatment, Week 12, Week 16, and Week 20 (ie, no change, improvement, worsening, or resolution). This review allowed for a standardized comparison of symptoms in each study arm based on the definitions by (Ljungman et al., 2001).

The key secondary endpoint was a composite endpoint which assessed achievement of CMV viremia 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 period (ie, 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.
- This endpoint was assessed regardless of whether patients completed the stipulated 8 weeks of study-assigned treatment.
- Patients who initiated alternative (nonstudy) anti-CMV therapy before Week 16 were counted as nonresponders.

6.4.1.2.3 Other Secondary Endpoints

For other secondary endpoints, any patient who initiated alternative (nonstudy) anti-CMV therapy before the time point of interest was counted as a nonresponder:

- The maintenance of CMV viremia clearance and CMV infection symptom control achieved at the end of Study Week 8 through Weeks 12 and 20
- Achievement of confirmed CMV viremia clearance after 8 weeks of receiving study-assigned treatment
- Achievement of confirmed CMV viremia clearance and CMV infection symptom control after 8 weeks of receiving study-assigned treatment

Recurrence of CMV viremia was an additional secondary endpoint and was defined as plasma CMV DNA concentrations ≥LLOQ, when assessed by the central specialty laboratory, in 2 consecutive plasma samples separated by at least 5 days after achieving confirmed viremia clearance. Recurrence of CMV viremia following confirmed CMV clearance, through Week 8 and after Week 8, was assessed using all CMV DNA measurements after achieving confirmed CMV viremia clearance, regardless of rescue or alternative treatment.

6.4.1.3 Selection of Study Population

The protocol-specified diagnosis and criteria for eligibility are listed below.

Inclusion Criteria: To be eligible to participate in Study 303, patients were required to meet all of the following criteria:

- The patient must have been able to provide written, personally signed, and dated informed consent to participate in the study before completing any study-related procedures. As applicable, a parent/both parents or legally authorized representative must have provided signature of informed consent and there must be documentation of assent by the patient before completing any study-related procedures.
- The patient must have been a recipient of HSCT or SOT.
- The patient must have had a documented CMV infection in whole blood or plasma, with a screening value of ≥2730 IU/mL in whole blood or ≥910 IU/mL in plasma in 2 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 randomization with second sample obtained within 5 days prior to randomization. The same laboratory and same sample type (whole blood or plasma) must have been used for these assessments.
- The patient must have had a current CMV infection that was refractory to the most recently administered of the 4 anti-CMV treatment agents. Refractory was 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.

  - Patients with documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir had to also have met the definition of refractory CMV infection. (Note: The investigator had the option to change the IAT to which the patient was refractory at entry into the study.)

- The investigator must have been willing to treat the patient with at least 1 of the available anti-CMV drugs (ganciclovir, valganciclovir, foscarnet, or cidofovir). Note: Combination therapy with foscarnet and cidofovir was not permitted in the IAT arm due to the potential for serious nephrotoxicity.
- The patient must have been ≥12 years of age at the time of consent.
- The patient must have weighed ≥35 kg.
- The patient must have had all of the following results as part of screening laboratory assessments (results from either the central laboratory or a local laboratory could have been used for qualification):
  - Absolute neutrophil count (ANC) ≥1000/mm^3 (1.0 × 10^9/L)
  - Platelet count ≥25,000/mm^3 (25 × 10^9/L)
  - Hemoglobin ≥8 g/dL
  - Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2 at screening as assessed by Modification of Diet in Renal Disease formula for patients ≥18 years of age or Schwartz formula for patients <18 years of age
- The patient must have had a negative serum β-human chorionic gonadotropin pregnancy test at screening, if a female of child-bearing potential. Additional urine pregnancy tests could be done per institutional requirements. Sexually active females of child-bearing potential must have agreed to comply with any applicable contraceptive requirements of the protocol. If male, the patient must have agreed to use an acceptable method of birth control, as defined in the protocol, during the study treatment administration period and for 90 days afterward if treated with maribavir, ganciclovir, valganciclovir, or cidofovir and for 180 days afterward if treated with foscarnet.
- The patient must have been able to swallow tablets, or receive tablets crushed and/or dispersed in water via a nasogastric or orogastric tube.
- The patient must have been willing and have an understanding and ability to fully comply with study procedures and restrictions defined in the protocol.
- The patient must have been willing to provide necessary samples (eg, biopsy) for the diagnosis of tissue-invasive CMV disease at baseline as determined by the investigator.

- The patient must have had a life expectancy of ≥8 weeks.

Exclusion Criteria: Patients were excluded from the study if any of the criteria listed below were met. Participants must **not** have:

- Had a current CMV infection that was considered refractory or resistant due to inadequate adherence to prior anti-CMV treatment, to the best knowledge of the investigator.
- Required ganciclovir, valganciclovir, foscarnet, or cidofovir administration for conditions other than CMV when study treatment was initiated (example: herpes simplex virus [HSV] coinfection requiring use of any of these agents after the randomization) or needed a coadministration with maribavir for CMV infection. Note: A patient who was not continuing with the same antiviral drug(s) (ganciclovir, valganciclovir, or foscarnet) for the study treatment (if randomized to the IAT arm), must have discontinued their use before the first dose of study drug. If patient was currently being treated with cidofovir and was assigned another anti-CMV therapy by the investigator, the patient must have discontinued its use at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment.
- Been receiving leflunomide, letermovir, or artesunate when study treatment was initiated. Patients receiving leflunomide must have discontinued the use at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment. Patients receiving letermovir must have discontinued use at least 3 days prior to the first dose of study treatment. Patients receiving artesunate must have discontinued the use prior to the first dose of study treatment.
- Had severe vomiting, diarrhea, or other severe GI illness within 24 hours prior to the first dose of study treatment that would have precluded administration of oral/enteral medication.
- Had known hypersensitivity to the active substance or to an excipient for a study treatment.
- Had tissue-invasive CMV disease with central nervous system involvement, including the retina (eg, CMV retinitis).
- Had serum aspartate aminotransferase (AST) or serum alanine aminotransferase (ALT) >5 times upper limit of normal (ULN) at screening or total bilirubin ≥3.0 × ULN at screening (except for documented Gilbert's syndrome), by local or central lab. Note: Patients with biopsy-confirmed CMV hepatitis were not excluded from study participation despite AST or ALT >5 times ULN at screening.
- Had known positive result for HIV. Patients had to have a confirmed negative HIV test result within 3 months of study entry or, if unavailable, be tested by a local laboratory during the screening period.

- Required mechanical ventilation or vasopressors for hemodynamic support at the time of enrollment.
- Been female and pregnant or breast feeding.
- Had previously received maribavir.
- Had received any investigational agent with known anti-CMV activity within 30 days before initiation of study treatment or investigational CMV vaccine at any time.
- Had received any unapproved agent or device within 30 days before initiation of study treatment.
- Had active malignancy with the exception of nonmelanoma skin cancer. Patients who had a HSCT and who experienced relapse or progression of the malignancy, as per investigator's opinion were not to be enrolled.
- Been undergoing treatment for acute or chronic hepatitis C.
- Had any clinically significant medical or surgical condition that in the investigator's opinion could have interfered with the interpretation of study results, contraindicated the administration of the assigned study treatment, or compromised the safety or well-being of the patient.

6.4.1.4 Statistical and Analytic Plans

Determination of Sample Size

Based on the proportion of patients with undetectable plasma CMV DNA within 6 weeks and 12 weeks in the Phase 2 Study 202, it was assumed that at least 60% of maribavir-treated patients would have achieved undetectable plasma CMV DNA at Visit 9/Week 7 and Visit 10/Week 8 when calculating the sample size for Study 303. A proportion of approximately 40% was considered as a reasonable estimate of the proportion of patients with confirmed undetectable plasma CMV DNA at Visit 9/Week 7 and Visit 10/Week 8 in a control group when calculating the sample size. It was believed that the treatment difference of 20% higher in maribavir group compared to control group was larger than a clinically meaningful difference.

In order to demonstrate statistical superiority in the reduction of CMV DNA, it was assumed that the proportion of patients with confirmed unquantifiable plasma CMV DNA at Visit 9/Week 7 and Visit 10/Week 8 in the maribavir and control groups was 60% and 40%, respectively. A total of 315 patients was required in the ratio of 2:1 (210 patients in maribavir group and 105 patients in the control group) to provide 90% power in hypothesis testing at an alpha level of 0.05 (2-sided test). The sample size was estimated based on a 2-arm continuity corrected Chi-square test of equal proportions by using nQuery Advisor 7.0. Considering 10% drop-outs, 351 patients (234 patients in maribavir group and 117 patients in the control group) were to be enrolled and randomized.

Efficacy Analysis

The primary efficacy analysis was based on the randomized set, with the Per Protocol set as supportive. For binary endpoints (responder or nonresponders), the difference in proportion of responders between treatment groups was 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 category (low vs. pooled intermediate and high) as 2 stratification factors. The 95% confidence limits of the weighted average of difference across strata were provided using the normal approximation.

The hypothesis testing of the primary and key secondary endpoint was 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 response for the primary efficacy endpoint was higher in the maribavir group and the test of adjusted difference in proportion of responders between treatment groups was statistically significant, and the proportion of response for the key secondary efficacy endpoint was higher in the maribavir group and the test was significant at the 0.05 level, it was concluded that the treatment effect was more durable for maribavir as compared to the IAT group. No adjustments were made for multiple comparisons for any of the other secondary efficacy endpoints.

Results for recurrence endpoints were reported as the number (%) of patients with recurrence in patients who had achieved confirmed viremia clearance after the study-assigned treatment for the respective study period.

The time to all-cause mortality on study in days was summarized descriptively and using the Kaplan-Meier method. Treatment groups were compared using the stratified log-rank test. Treatment difference between the maribavir and IAT groups were estimated using the stratified Cox's regression model with transplant type and baseline plasma CMV DNA level as 2 stratification factors, and presented as hazard ratio, and its 95% CI.

6.4.2 Study Patients

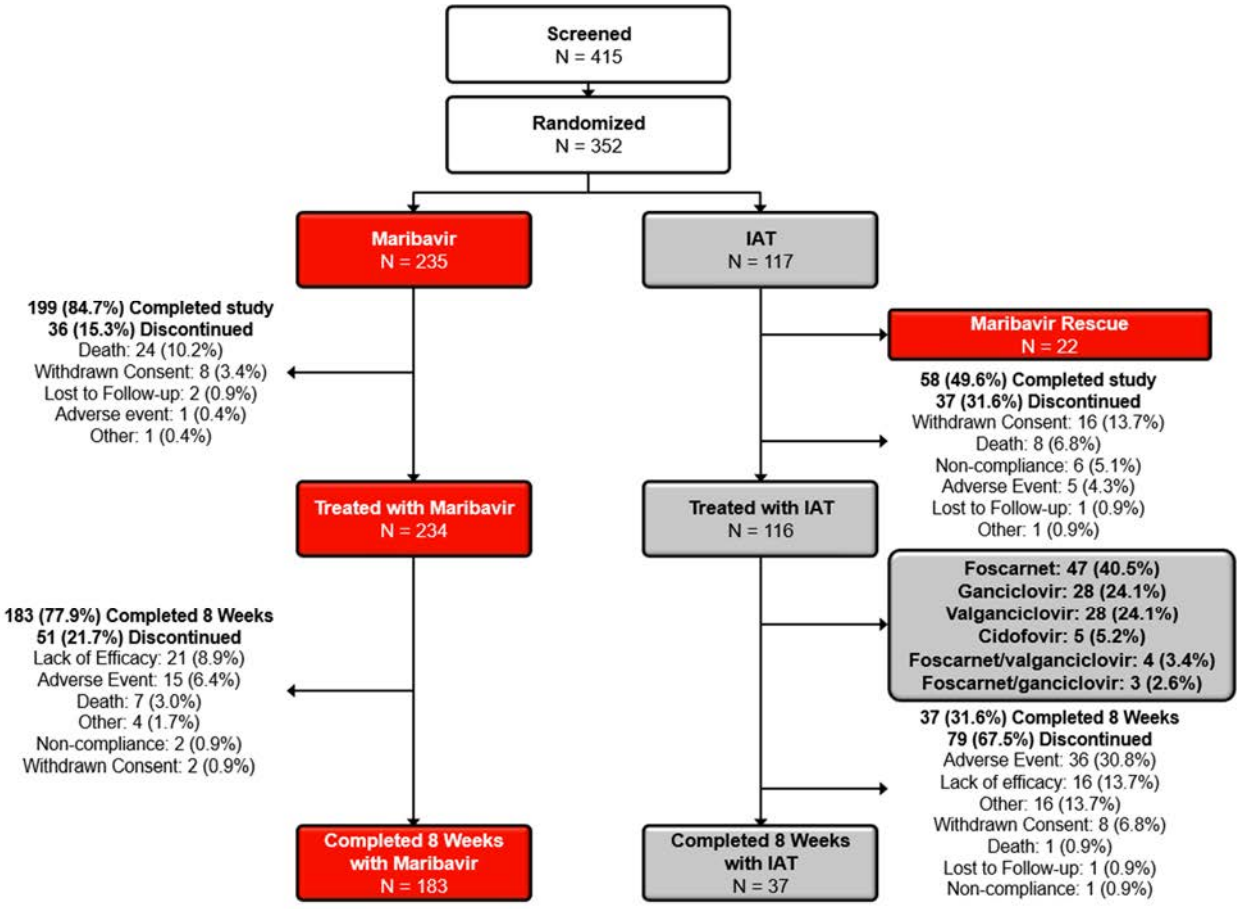
6.4.2.1 Disposition

There were 415 patients screened and 352 enrolled in Study 303, with 235 randomized to maribavir and 117 randomized to IAT (Figure 14). Overall, 220 (62.5%) randomized patients completed 8 weeks of study-assigned treatment, and the treatment completion rate was over twice as high in the maribavir group compared to the IAT group (77.9% vs 31.6%, respectively).

Treatment discontinuation due to AEs, the most frequently reported reason, was less frequent for maribavir-treated patients compared to patients in the IAT group (6.4% vs 30.8%). Treatment discontinuation for lack of efficacy (maribavir: 8.9%; IAT: 13.7%) was 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 14: Study 303 -Flow Diagram of Patient Disposition (Enrolled Set)



CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir)
All percentages are based on the number of randomized patients.
The investigator provided/assessed the primary reason of discontinuation of study-assigned treatment, or end of study.

6.4.2.2 Baseline Demographics

Patient demographic characteristics were broadly similar between the maribavir and IAT groups for race, ethnicity, height, weight, and body mass index (BMI) (Table 12), with 2 exceptions: the maribavir group had a higher proportion of patients ≥65 years of age compared with IAT (23.0% and 13.7%, respectively) and a higher proportion of male patients (63.0% and 55.6%, respectively). The median age was similar between the maribavir and IAT groups (57 [range: 19 to 79] and 54 [range: 19 to 77] years, respectively).

Although adolescent patients ≥12 years of age were permitted by the protocol to enroll, no patients <18 years of age were enrolled.

Table 12: Study 303 - Demographics by Treatment Group (Randomized Set)

Parameter	Maribavir 400 mg BID (N=235)	IAT (N=117)
Age (years)		
Mean (SD)	53.8 (13.39)	51.5 (12.80)
Median (min, max)	57.0 (19, 79)	54.0 (19, 77)
Male, n (%)	148 (63.0%)	65 (55.6%)
Female, n (%)	87 (37.0%)	52 (44.4%)
Race		
White, n (%)	179 (76.2%)	87 (74.4%)
Black or African American, n (%)	29 (12.3%)	18 (15.4%)
Asian, n (%)	9 (3.8%)	7 (6.0%)
Other, n (%)	16 (6.8%)	5 (4.3%)
Missing, n (%)	2 (0.9%)	0
Regions		
North America, n (%)	134 (57.0%)	71 (60.7%)
Europe, n (%)	97 (41.3%)	39 (33.3%)
Asia, n (%)	4 (1.7%)	7 (6.0%)

BID=twice daily; IAT=investigator-assigned anti-cytomegalovirus treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); N=number of patients; SD=standard deviation
Source: Study 303 CSR, Table 14.1.4.1.1 and Table 14.1.4.2.1

6.4.2.3 Baseline Characteristics

The study population was generally representative of the epidemiology of SOT and HSCT patients with CMV infection. Risk factors were balanced between the 2 treatment groups. Patients enrolled in the study were refractory to at least 1 anti-CMV agent (with or without resistance). The study population included a sufficient number of patients of each transplant type to make meaningful conclusions (SOT: 59.9%; HSCT: 40.1%) (Table 13).

The baseline disease characteristics of study participants generally reflected real world prevalence. For the majority of enrolled patients, the current CMV infection resulted from donor positive/recipient negative transplant (SOT) or recipient positive transplant, regardless of donor status (HSCT). For the virologic inclusion criteria assessment, the majority of patients fell into the category of low CMV DNA viral load (<9100 IU/mL), and most did not have EAC-confirmed CMV tissue-invasive disease or CMV syndrome at baseline.

Additional details on baseline characteristics of patients in Study 303 are provided in a table in Appendix 10.3.

Table 13: Study 303 - Baseline Characteristics

Parameter	Maribavir 400 mg BID (N=235) n (%)	IAT (N=117) n (%)
Current transplant type		
Solid organ transplant	142 (60.4%)	69 (59.0%)
Hematopoietic stem cell transplant	93 (39.6%)	48 (41.0%)
Current graft status at baseline		
Solid organ transplant		
Functioning	127 (89.4%)	61 (88.4%)
Functioning with complications	12 (8.5%)	8 (11.6%)
Other[a]	3 (2.1%)	0
HSCT		
Functioning	78 (83.9%)	42 (87.5%)
Functioning with complications	11 (11.8%)	5 (10.4%)
Partially Engrafted	4 (4.3%)	1 (2.1%)
Confirmed GvHD		
Acute GvHD (Yes)	23 (9.8%)	8 (6.8%)
Chronic GvHD (Yes)	6 (2.6%)	5 (4.3%)
Renal Impairment		
No impairment (creatinine clearance >80 mL/minute)	81 (34.5%)	39 (33.3%)
Mild (creatinine clearance 50 to 80 mL/minute)	71 (30.2%)	42 (35.9%)
Moderate (creatinine clearance 30 to <50 mL/minute)	60 (25.5%)	22 (18.8%)
Severe (creatinine clearance <30 mL/minute)	8 (3.4%)	3 (2.6%)
Missing	15 (6.4%)	11 (9.4%)
Solid organ transplant, by organ type	142 (60.4%)	69 (59.0%)
Heart	14 (9.9%)	9 (13.0%)
Lung	40 (28.2%)	22 (31.9%)
Liver	6 (4.2%)	1 (1.4%)
Pancreas	2 (1.4%)	0
Intestine	1 (0.7%)	0
Kidney	74 (52.1)	32 (46.4%)
Multiple	5 (3.5%)	5 (7.2%)
Baseline symptomatic CMV infection by EAC		
No	214 (91.1%)	109 (93.2%)
Yes[b,c]	21 (8.9%)	8 (6.8%)
CMV Syndrome in SOT patients	10 (47.6%)	7 (87.5%)
Tissue-invasive disease	12 (57.1%)	1 (12.5%)
Presence of CMV mutation resistant to ganciclovir, foscarnet, and/or cidofovir per central laboratory		
No	96 (40.9%)	34 (29.1%)
Yes	121 (51.5%)	69 (59.0%)
Unable to genotype	18 (7.7%)	14 (12.0%)
Baseline CMV DNA levels category as reported by central laboratory[d]		
Low (≥910 and <9,100 IU/mL in plasma)	153 (65.1%)	85 (72.6%)
Intermediate (≥9,100 IU/mL and <91,000 IU/mL in plasma)	68 (28.9%)	25 (21.4%)
High (≥91,000 IU/mL in plasma)	14 (6.0%)	7 (6.0%)
CMV serostatus for SOT[c]		
Donor positive / recipient negative (D+ / R-)	120 (84.5%)	56 (81.2%)
CMV serostatus for HSCT[c]		

Table 13: Study 303 - Baseline Characteristics

Parameter	Maribavir 400 mg BID (N=235) n (%)	IAT (N=117) n (%)
Donor positive / recipient positive (D+ / R+)	42 (45.2%)	17 (35.4%)
Donor negative / recipient positive (D- / R+)	39 (41.9%)	26 (54.2%)

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 (ganciclovir, valganciclovir, foscarnet, or cidofovir); N=number of patients; SOT=solid organ transplant.

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

[b] Percentages are based on the number of patients within the category.

[c] Patients could have multiple reasons.

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

Source: Study 303 CSR, Table 14.1.4.2.1

6.4.3 Primary Efficacy Endpoint

6.4.3.1 Confirmed CMV Viremia Clearance at End of Study Week 8

The proportion of maribavir-treated patients who achieved confirmed CMV viremia clearance at Week 8 was statistically superior, being more than 2-fold greater than among patients who received standard of care treatment with IAT (maribavir: 55.7% [131/235]; IAT: 23.9% [28/117]). The adjusted difference using Cochran-Mantel-Haenszel weights across stratification factors was 32.8% (95% confidence interval [CI]: 22.80, 42.74; p<0.001) (Figure 2).

While there is an overall paucity of historical post-transplant CMV response rate data in clinical practice, outcomes are especially not well characterized in the R/R population. Available literature consists of mostly single-center, retrospective case series with a limited number of subjects, where outcome is generally assessed at variable time points from the initiation of therapy without consideration for changes/switches in therapy in the assignment of success (Avery et al., 2016; Mehta Steinke et al., 2021). The lower-than-expected response rates observed in the IAT arm underscore the unmet need in this patient population and illustrate the severity of the limitations of existing therapy when the analysis of outcome requires demonstrating durability of viral suppression, such as in Study 303.

6.4.3.2 Primary Efficacy Endpoint: Sensitivity Analyses

Multiple sensitivity analyses were performed to test the robustness of the results and address any potential concerns arising from the study design, including its open-label nature:

- A sensitivity analysis included patients in both treatment groups who met the criteria of confirmed clearance at the time of study discontinuation as responders, (ie, last observation carried forward [LOCF]). This analysis eliminated any beneficial effect accruing from early study discontinuations due to drug toxicity,

withdrawal of consent, or other reasons. However, the analysis included only patients who met the criteria of confirmed CMV viremia clearance at the time of study discontinuation and did not receive alternative treatment. In this analysis, maribavir remained statistically significantly better at clearing CMV viremia compared to IAT (58.3% [137/235] vs 33.3% [39/117], respectively; p-value: <0.001) (Table 14).

- Another sensitivity analysis counted patients who had viremia clearance anytime within 8 weeks as responders. This analysis counted patients as responders regardless of when in the treatment period they achieved CMV viremia clearance. Thus, it assumed viremia clearance even if other factors, such as lack of tolerability, led to treatment switching or discontinuation after the initial viremia clearance was achieved. In this sensitivity analysis, maribavir maintained its superior CMV viremia clearance compared to IAT (74.0% [174/235] vs 52.1% [61/117], respectively; p-value: <0.001) (Table 14).
- Finally, a sensitivity analysis examined CMV viremia clearance regardless of the use of alternative anti-CMV treatment (including rescue). This analysis assessed efficacy at Week 8, even if alternative anti-CMV treatment (including rescue) was utilized. In essence, the tolerability benefit of maribavir enabling better efficacy was eliminated in this analysis, as IAT patients were not penalized for taking nonstudy anti-CMV agents after premature treatment discontinuation. The results of the analysis confirmed the true virologic effect of maribavir, which maintained its superior CMV clearance at Week 8 compared to the IAT group (59.1% [139/235] vs 42.7% [50/117], respectively; p-value: 0.002) (Table 14).

Table 14: Study 303 - Sensitivity Analyses of the Primary Efficacy Endpoint Based on Alternate Definitions of Response

Description of Sensitivity Analysis **CMV Viremia Clearance Response**	**Maribavir 400 mg BID (N=235) n (%)**	**IAT (N=117) n (%)**
Analysis that includes patients who met the criteria of confirmed CMV viremia clearance at the time of study discontinuation as a responder		
Responders Nonresponders Adjusted difference in proportion of responders (95% CI)[a] p-value: adjusted[a]	137 (58.3%) 98 (41.7%) 26.1 (15.61, 36.67) <0.001	39 (33.3%) 78 (66.7%)
Analysis including patients with confirmed CMV viremia clearance at any time during the treatment phase as a responder		
Responders Nonresponders Adjusted difference in proportion of responders (95% CI)[a] p-value: adjusted[a]	174 (74.0%) 61 (26.0%) 23.6 (13.18, 33.93) <0.001	61 (52.1%) 56 (47.9%)
Analysis including patients as responder who met criteria of confirmed CMV viremia clearance at Week 8 based on CMV DNA levels, regardless of alternative CMV antiviral or rescue treatment for both treatment groups		
Responders Nonresponders Adjusted difference in proportion of responders (95% CI)[a] p-value: adjusted[a]	139 (59.1%) 96 (40.9%) 17.7 (6.76, 28.59) 0.002	50 (42.7%) 67 (57.3%)

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); N=number of patients

[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 patients in the randomized set.

Patients 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 patients with no efficacy data were treated as nonresponders.

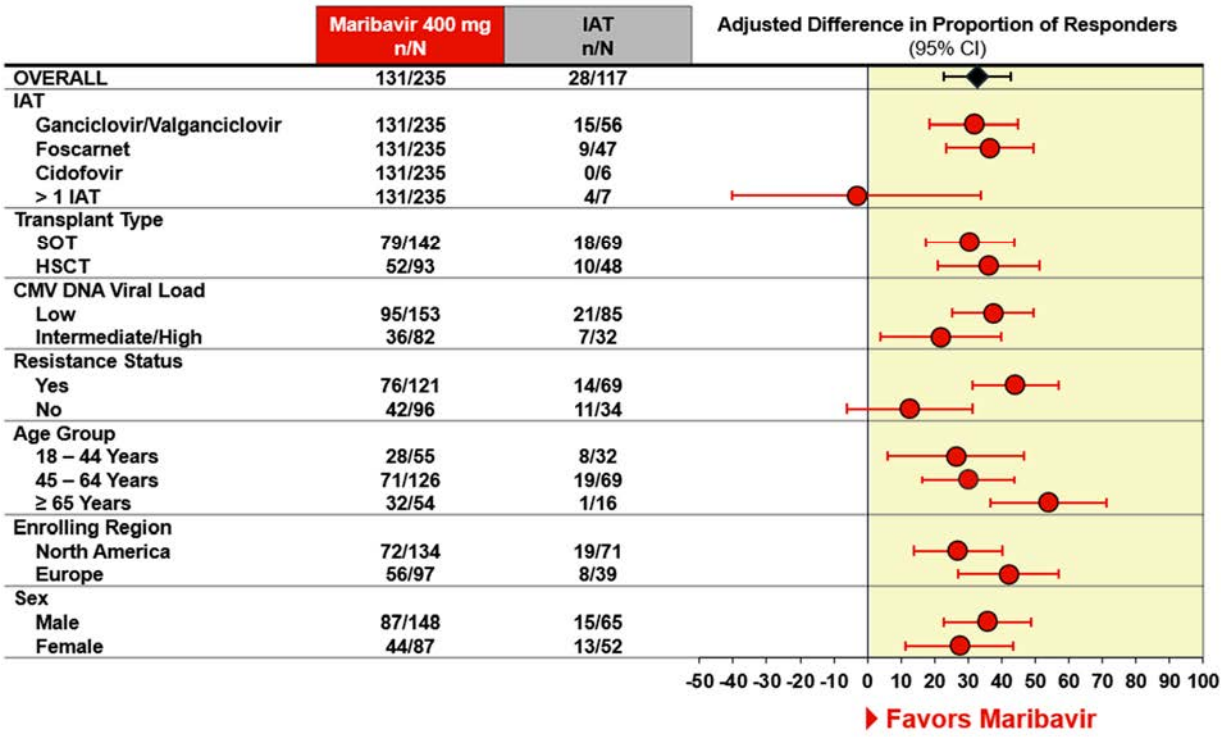
Source: Study 303 CSR, Table 14.2.1.3, Table 14.2.1.7, Table 14.2.1.9, and Table st00383_ir_vc_wk8

6.4.3.3 Subgroup Analyses

The proportions of responders were generally consistent across subgroups (Figure 15). The benefit of maribavir was observed for the primary endpoint regardless of IAT chosen, as well as across disease-related subgroups. These subgroups included IAT type chosen, transplant type, patients with symptomatic CMV infection, patients with genotypic resistance to other anti-CMV agents, patients with antilymphocyte use, and

baseline viral load. The subgroup of patients who received more than 1 IAT type did not favor maribavir, but the number of patients in that IAT subgroup was small.

Figure 15: Study 303 -Primary Efficacy Results Across Subgroups



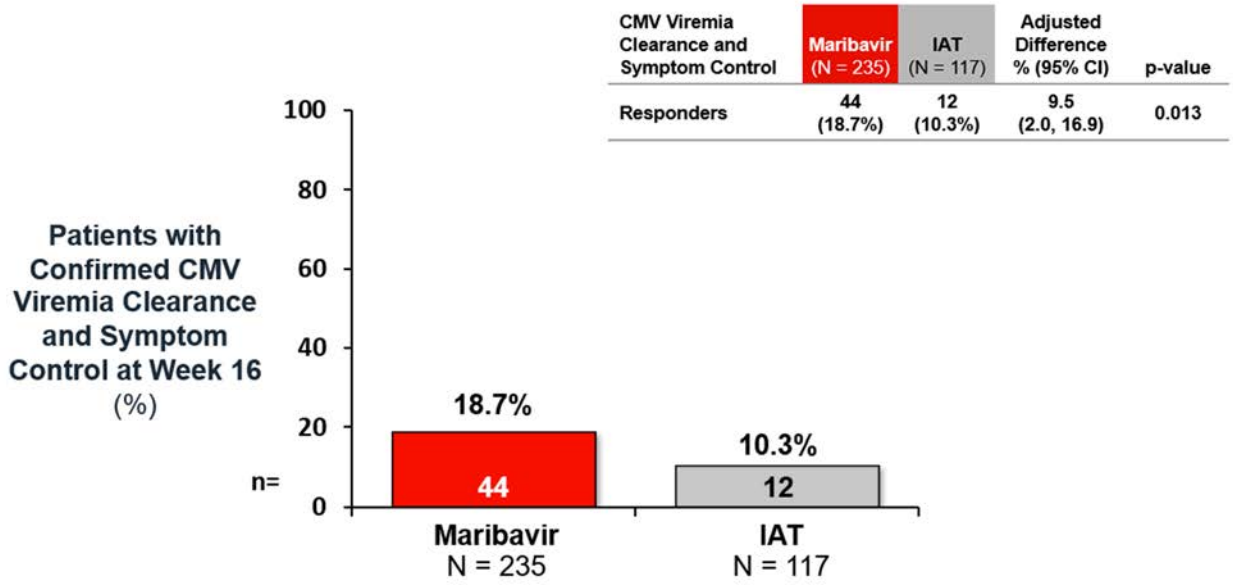
CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir)
Note: The comparisons between maribavir and individual IATs should be interpreted with caution, since the subgroup for each IAT was not randomized.
Source: Study 303 CSR, Table 14.2.1.10 and Figure 14.2.1.1

6.4.4 Secondary Efficacy Endpoints

6.4.4.1 Key Secondary Endpoint: CMV Viremia Clearance and Infection Symptom Control at Week 16

Maribavir achieved favorable CMV viremia 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: 44/235 (18.7%) maribavir-treated patients compared with 12/117 (10.3%) patients in the IAT group. The adjusted treatment difference (95% CI) in proportion of responders between the treatment groups was 9.5 (2.02, 16.88); p=0.013 (Figure 16).

Figure 16: Study 303 - Viral Clearance and Symptom Control at Week 16



CI=confidence interval; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment
Source: Study 303 CSR, Table 14.2.2.1.1

6.4.4.2 Symptomatic CMV Infection/Disease

The data from Study 303, in addition to demonstrating maribavir's efficacy in CMV viremia clearance, also showed a benefit in the improvement and resolution of symptomatic CMV infection (i.e. CMV tissue-invasive disease or CMV syndrome [SOT only]), albeit in a more limited sample size.

For the composite key secondary endpoint assessments, all investigator-assessed cases of symptomatic CMV infection were reviewed and adjudicated by an independent, blinded Endpoint Adjudication Committee (EAC).

In total, 29 patients (8.5%) were adjudicated by the EAC to have documented symptomatic CMV infection, a number consistent with the declining incidence of symptomatic CMV infection in this patient population. Of the 21 patients in the maribavir group with EAC-confirmed tissue-invasive disease/CMV syndrome at baseline, the EAC-confirmed resolution or improvement of the baseline tissue-invasive disease/CMV syndrome occurred for 16/21 (76.2%) maribavir-treated patients; there was no change for 5/21 (23.8%) maribavir-treated patients, and no worsening of symptoms for any maribavir-treated patients at the Week 8/end of treatment assessment. There were only 8 patients with symptomatic CMV infection in the IAT arm, limiting the interpretation of results in this treatment group. However, of the 8 patients in the IAT group with EAC confirmed tissue-invasive disease/CMV syndrome at baseline, the EAC-confirmed resolution or improvement of the baseline tissue-invasive disease/CMV syndrome occurred for 5/8 (62.5%) patients; there was no change for 1/8

(12.5%) patients and worsening for 2/8 (25.0%) patients at the Week 8/end of treatment assessment.

The EAC confirmed 22 total cases of new onset (i.e., post-baseline) symptomatic CMV infection in 21 patients (maribavir: 14 [6.0%] patients; IAT: 7 [6.0%] patients (Table 15). One patient in the IAT group had 2 different episodes of new onset symptomatic CMV infection at 2 different times post-baseline. The development of new onset symptomatic CMV infection was predictive of a poor outcome. While the numbers are small and the response rates lower than the overall asymptomatic population, a higher proportion of maribavir patients in this high risk population were primary endpoint responders; 5/14 maribavir-treated patients vs 0/7 IAT-treated patients. Of these 5 maribavir-treated patients, the new onset symptomatic CMV infection developed at Week 12, four weeks after cessation of maribavir therapy (Table 15).

Table 15: Study 303 - New Onset Symptomatic CMV Infection/Disease

New Onset Symptomatic CMV Infections	Maribavir 400 mg BID (N=235) n (%)	IAT (N=117) n (%)
EAC-confirmed new onset CMV disease post-baseline	14 (6.0%)	7 (6.0%)
Week 8*	7 (3.0%)	5 (4.3%)
Week 12	5 (2.1%)	1 (0.9%)
Week 16	1 (0.4%)	2 (1.7%)
Week 20	1 (0.4%)	0 (0.0%)

BID=twice daily; CMV=cytomegalovirus; EAC=Endpoint Adjudication Committee; IAT=investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir)
* All were nonresponders for primary endpoint.
Source: Study 303 CSR, Auxiliary Table 14.4.1.2a

6.4.4.3 Recurrence Following Confirmed CMV Clearance

Recurrence of CMV viremia was assessed for patients who had achieved viremia clearance. Note that recurrence is not always considered a clinically relevant viremia endpoint; patients can have transient fluctuations in viral load that many physicians consider inconsequential.

Recurrence of CMV viremia 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 viremia clearance.

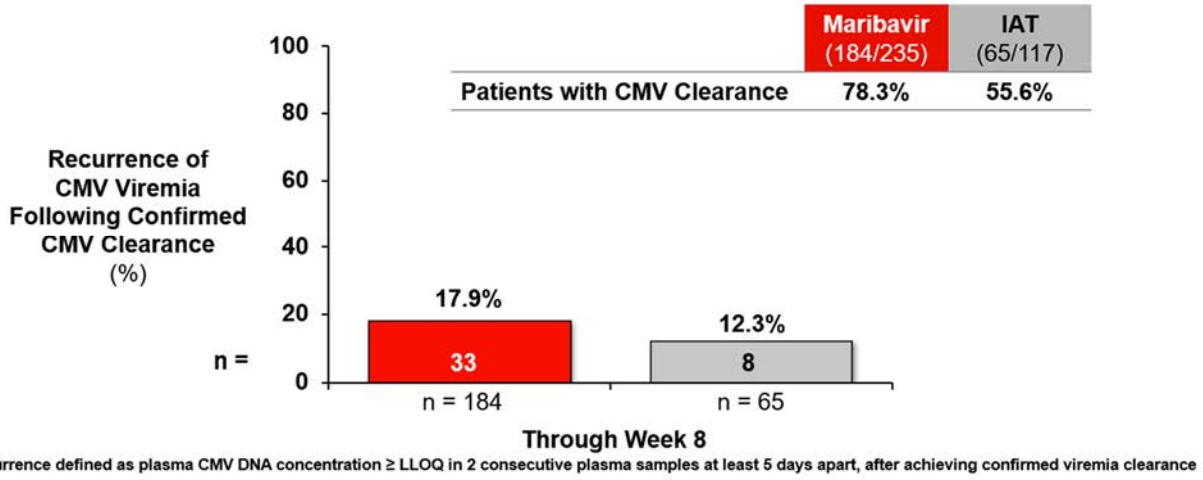
On-treatment phase recurrence (i.e., through Week 8) was generally low and numerically higher in the maribavir arm, this despite a higher proportion of maribavir treated patients (78.3% [184/235]) vs. IAT (55.6% [65/117]) achieving CMV viremia clearance at any time on study and hence having a higher at risk population available to recur (Figure 17).

Of these patients, 17.9% of patients in the maribavir group and 12.3% of patients in the IAT group had a recurrence of CMV viremia during the first 8 weeks of the study.

Post-treatment phase recurrence (i.e., after Week 8) was assessed from Week 9 through the end of the study, including rescue visits, if applicable. Patients in both arms were generally off treatment after Week 8 unless the investigator placed the patient on another therapy. In this analysis, 38.6% (71/184) of patients in the maribavir group and 21.5% (14/65) in the IAT group had a recurrence of CMV viremia during the follow-up weeks.

Of note, CMV recurrence while off therapy in the setting of continuing immunosuppression is not illustrative of lack of effect, but more likely is due to the ongoing immunocompromised state of the host, which renders them unable to mount an adequate immune response to the virus. In addition, Study 303 included patients with multiple previous recurrences of CMV. These patients may have been phenotypically predisposed to recurrence upon discontinuation of CMV treatment. Furthermore, Study 303 did not allow for secondary prophylaxis, so recurrence may not be inherent to maribavir treatment itself but may reflect what occurs when CMV treatment is limited to a maximum of 8 weeks with no secondary prophylaxis given.

Figure 17: Study 303 - Recurrence Following Confirmed CMV Clearance at Any Time on Study



CMV=cytomegalovirus; DNA=DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment; LLOQ=lower limit of quantification
Source: Study 303 CSR, Table 14.2.3.4.1

6.4.4.4 Efficacy for Maribavir as Rescue Therapy

Patients unresponsive to IAT could receive maribavir during the 8-week treatment period. Overall, 22 patients in the IAT group received maribavir as rescue therapy. Of these, half (50.0%) achieved confirmed CMV viremia clearance at Week 8 relative to first dose of maribavir rescue treatment.

6.4.5 Resistance

Resistance analysis in Study 303 was frequent, scheduled and more intensive than in clinical practice (where treatment is generally empiric and resistance testing only performed when there is a rapidly rising viral load and/or deterioration in clinical signs/symptoms despite treatment).

In addition, this was a study of 2nd line treatment of CMV infection, meaning that the 60% of patients with reported baseline resistance to IAT at the beginning of this study represents the frequency of treatment emergent resistance associated with use of IAT therapy prior to the infection being declared refractory.

Genotypic sequencing was performed for study patient samples with CMV DNA viral load above the predefined cutoff level of 500 copies/mL (455 IU/mL) at protocol defined time points at baseline, during the treatment phase (Week 4 and 8), during the study follow-up phase (Week 16), and at the end of the study (Week 20). Samples were also genotyped in patients with ≥500 copies/mL (455 IU/mL), at the time of breakthrough or recurrence and in patients with viremia rebound if >1 $\log_{10}$ above nadir while on treatment.

UL54 encodes for the CMV DNA polymerase that is the target for GCV, VGC, foscarnet and cidofovir and mutations in *UL54* confer resistance to all these agents. *UL97* encodes for a CMV kinase that is the maribavir target and is also required to convert ganciclovir/valganciclovir to its active form. For this reason, mutations in pUL97 may confer resistance to both maribavir and GCV/VGC but locations of most of the mutations causing resistance to maribavir and to GCV/VGC are at different sites of pUL97.

As expected, mutations associated with resistance to maribavir at baseline were rare, identified in only 4/314 patients (1.3%), with 3/4 carrying a cross-resistant mutation to maribavir and ganciclovir (F342Y in pUL97).

Following its use for treatment, for the 1st time in these R/R patients, maribavir resistance associated mutations developed in 27.1% (58 out of 214 [with genotypic data available]) of patients post-baseline in the maribavir arm (all at pUL97). This number compares favorably with the 60% resistance associated with 1st time use of IAT.

Maribavir resistance associated mutations were all in pUL97 at codon positions 342, 409, 411 and 480, all positions previously described in phase 2 studies (Chou et al., 2020). Table 16 provides a breakdown of the particular mutations and frequency observed.

Table 16: Study 303 - Maribavir Mutations Appearing Post-baseline, Resistance Conferred by Mutation Based on In Vitro Phenotyping and Frequency of Each Mutation

Mutation	Mutant EC_{50}/WT EC_{50}	N
T409M	78	14
H411Y	15	12
C480F*	224	11
T409M+H411Y	-	8
T409M+C480F	-	6
H411Y+C480F	-	2
F342Y*	4.5	1
H411N	-	1
F342Y+T409M+H411N	-	1
F342Y+H411Y	56	1
H411L+H411Y+C480F	-	1

*Mutations cross-resistant to maribavir and ganciclovir/valganciclovir

Of the 58 patients that developed a maribavir mutation, 11 met the primary endpoint and 47 did not. The vast majority of maribavir mutations appeared after Week 6 (55/58=95%). The maribavir mutations of interest included T409M, H411Y/N/L and C480F. Overall 43.2% of subjects (32/74) without any of these mutations of interest failed to achieve the primary endpoint. In contrast, 50.0% of patients (7/14) with the H411Y/N/L but without the other mutations, 78.6% of patients (11/14) with the T409M but without the other mutations, and 90.9% of patients (10/11) with the C480F but without the other mutations failed to achieve the primary endpoint. No patient with any 2 mutations from T409M, H411Y/N/L and C480F achieved the primary endpoint.

Exploratory analyses suggested the only risk factor for developing maribavir resistance that met statistical significance was baseline viral load. Patients with baseline CMV DNA ≥9100 IU/mL were somewhat more likely to be identified with post-baseline maribavir mutations (37.8%; 31/82) compared with patients with baseline CMV DNA <9100 IU/mL (20.5%; 27/132).

Patients that develop maribavir resistance mutations may be treated with alternative anti-CMV agents and achieve viremia clearance. Of the 58 patients with maribavir mutations, 48 took an alternative anti-CMV treatment after maribavir treatment. Of these patients, 9 were treated with only foscarnet and 5 (56%) achieved viremia clearance;19 patients were treated with only ganciclovir/valganciclovir, 16 (84%) of them achieved viremia clearance. Of these 19 patients, 8 had mutations at cross-resistant positions (resistant to maribavir and ganciclovir/valganciclovir) and 8/8 (100%) achieved viremia clearance.

7 CLINICAL SAFETY

Summary

- Maribavir provides a safety advantage over currently used CMV antivirals, as it lacks the treatment-limiting toxicities of these other agents.
- In Study 303, the most common AE was the AESI class of taste disturbance (dysgeusia), which included events with the preferred terms ageusia, dysgeusia, hypogeusia, and taste disorder. Dysgeusia is known to be associated with maribavir use.
  - Dysgeusia as an AESI class occurred more frequently for patients in the maribavir group compared to patients in the IAT group during the on-treatment observation period (maribavir: 108 [46.2%] patients; IAT: 5 [4.3%] patients).
  - These dysgeusia events led to treatment discontinuation for only 2 (0.9%) maribavir-treated patients and no patients in the IAT group. Most events were mild to moderate in severity and none were assessed as serious. Dysgeusia generally resolved either during treatment with maribavir or shortly after discontinuation of treatment.
- Treatment-limiting AEs associated with currently available anti-CMV treatments were uncommon in patients treated with maribavir.
  - Neutropenia as an AESI class (ie, febrile neutropenia, neutropenia, and neutrophil count decreased combined) was less common for maribavir-treated patients than for IAT patients (maribavir, 10.3% of patients; IAT, 25.9% of patients; patients who received ganciclovir/valganciclovir as the IAT, 39.3%).
  - Severe renal and urinary disorders were less common in maribavir-treated patients compared with patients in the IAT group (maribavir, 0.9% of patients; IAT, 4.3%, of patients; patients who received foscarnet as the IAT, 8.5%).
- The incidence of GvHD during the treatment period was 9.0% (21 patients) in the maribavir group and 4.3% (5 patients) in the IAT group. Baseline imbalance in the percentage of patients with GvHD between treatment arms may have contributed to this difference: 9.8% (23 patients) in maribavir group vs 6.8% (8 patients) in IAT group. One-third of the maribavir-treated patients (7/21 patients) with GvHD during the on-treatment observation period had acute GvHD at baseline compared with one-fifth (1/5 patients) of the IAT group.
- 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%).
- The percentage of patients with SAEs was 38.5% in the maribavir group and 37.1% in the IAT group.
  - Serious AEs considered related to study-assigned treatment occurred less frequently in the maribavir group than in the IAT group (5.1% and 14.7%, respectively).
- In Study 303 a total of 40 patient deaths were reported.
  - During the study, AEs that led to death were reported for 11.5% (27/235) of patients in the maribavir group and 11.2% (13/116) of patients in the IAT group.

- Treatment discontinuation due to AEs was more frequent among IAT patients compared to maribavir patients (maribavir: 13.2%; IAT: 31.9%).

7.1 Treatment Exposure

Since discontinuations from study treatment were more common in the IAT group than in the maribavir group, the duration of exposure to maribavir was approximately 1.5 times longer than to IAT (52.5 days vs 36.0 days).

7.1.1 Overall Extent of Exposure

To date, in the completed studies a total of 1,555 individuals (healthy subjects and patients) have been exposed to maribavir across both the prophylaxis and treatment programs, covering a broad range of doses (50 mg to 2400 mg per day) and a range of treatment durations up to 24 weeks (Table 17).

A total of 495 transplant recipients with CMV infection have received maribavir doses of 400 mg BID or greater for 8 weeks to 24 weeks, and a total of 337 patients have received at least 1 dose of maribavir 400 mg BID, the proposed dose, including 314 transplant patients with CMV infection.

Table 17: Patients Exposed to Maribavir

Participants	Number of Participants	Studied Doses	Duration of Treatment
Transplant patients with CMV infection	495	400 – 1200 mg BID	8-24 weeks
Prophylaxis in transplant patients	680	100 – 400 mg BID 400 mg QD	12-24 weeks
Dose-ranging Phase 1 studies	380		

BID=twice daily; CMV=cytomegalovirus; QD=once daily
Source: Module 2.7.4, Section 1.1.1

Duration of treatment was not consistent across the 3 treatment studies, as shown in Table 18. Pivotal Study 303 had a fixed 8 week treatment duration, whereas patients could be treated for up to 12 weeks in Study 203 and 24 weeks in Study 202.

In Study 303, mean exposures to study drug were longer in the maribavir group than the IAT group: 52.5 (SD: 11.81) days vs 36.0 (SD: 18.06), respectively, based on the interval between first and last dose.

Table 18: Exposure to Study Drug in the Three CMV Treatment Studies (Studies 303, 202, and 203)

	Study 303[a]		Study 202[b]	Study 203[c]	
Exposure to Study Drug (days)	Maribavir 400 mg BID (N=234)	IAT (N=116)	Maribavir 400 mg BID (N=40)	Maribavir 400 mg BID (N=40)	Val (N=40)
Mean	52.5	36.0	85.2	50.8	43.1
Standard Deviation	11.81	18.06	55.35	29.10	30.22
Median	57.0	34.0	72.0	45.5	30.0
Minimum, Maximum	2; 64	4, 64	9, 177	1, 92	1, 88

BID=twice daily; CMV=cytomegalovirus; IAT=investigator-assigned anti-cytomegalovirus treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); val=valganciclovir
[a] Planned study duration was 8 weeks.
[b] Planned study duration was up to 24 weeks; patients must have achieved a minimum virologic response at Weeks 3 and 6 for study drug to have been continued beyond each of these time points.
[c] Planned study duration was up to 12 weeks; patients must have achieved a minimum virologic response at Weeks 3 and 6 for study drug to have been continued beyond each of these time points.
Source: Study 303 CSR, Table 14.3.7.1.1.1; Study 202 CSR, Table 53; Study 203 CSR, Table 47

7.2 Pivotal Study 303: Adverse Events

Transplant patients often have comorbidities and take multiple concomitant medications with accompanying side effects. This is reflected in the analysis of overall adverse events (AEs) in Study 303, where a high proportion of patients in both treatment arms had at least one adverse event.

A higher percentage of patients in the maribavir group reported AEs than patients in the IAT group (maribavir, 97.4%; IAT, 91.4%); however, a lower percentage of patients in the maribavir group reported severe AEs compared to the IAT group (maribavir, 32.1%; IAT, 37.9%) (Table 19). Patients on maribavir were also less likely to discontinue treatment due to AEs. Slightly more maribavir-treated patients that IAT-treated patients reported an SAE (maribavir, 38.5%; IAT, 37.1%).

Patient deaths during the study are discussed in Section 7.2.5.

Table 19: Study 303 - Safety Overview

Parameter	Maribavir* 400 mg BID (N=234) n (%)	IAT (N=116) n (%)
Any AE	228 (97.4%)	106 (91.4%)
Any severe AE	75 (32.1%)	44 (37.9%)
Any AE leading to discontinuation of treatment	31 (13.2%)	37 (31.9%)
Any AE leading to study withdrawal	17 (7.3%)	9 (7.8%)
Any SAE	90 (38.5%)	43 (37.1%)

BID=twice daily; IAT=investigator-assigned anti-cytomegalovirus treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); SAE=serious adverse event; AE=adverse event.
* Patients remained on maribavir therapy 46% longer than IAT (ganciclovir, valganciclovir, foscarnet, cidofovir).
Source: Study 303 CSR, Table 14.3.1.1.1

7.2.1 Common Adverse Events

The unadjusted incidence rates of AEs with a frequency of ≥10% in either treatment arm were similar between the maribavir and IAT groups (Table 20). Dysgeusia, the most frequently reported AE overall, occurred predominantly in maribavir-treated patients (maribavir: 37.2%; IAT: 3.4%). Adverse events that occurred with comparable incidence in both maribavir and IAT groups during the on-treatment observation period included nausea (21.4% and 21.6%), diarrhea (18.8% and 20.7%), vomiting (14.1% and 16.4%), fatigue (12.0% and 8.6%), pyrexia (10.3% and 14.7%), and headache (8.1% and 12.9%). Overall, the incidence of GI AEs was similar for maribavir (50.4%) and IAT (49.1%).

In addition to these events reported for ≥10% of patients in either treatment arm, the AE of immunosuppressant drug level increased, which is of interest because of known drug interactions with maribavir, was reported for 9.0% of patients in the maribavir group and 0.9% of patients in the IAT group. Also, during on-treatment observation (ie, on-treatment or during post-treatment follow-up), 9.0% of maribavir-treated patients had an AE of new or worsening GvHD compared with 4.3% patients in the IAT group.

Table 20: Study 303 - Common Adverse Events

Preferred Term (≥ 10%)	Maribavir* 400 mg BID (N=234) n (%)	IAT (N=116) n (%)
Any AE	228 (97.4)	106 (91.4)
Dysgeusia	87 (37.2%)	4 (3.4%)
Nausea	50 (21.4%)	25 (21.6%)
Diarrhea	44 (18.8%)	24 (20.7%)
Vomiting	33 (14.1%)	19 (16.4%)
Anemia	29 (12.4%)	14 (12.1%)
Fatigue	28 (12.0%)	10 (8.6%)
Pyrexia	24 (10.3%)	17 (14.7%)
CMV viremia	24 (10.3%)	6 (5.2%)
Neutropenia	22 (9.4%)	26 (22.4%)
Headache	19 (8.1)	15 (12.9)

BID=twice daily; IAT=investigator-assigned anti-cytomegalovirus treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); AE=adverse event
* Patients remained on maribavir therapy 46% longer than IAT (ganciclovir, valganciclovir, foscarnet, cidofovir).
Source: Study 303 CSR, Table 14.3.1.3.1

7.2.2 Severe Adverse Events

During the on-treatment observation period, severe AEs were reported for 75 (32.1%) patients in the maribavir group and 44 (37.9%) patients in the IAT group (Table 21). The incidence of severe AEs was similar for patients who received ganciclovir/valganciclovir (39.3%) or foscarnet (40.4%) as the IAT.

Severe AEs occurred most frequently in the system organ class (SOC) of infections and infestations (maribavir: 12.8%; IAT: 9.5%), as expected for a post-transplant population.

Cytomegalovirus viremia/CMV infection (ie, the disease under study) were the most frequently reported severe infections. In general, the proportions of patients with these AEs were low in both treatment groups (2.6% of patients in each treatment group for CMV viremia; 0.9% of patients in the maribavir group and 1 (0.9%) patient in the IAT group for CMV infection).

Maribavir-treated patients had a lower incidence of severe AEs associated with blood and lymphatic system disorders compared with IAT (7.3% vs 18.1%, respectively). The known hematologic toxicities with ganciclovir/valganciclovir drove this difference between treatment groups (ganciclovir/valganciclovir: 26.8% vs overall IAT: 18.1%). Compared with ganciclovir/valganciclovir-treated patients, maribavir-treated patients had a lower percentage of severe neutropenia (1.7% vs 10.3%), including severe febrile neutropenia (0.4% vs 3.4%); severe thrombocytopenia (2.1% vs 3.4%); severe anemia (2.1% vs 4.3%); and severe leukopenia (0.4%vs 3.4%).

Maribavir-treated patients had a lower incidence of severe renal and urinary disorders compared with IAT (0.9% vs 4.3%, respectively). The known renal toxicity of foscarnet accounted for much of this difference between treatment groups; the incidence of severe AEs in the renal and urinary disorders SOC was 8.5% for foscarnet-treated patients (N=4) and 16.7% for cidofovir-treated patients (N=1).

Table 21: Study 303 - Severe Adverse Events

Preferred Term (≥ 1%)	Maribavir* 400 mg BID (N=234) (%)	IAT (N=116) (%)
Any severe AE	75 (32.1)%	44 (37.9%)
CMV viremia	6 (2.6%)	3 (2.6%)
CMV infection	2 (0.9%)	1 (0.9)
Anemia	5 (2.1%)	5 (4.3%)
Febrile neutropenia	1 (0.4%)	4 (3.4%)
Leukopenia	1 (0.4%)	4 (3.4%)
Neutropenia	4 (1.7%)	12 (10.3%)
Renal and urinary disorders	2 (0.9%)	5 (4.3%)
Thrombocytopenia	5 (2.1%)	4 (3.4%)

AE=adverse event; BID=twice daily; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir).
* Patients remained on maribavir therapy 46% longer than IAT (ganciclovir, valganciclovir, foscarnet, cidofovir).
Source: Study 303 CSR, Table 14.3.1.4.1

7.2.3 Adverse Events Leading to Discontinuation

During the on-treatment observation period, AEs 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%) (Table 22). Treatment discontinuation due to AEs by IAT type was 32.1% for ganciclovir/valganciclovir, 36.2% for foscarnet, and 33.3% for cidofovir.

While no patients in the maribavir group discontinued treatment for AEs in the SOC of blood and lymphatic system disorders, hematologic toxicities led to treatment discontinuation for 13 (11.2%) patients in the IAT group. All of these hematologic AEs occurred in patients who received ganciclovir/valganciclovir (ie, 23.2% of ganciclovir/valganciclovir-treated patients), and all were considered related to treatment. Neutropenia led to treatment discontinuation for 11 (19.6%) ganciclovir/valganciclovir-treated patients.

Also, while no patients in the maribavir group discontinued treatment for AEs in the SOC of renal and urinary disorders, renal events led to treatment discontinuation for 11 (9.5%) patients in the IAT group. Renal AEs that led to treatment discontinuation for more than 1 patient in the IAT group included acute kidney injury (6 patients on foscarnet), renal impairment (2 patients on foscarnet), and renal failure (1 patient on foscarnet and 1 on cidofovir). Ten (8.6%) patients had AEs in the SOC of renal and urinary disorders that were considered related to treatment with either foscarnet (9 patients) or cidofovir (1 patient).

In the maribavir group, infections and infestations were the most common type of AE that led to treatment discontinuation, and the incidence of AEs in this SOC was comparable between the maribavir and IAT groups (7.3% and 6.9%, respectively). Cytomegalovirus infection (maribavir: 7 [3.0%] patients; IAT: 1 [0.9%] patient) was the most frequently reported type of infection that led to discontinuation of maribavir. Within the infections and infestations SOC, the percentage of patients with treatment-related AEs leading to treatment discontinuation was balanced between treatment groups (maribavir: 3 [1.3%] patients; IAT: 2 [1.7%] patients).

Of note, dysgeusia, which was by far the most frequently reported on-treatment AE for maribavir and the most common AE considered related to maribavir, led to treatment discontinuation for only 2 (0.9%) maribavir-treated patients.

Table 22: Study 303 – Adverse Events Leading to Discontinuation

Preferred Term (≥1%)	**Maribavir* 400 mg BID (N=234) n (%)**	**IAT (N=116) n (%)**
Any AE leading to discontinuation of treatment	31 (13.2%)	37 (31.9%)
CMV infection	7 (3.0%)	1 (0.9%)
CMV viremia	4 (1.7%)	2 (1.7%)
Neutropenia	0	11 (9.5%)
Acute kidney injury	0	6 (5.2%)
Leukopenia	0	3 (2.6%)
Thrombocytopenia	0	4 (3.4%)
Anemia	0	2 (1.7%)
Renal failure	0	2 (1.7%)
Renal impairment	0	2 (1.7%)

BID=twice daily; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); AE=adverse event.
* Patients remained on maribavir therapy 46% longer than IAT (ganciclovir, valganciclovir, foscarnet, cidofovir).
Source: Study 303 CSR, Table 14.3.1.9.1

7.2.4 Serious Adverse Events

Similar percentages of patients in the maribavir and IAT groups reported SAEs (38.5% and 37.1%, respectively) despite the fact that the duration of exposure to maribavir was approximately 46% longer than to IAT. In both treatment groups, most SAEs were reported for 1 patient only. Serious AEs reported for at least 2% of patients are shown in Table 23.

As would be expected for a post-transplant population, SAEs most commonly occurred in the infections and infestations SOC in both treatment groups (maribavir: 22.6%; IAT: 14.7%). The incidence of SAEs in the SOC of infections and infestations with onset within 28 days after treatment initiation (ie, first half of the treatment period) was similar between the maribavir and IAT groups (26 [11.1%] patients and 11 [9.5%] patients, respectively).

During the on-treatment observation period, SAEs in the SOC of blood and lymphatic system disorders were reported for 3.8% of maribavir-treated patients compared with 6.0% of patients in the IAT group, all of whom had received ganciclovir/valganciclovir (ie, 12.5%). Serious AEs in the SOC of renal and urinary disorders were reported for 3.8% of maribavir-treated patients, compared with 5.2% of patients in the IAT group, all of whom had received foscarnet.

Serious AEs considered related to study-assigned treatment occurred less frequently in the maribavir group than in the IAT group (5.1% and 14.7%, respectively). Neutropenia and febrile neutropenia, which were reported as related to treatment only for ganciclovir/valganciclovir-treated patients (3.6% and 7.1%, respectively), were the main contributors to the difference between the maribavir and IAT treatment groups in the proportion of patients with treatment-related SAEs.

Table 23: Study 303 - Serious Adverse Events

Preferred Term (≥2%)	Maribavir* 400 mg BID (N=234) n (%)	IAT (N=116) n (%)
Any SAE	90 (38.5%)	43 (37.1%)
CMV infection	6 (2.6%)	4 (3.4%)
Acute kidney injury	8 (3.4%)	4 (3.4%)
CMV viremia	7 (3.0%)	3 (2.6%)
Febrile neutropenia	2 (0.9%)	4 (3.4%)
Neutropenia	0	3 (2.6%)

BID=twice daily; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); SAE=serious adverse event.
* Patients remained on maribavir therapy 46% longer than IAT (ganciclovir, valganciclovir, foscarnet, cidofovir).
Source: Study 303 CSR, Table 14.3.1.6.1

7.2.5 Deaths

7.2.5.1 Description of Patient Deaths in Study 303

A total of 40 patient deaths were reported in Study 303: 27 (11.5%) patients in the maribavir group and 13 (11.2%) patients in the IAT group (Table 24). This included 2 patients in the maribavir group who died within the first week of initiating treatment (ie, before receiving a full 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 (ie, 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.

Table 24: Study 303 - Timing of Deaths (Based on Death Date) Relative to First Dose of Study-assigned Treatment by Treatment Group and IAT Type)

			IAT Type[a]	
Statistic	**Maribavir 400 mg BID (N=235) n (%)**	**IAT (N=116) n (%)**	**Ganciclovir/ Valganciclovir (N=56) n (%)**	**Foscarnet (N=47) n (%)**
Number of reported deaths at any time	27 (11.5)	13 (11.2)	6 (10.7)	7 (14.9)
Timing of death relative to first dose				
Within 72 hours	1 (0.4)	0	0	0
Within 7 days	2 (0.9)	0	0	0
Within 14 days	2 (0.9)	1 (0.9)	0	1 (2.1)
Within 21 days	4 (1.7)	2 (1.7)	0	2 (4.3)
Within 28 days	8 (3.4)	3 (2.6)	1 (1.8)	2 (4.3)
Within 8 weeks	14 (6.0)	5 (4.3)	2 (3.6)	3 (6.4)
Within 20 weeks	25 (10.7)	11 (9.5)	4 (7.1)	7 (14.9)
After 20 weeks	2 (0.9)	2 (1.7)	2 (3.6)	0

BID=twice daily; IAT=investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir)
The calculation of death days was (death date – date of first dose of study-assigned treatment + 1)
[a] No deaths were reported for patients who received cidofovir or >1 IAT.
Source: 303 CSR Section 14, Auxiliary Table 14.4.1.1b

With respect to the onset (rather than death date) for the 40 AEs that resulted in death, 38 had onset during either the 8 weeks of treatment or 12 weeks of follow-up, 1 occurred in a patient who received maribavir as rescue therapy after failing IAT, and 1 had an onset date that was prior to the first dose of study treatment (maribavir). Additional details for these 40 AEs that resulted in death are as follows:

- 38/350 (10.9%) patients experienced AEs leading to death with onset in the overall study observation period (ie, 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 AE preferred terms leading to death were reported for 1 patient

each. The most common AEs leading to death were due to respiratory failure or relapse or progression of underlying disease.

  - 22/350 (6.3%) patients had AEs leading to death 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 AEs leading to death within or between treatment groups. The only AEs leading to death 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 leukemia (recurrent) (maribavir: 1 patient; IAT:1 patient [foscarnet])
    - Leukemia (recurrent) (maribavir: 1 patient; IAT: 1 patient [ganciclovir/valganciclovir])
  - Fatal AEs 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 AEs leading to death 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 AEs leading to death are consistent with progression of disease in the population under study. Fatal AEs 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 an AE leading to death in the maribavir rescue period. This patient received foscarnet as IAT for approximately 1 month before switching to maribavir rescue therapy on Day 36 due to persistent CMV viremia and an acute increase in creatinine. On Day 38 (2 days after receiving the first dose of rescue treatment with maribavir), the patient was hospitalized for an SAE of encephalitis CMV, which was assessed as severe intensity and not related to study treatment (foscarnet) or to rescue treatment with maribavir. A magnetic resonance imaging scan confirmed CMV tissue-invasive disease, which was attributed to progression of the disease under study. The patient was discharged on Day 50. Maribavir was discontinued on Day 57, and the patient died on Day 106 (7 weeks after the last dose of maribavir rescue therapy). (This patient is included in the IAT group because the all-cause mortality analysis was based on randomized

treatment group and not on the most recent study treatment taken before the patient died.)

- 1/234 (0.4%) patients died after receiving maribavir, however the onset of the AE that led to death 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) and is included in the evaluation of all-cause mortality for Study 303 CSR, but is not included in the tabulation of AEs because the fatal event did not meet the definition of treatment-emergent.

7.2.5.2 Patient Deaths in Study 303 Considered Treatment-Related (Investigator Assessment)

Adverse events leading to death that were considered related to study-assigned treatment (per the investigator) included events for 1 (0.4%) maribavir-treated patient and 1 (0.9%) IAT-treated patient.

- In the maribavir group, the investigator reported the sudden death of 1 patient, a 58-year-old White male, as due to a drug interaction (verbatim term: drug-drug interaction with outcome of sudden death). Before randomization into Study 303, this patient was hospitalized to receive IV ganciclovir for CMV infection and voriconazole followed by posaconazole for upper respiratory tract infection with Aspergillus. The patient also began treatment with domperidone during hospitalization and continued treatment with it as well as posaconazole at discharge. The patient enrolled in Study 303, initiated maribavir, and was discharged home (patient lived alone). Day 4 was the last day the site had contact with the patient, and solely for that reason was reported as the last day of study treatment. Four days later (Day 7), the patient was found dead at home by a family member. 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. An autopsy was not performed to confirm the cause of death. Of note, the package insert for domperidone indicates that it is associated with QTc prolongation and increased risk of sudden cardiac death (presumably via Torsade de Pointes arrhythmia), with increased risk in persons over age 60 years and/or with significant comorbidities. Further, domperidone is a substrate of CYP3A4 and consequently, "concurrent use of domperidone with potent CYP3A4 inhibitors is contraindicated." Posaconazole has been reported to cause QTc prolongation, but that is not supported by careful studies in healthy volunteers. Posaconazole is a strong inhibitor of CYP3A4 and the label specifically states it should not be administered "with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4." However, maribavir cannot be excluded as a possible contributor to the fatal event.

- In the IAT group, the investigator reported febrile neutropenia, pneumonia, and tuberculosis as AEs leading to death that were related to treatment with valganciclovir (all in the same patient). On Days 21, 41 and 55 of treatment with valganciclovir, the patient had low neutrophil counts of 1.0 × 10^9/L (normal range: 1.7 to 7.9 × 10^9/L), which were reported as an ongoing AE of neutropenia, moderate in intensity, with onset on Day 34. Valganciclovir was discontinued on Day 48. The patient was hospitalized on Day 55 with severe febrile neutropenia (considered part of the on-treatment observation period). On Day 61, the patient's respiratory condition deteriorated. A computed tomography scan showed bilateral pneumonia. The patient was intubated and mechanically ventilated, but despite this, the patient's conditioned worsened. On Day 63, the patient was diagnosed with tuberculosis. Despite aggressive anti-infectious therapy, the patient died from tuberculosis on Day 73. The investigator assessed that the event of febrile neutropenia was related to the patient's IAT (valganciclovir). The events of pneumonia and tuberculosis were considered to be due to the febrile neutropenia, and thus also related to valganciclovir.

7.2.6 Adverse Events of Special Interest in Pivotal Study 303

Adverse events of special interest (AESIs) for Study 303 included dysgeusia, immunosuppressant drug level increased, neutropenia, renal adverse events, tissue-invasive CMV disease/syndrome, and GvHD. Data regarding dysgeusia in Study 303 and other clinical studies is discussed in Section 7.3 and findings for each of the other events of special interest in Study 303 are described below.

- 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 as an AESI class (ie, febrile neutropenia, neutropenia, and neutrophil count decreased combined) was reported for 10.3% of maribavir-treated patients compared to 25.9% of IAT patients overall and 39.3% of ganciclovir/valganciclovir-treated IAT patients (Table 25). Neutropenia was reported as an SAE for no maribavir-treated patients, compared with 3 (5.4%) ganciclovir/valganciclovir-treated patients.

Table 25: Study 303 - Neutropenia Rates

Statistic	Maribavir 400 mg BID (N=235) n (%)	IAT (N=116) n (%)	IAT Type[a] Ganciclovir/ Valganciclovir (N=56) n (%)	IAT Type[a] Foscarnet (N=47) n (%)
Neutropenia as an AESI class (febrile neutropenia, neutropenia, and neutrophil count decreased combined)	24 (10.3%)	30 (25.9%)	22 (39.3%)	8 (17.0%)
Any neutropenia AE	22 (9.4%)	26 (22.4%)	19 (33.9%)	7 (14.9%)
Any febrile neutropenia AE	2 (0.9%)	5 (4.3%)	4 (7.1%)	1 (2.1%)
Any severe neutropenia AE	4 (1.7%)	12 (10.3%)	11 (19.6%)	1 (2.1%)
Any severe febrile neutropenia AE	1 (0.4%)	4 (3.4%)	3 (5.4%)	1 (2.1%)
Any neutropenia SAE	0	3 (2.6%)	3 (5.4%)	0
Neutropenia AE leading to discontinuation	0	11 (9.5%)	11 (19.6%)	0

AE=adverse event; AESI=adverse event of special interest; BID=twice daily; IAT=investigator-assigned anti-cytomegalovirus treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); SAE=serious adverse event.
Source: Study 303 CSR, Table 14.3.1.3.1, Table 14.3.1.4.1, Table 14.3.1.6.1, Table 14.3.1.9.1, and Table 14.3.1.15.1

- Regarding renal and urinary disorders in Study 303, AEs in this SOC were reported for 24.8% (58/234) of patients in the maribavir group and 31.9% (37/116) of patients in the IAT group. Maribavir-treated patients had a lower incidence of severe renal and urinary disorders compared with IAT patients (0.9% [2/234] vs 4.3% [5/116], respectively). The known renal toxicity of foscarnet accounted for much of this difference between treatment groups; the incidence of severe AEs in the renal and urinary disorders SOC was 8.5% (4/47) for foscarnet-treated patients and 16.7% (1/6) for cidofovir-treated patients. Renal and urinary SAEs were reported for 6.8% (16/234) of patients in the maribavir group and 8.6% (10/116) patients in the IAT group.
- Adverse events 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) during the on-treatment observation period (the 8-week treatment period and 12 weeks of follow-up). Preferred terms for tissue-invasive CMV disease/syndrome reported during the on-treatment observation period are summarized in Table 26.

Table 26: Study 303 – AESIs of Tissue-Invasive CMV Disease/Syndrome

Preferred Term	Maribavir 400 mg BID (N=234) n (%)	IAT (N=116) n (%)
Any Tissue-Invasive CMV Disease/Syndrome	8 (3.4%)	4 (3.4%)
CMV syndrome	3 (1.3%); SAE for 2 (0.9%)	1 (0.9%)
CMV chorioretinitis	2 (0.9%); both SAEs	1 (0.9%); SAE
CMV colitis	1 (0.4%); SAE	1 (0.9%)
CMV mucocutaneous ulcer	1 (0.4%); SAE	0
CMV GI infection	1 (0.4%)	0
CMV enteritis	0	1 (0.9%)

AESI=adverse event of special interest; BID=twice daily; CMV=cytomegalovirus; GI=gastrointestinal; IAT=investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir); SAE=serious adverse event.
Source: Study 303 CSR, Table 14.3.1.6.1 and Table 14.3.1.15.1.

- During the on-treatment observation period (the 8-week treatment period and 12 weeks of follow-up), 21 (9.0%) maribavir-treated patients had an AE of new or worsening GvHD compared with 5 (4.3%) patients in the IAT group. Of note, at baseline the percentage of patients with acute GvHD was numerically higher in the maribavir group compared to the IAT group (9.8% [23 patients] vs 6.8% [8 patients]). This imbalance may have contributed to the difference in the incidence rates of acute GvHD between treatment groups during the study. One-third of the maribavir-treated patients (7/21 patients) with GvHD during the on-treatment observation period had acute GvHD at baseline compared with one-fifth (1/5 patients) of the IAT group.

7.3 Taste Disturbance (Dysgeusia)

As previously noted, taste disturbance (dysgeusia) is known to be associated with maribavir use and is the most frequently observed AE with maribavir treatment. There was no consistent relationship between maribavir dose and reported events of dysgeusia across the dose-ranging Phase 2 studies (Study 202 and Study 203). In Study 202, dysgeusia was observed in 60.0%, 62.5% and 72.5% of patients in the maribavir 400 mg BID, 800 mg BID and 1200 mg BID groups, respectively, but in Study 203 dysgeusia was observed in 45.0%, 40.0% and 35.9% of patients in the maribavir 400 mg BID, 800 mg BID and 1200 mg BID groups, respectively. Dysgeusia led to treatment discontinuation for only 1 patient in Study 202 and no patients in Study 203 discontinued because of dysgeusia.

Dysgeusia as an AESI class included events with the preferred terms ageusia, dysgeusia, hypogeusia, and taste disorder. In Study 303, dysgeusia as an AESI class occurred more frequently for patients in the maribavir group compared to patients in the IAT group during the on-treatment observation period (maribavir: 108 [46.2%] patients; IAT: 5 [4.3%] patients). However, these events led to treatment discontinuation for only

2 (0.9%) maribavir-treated patients and no patients in the IAT group. Most events were mild to moderate in severity and none were assessed as serious. Dysgeusia generally resolved either during treatment with maribavir or shortly after discontinuation of treatment. For the 119 patients who had dysgeusia as an AESI class while on maribavir treatment, the event(s) resolved during treatment for 44 (37.0%) patients; the median duration of dysgeusia while on treatment was 43 days (range: 7 to 59 days). For patients who had dysgeusia (as an AESI class) that was ongoing at the time of the last dose of maribavir treatment, the observed median duration of the event was 6 days. A post-hoc analysis showed that the AEs of dysgeusia were not associated with weight loss.

7.4 Drug-Drug Interactions

Pharmacokinetic-based DDI risk is low, and dose adjustment of maribavir is only needed when maribavir is co-administered with a strong or moderate CYP3A4 inducer.

Maribavir may increase drug concentrations of immunosuppressant drugs that are cytochrome P4503A/P-gp substrates where minimal concentration changes may lead to SAEs (including tacrolimus, cysclosporine, sirolimus, and everolimus). Immunosuppressant drug levels should be frequently monitored throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir and adjust the immunosuppressant dose, as needed; see Section 5.5 for additional details. Appropriate cautions are planned for the proposed product labeling.

With the exception of selected immunosuppressants, rosuvastatin and digoxin, coadministration with maribavir does not impact the use or outcomes of a wide range of other drugs commonly used in the target patient population.

7.5 Supportive Safety Data

Although not directly comparable to the Phase 3 study results due to differences in the study designs, the safety data from the Phase 2 dose-ranging studies are consistent with and support the safety conclusions of Study 303.

7.5.1 Safety Findings in Study 202

Key safety findings in Study 202 were:

- All 120 treated patients reported at least 1 AE, as would be expected in this medically complex population (ie, recipients of organ transplants who had refractory CMV infection).
- The most frequently occurring AE was dysgeusia (taste disturbance), with the frequency showing some evidence of dose dependence (60.0% [24/40], 62.5% [25/40], and 72.5% [29/40] of patients in the maribavir 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively).

- Similar proportions of patients in each dose group reported an SAE: 70.0% (28/40), 67.5% (27/40), and 65.0% (26/40) in the 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively.
- Adverse events resulting in death were reported for 32 patients, with similar proportions of these deaths occurring across the treatment groups: 25% (10/40), 30% (12/40), and 25% (10/40) in the 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively.
- Maribavir was discontinued due to an AE in 27.5% (11/40), 42.5% (17/40), and 32.5% (13/40) of patients in the 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively. Maribavir treatment was interrupted due to an AE in 15.0% (6/40), 12.5% (5/40), and 22.5% (9/40) of patients in the 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively.
- An increase in immunosuppressant drug levels occurred in 10.0% (12/120) of patients in the overall maribavir group, with the reporting frequency highest in the 1200 mg BID group (15.0%; 6/40); 10.0% (4/40) of 400 mg BID patients and 5.0% (2/40) of 800 mg BID patients had increased immunosuppressant drug levels.

7.5.2 Safety Findings in Study 203

In Study 203, the median duration of exposure to maribavir (45.5, 43.5, and 44.0 days in the 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively) was longer than the median exposure to valganciclovir (30.0 days).

Key safety findings in Study 203 were:

- The proportion of patients with at least 1 AE was higher in the maribavir 400 mg BID group (97.5%; 116/119) than in the valganciclovir group (82.5%; 33/40); these proportions did not appear to be related to maribavir dose.
- Dysgeusia, the most frequently occurring AE in each maribavir group, occurred in 45.0% (18/40) of maribavir 400 mg BID patients and in 2.5% (1/40) of valganciclovir patients.
- The proportion of patients with at least 1 SAE was higher in the maribavir 400 mg BID group (40.0%; 16/40) than in the valganciclovir group (32.5%; 13/40). The occurrence of SAEs was related to dose: 40.0% (16/40) in the 400 mg BID group, 42.5% (17/40) in the 800 mg BID group, and 48.7% (19/39) in the 1200 mg BID group; however, numerical differences in these proportions were small.
- Adverse events resulting in death were reported in 9 patients and they occurred in similar proportions of patients in each treatment group: 5% (2/40 patients), 2.5% (1/40), 7.7% (3/39), and 7.5% (3/40) in the maribavir 400 mg BID, 800 mg BID, 1200 mg BID, and valganciclovir 900 mg BID groups, respectively.

- Study drug was discontinued due to an AE in 30.0% (12/40) of maribavir 400 mg BID patients and in 12.5% (5/40) of patients in the valganciclovir group; there was no apparent association with maribavir dose. Treatment with study drug was interrupted in similar proportions of patients in the maribavir 400 mg group (7.5%; 3/40) and the valganciclovir group (5.0%; 2/40), with no apparent association with maribavir dose.

8 BENEFIT-RISK CONCLUSIONS

Transplantation is a transformative and lifesaving medical procedure made possible by immunosuppression to prevent graft rejection. However, immunosuppression also puts the patient and the transplant at risk of opportunistic infections such as CMV.

Ganciclovir, valganciclovir, foscarnet, and cidofovir are currently used to treat post-transplant CMV infection, although none are approved for this indication and their use can be limited by 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). Neutropenia in transplant recipients is associated not only with increased risk for secondary bacterial and fungal infections, but also increased mortality in HSCT recipients (Salzberger et al., 1997) and increased risk for rejection and graft loss in kidney transplant recipients (Dube et al., 2021). Up to half of patients treated with foscarnet for CMV experience renal dysfunction, which can be long-lasting (Avery et al., 2016).

Thus, transplant patients with R/R CMV infection and/or disease are faced with the potential for significant morbidity and mortality as well as limited treatment options. These patients are in need for new therapeutic agents that are effective, less toxic, and can overcome resistance to existing antiviral agents. Maribavir meets this important need.

8.1 Benefits

- In the pivotal Phase 3 Study 303, maribavir demonstrated statistically superior CMV viremia clearance compared to IAT for the primary endpoint.
    - Overall, 55.7% of maribavir-treated patients achieved confirmed CMV viremia clearance at Week 8, compared to 23.9% of IAT-treated patients (adjusted difference using CMH weights across stratification factors: 32.8%; 95% confidence interval [CI]: 22.80, 42.74, p<0.001).
    - The beneficial virologic effect of maribavir compared to IAT was consistent in various sensitivity analyses of the primary endpoint, which controlled for potential confounding variables associated with the study design.
    - This benefit was also consistent across key subpopulations, including transplant type (SOT vs HSCT), patients with symptomatic CMV infection, and patients with genotypic resistance to other anti-CMV agents, as well as in demographic subgroups by gender and age. This beneficial effect was achieved regardless of baseline viral load.
- Maribavir has been shown to have a favorable safety and tolerability profile compared to IAT in the Phase 3 pivotal study:

- Maribavir 400 mg BID was well-tolerated in Study 303 based on the overall AE profile, with a higher proportion of maribavir-treated patients able to remain on treatment compared with the IAT group. As a result, the mean duration of exposure to maribavir was approximately 1.5 times longer than IAT (52.5 days vs 36.0 days).
- Maribavir was not found to have any of the treatment-limiting toxicities which are critical disadvantages of current CMV antivirals (myelotoxicity of ganciclovir/valganciclovir and nephrotoxicity of foscarnet and cidofovir), which offers a safety advantage that translates to better efficacy.
    - Neutropenia as an AESI class (ie, febrile neutropenia, neutropenia, and neutrophil count decreased combined) was less common for maribavir-treated patients than for IAT during the on-treatment observation period (maribavir, 10.3% of patients; IAT, 25.9% of patients; patients who received ganciclovir/valganciclovir as the IAT, 39.3%).
    - Maribavir-treated patients had a lower incidence of severe renal and urinary disorders compared with IAT (maribavir, 0.9% of patients; IAT, 4.3%, of patients; patients who received foscarnet as the IAT, 8.5%).
- Maribavir does not require dose adjustment for mild, moderate, or severe renal impairment, unlike conventional antiviral drugs such as foscarnet and cidofovir whose toxicities are enhanced in the setting of renal impairment.
- Maribavir does not require dose adjustment for mild or moderate hepatic impairment.

- Maribavir is administered orally, making it more convenient for patients than ganciclovir, foscarnet, and cidofovir, all of which require IV administration with the associated need for monitoring, IV access, and more frequent hospitalizations.

8.2 Risks

- Maribavir causes dysgeusia in almost half of treated patients, though most cases are mild or moderate, nonserious, and <1% result in treatment discontinuation.
- Pharmacokinetic based DDI risk is low, and dose adjustment of maribavir is only needed when maribavir is co administered with a strong or moderate CYP3A4 inducer. Coadministration of maribavir may increase the concentrations of certain immunosuppressants (eg, tacrolimus) as well as rosuvastatin and digoxin. Immunosuppressant and digoxin drug levels should be closely monitored throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir, and adjust the dose as needed. Patients on

rosuvastatin should be monitored for myopathies or other symptoms associated with the AE profile of rosuvastatin.

- Regardless of treatment, recurrences of CMV are expected in an immunosuppressed transplant patient population (Kotton et al., 2018). This illustrates the challenge of stopping antiviral therapy at an arbitrary time point unrelated to the reconstitution of the immune system of the CMV-infected transplant recipients and their ability to control the CMV infection.
- Antiviral resistance has been demonstrated against all approved anti-CMV drugs and nearly all effective antiviral drugs. In Study 303, 58/214 patients (27.1%) were identified with treatment-emergent mutations in pUL97 that confer resistance to maribavir. The possibility of antiviral resistance should be considered in patients who show poor clinical response or who experience persistent viremia during therapy (Kotton et al., 2018). Resistance to one drug may confer cross-resistance to other drugs with a similar mechanism of action. Maribavir targets the pUL97 encoded kinase that initially phosphorylates ganciclovir to its active form. Many ganciclovir resistance pathways involve pUL97, which abrogate ganciclovir activation.

8.3 Conclusion

Maribavir presents an important option for care providers who manage patients with post-transplant CMV infection and/or disease that is resistant and/or refractory to prior antiviral treatment. Its novel mechanism of action, proven efficacy in this condition, favorable safety and tolerability profile, lack of known treatment-limiting toxicities, wide therapeutic window, and oral dosing render it an important advance in the therapeutic armamentarium for these vulnerable patients.

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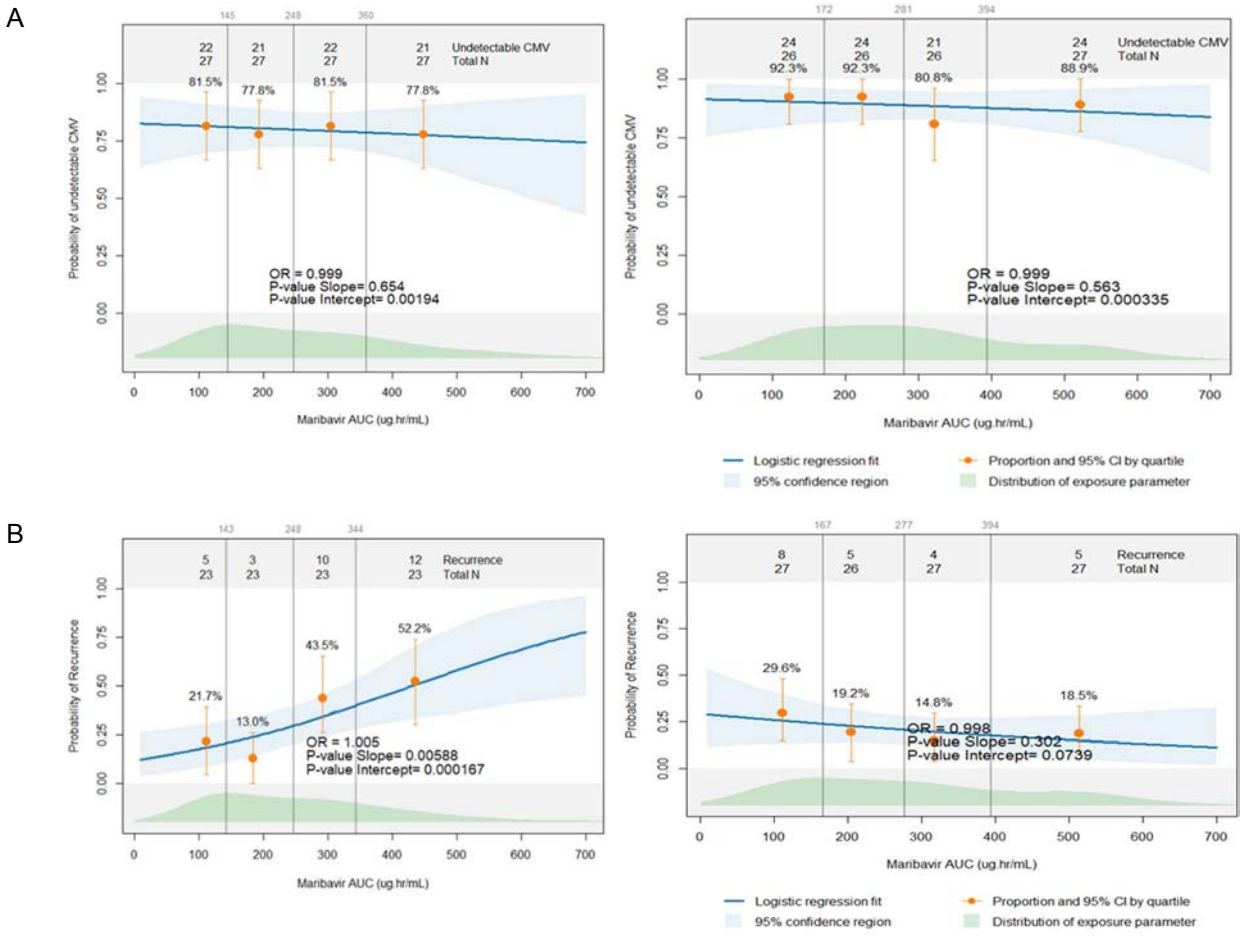
10 APPENDICES

10.1 Maribavir Exposure-Response Relationship in Phase 2 Studies

Based on the results from Phase 2 dose-ranging studies for CMV treatment, maribavir has a wide therapeutic window. Doses of 400 mg BID, 800 mg BID, and 1200 mg BID demonstrated similar antiviral activity with flat dose- or exposure-response relationships for viremia clearance (Figure 18, Panel A). Thus, the 400 mg BID regimen is expected to result in similar antiviral activity in comparison with the 2 higher doses that were studied. With regards to recurrence, there was a positive correlation between exposure and rate of recurrence in Study 202 while a negative correlation in Study 203 (Figure 18, Panel B).

Figure 18: Exposure-Efficacy Relationships of Maribavir in Study 202 and Study 203

Study 202 (Left Panels) and Study 203 (Right Panels): (A) Probability of Undetectable Plasma CMV DNA vs. AUC_{0-t}, and (B) Probability of Recurrence vs. AUC_{0-t}



AUC_{0-t}=area under the plasma concentration vs time curve during a dosing interval; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; OR=odds ratio

10.2 Study 202: Baseline Characteristics

Details on baseline characteristics of patients in Study 202 are provided for transplant and CMV History in Table 27 and transplant information in Table 28.

Table 27: Study 202 - Baseline Characteristics – Summary of Transplant and CMV History (ITT-S Population)

Characteristic	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 patients, 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)
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)
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)

ALA=antilymphocyte antibody; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; CMV=cytomegalovirus; D=donor; ITT-S=Intent-to-treat Safety; R=recipient; SD=standard deviation; ULN=upper limit of normal

Note: Percentages are based on the number of patients in each treatment group (ITT-S Population).

Source: Study 202 CSR Section 14, Table 11.1.4.2.1.1

Table 28: Study 202 - Baseline Characteristics - Transplant Information (ITT-S Population)

Stem Cell Transplant Information (ITT-S Population with Stem Cell Transplants)				
	Maribavir 400 mg BID N=16	**Maribavir 800 mg BID N=16**	**Maribavir 1200 mg BID N=15**	**Maribavir All Doses N=47**
Stem cell source, n (%)				
Bone marrow	4 (25.0)	3 (18.8)	3 (20.0)	10 (21.3)
Peripheral blood stem cell	10 (62.5)	12 (75.0)	7 (46.7)	29 (61.7)
Cord Blood	2 (12.5)	1 (6.3)	5 (33.3)	8 (17.0)
Type of transplant, n (%)				
Myeloablative	8 (50.0)	7 (43.8)	4 (26.7)	19 (40.4)
Non-myeloablative	4 (25.0)	3 (18.8)	5 (33.3)	12 (25.5)
Reduced intensity	4 (25.0)	6 (37.5)	6 (40.0)	16 (34.0)
Solid Organ Transplant Information (ITT-S Population with Solid Organ Transplants)				
	Maribavir 400 mg BID N=24	**Maribavir 800 mg BID N=24**	**Maribavir 800 mg BID N=24**	**Maribavir All Doses N=73**
Type of transplant [a], n (%)				
Kidney	9 (37.5)	11 (45.8)	10 (40.0)	30 (41.1)
Lung	6 (25.0)	7 (29.2)	7 (28.0)	20 (27.4)
Pancreas	5 (20.8)	1 (4.2)	5 (20.0)	11 (15.1)
Liver	5 (20.8)	2 (8.3)	3 (12.0)	10 (13.7)
Heart	2 (8.3)	2 (8.3)	2 (8.0)	6 (8.2)
Intestine	3 (12.5)	1 (4.2)	0	4 (5.5)
Other	2 (8.3)	0	1 (4.0)	3 (4.1) [b]

BID=twice daily; ITT-S=Intent-to-treat Safety; SCT=stem cell transplant; SOT=solid organ transplant
Note: Percentages are based on the number of patients with a SCT or SOT in each treatment group (ITT-S Population).
[a] Patients may have reported more than 1 solid organ transplant, therefore, percentages may not add to 100%.
[b] Stomach (n=1), stomach/duodenum (n=1), small bowel (n=1)
Source: Study 202 CSR Section 14, Table 11.1.4.2.1.1

10.3 Study 303: Baseline Characteristics

Details on baseline characteristics of patients in Study 303 are provided in Table 29.

Table 29: Study 303 - Baseline Disease Characteristics by Treatment Group (Randomized Set)

Characteristic	**Maribavir 400 mg BID (N=235) n (%)**	**IAT (N=117) n (%)**	**Total (N=352) n (%)**
Current transplant type			
Solid organ transplant	142 (60.4)	69 (59.0)	211 (59.9)
Heart	14 (9.9)	9 (13.0)	23 (10.9)
Lung	40 (28.2)	22 (31.9)	62 (29.4)
Liver	6 (4.2)	1 (1.4)	7 (3.3)
Pancreas	2 (1.4)	0	2 (0.9)
Intestine	1 (0.7)	0	1 (0.5)
Kidney	74 (52.1)	32 (46.4)	106 (50.2)
Multiple	5 (3.5)	5 (7.2)	10 (4.7)
Hematopoietic stem cell transplant	93 (39.6)	48 (41.0)	141 (40.1)
Autologous	1 (1.1)	0	1 (0.7)
Allogeneic	92 (98.9)	48 (100.0)	140 (99.3)
Underlying disease			

Table 29: Study 303 - Baseline Disease Characteristics by Treatment Group (Randomized Set)

Characteristic	Maribavir 400 mg BID (N=235) n (%)	IAT (N=117) n (%)	Total (N=352) n (%)
Leukemia (acute myeloid)	36 (38.7)	18 (37.5)	54 (38.3)
Leukemia (chronic myeloid)	2 (2.2)	0	2 (1.4)
Leukemia (acute lymphocytic)	12 (12.9)	7 (14.6)	19 (13.5)
Lymphoma (non-Hodgkin's)	9 (9.7)	4 (8.3)	13 (9.2)
Myelodysplastic syndrome	11 (11.8)	8 (16.7)	19 (13.5)
Other myeloid malignancy	2 (2.2)	1 (2.1)	3 (2.1)
Other	21 (22.6)	10 (20.8)	31 (22.0)
Current graft status at baseline			
Solid organ transplant			
Functioning with complications	12 (8.5)	8 (11.6)	20 (9.5)
Functioning	127 (89.4)	61 (88.4)	188 (89.1)
Other[a]	3 (2.1)	0	3 (1.4)
Hematopoietic stem cell transplant			
Partially engrafted	4 (4.3)	1 (2.1)	5 (3.5)
Functioning with complications	11 (11.8)	5 (10.4)	16 (11.3)
Functioning	78 (83.9)	42 (87.5)	120 (85.1)
Acute GvHD confirmed			
No	212 (90.2)	109 (93.2)	321 (91.2)
Yes	23 (9.8)	8 (6.8)	31 (8.8)
Chronic GvHD confirmed			
No	229 (97.4)	112 (95.7)	341 (96.9)
Yes	6 (2.6)	5 (4.3)	11 (3.1)
Renal impairment			
No impairment	81 (34.5)	39 (33.3)	120 (34.1)
Mild	71 (30.2)	42 (35.9)	113 (32.1)
Moderate	60 (25.5)	22 (18.8)	82 (23.3)
Severe	8 (3.4)	3 (2.6)	11 (3.1)
Missing	15 (6.4)	11 (9.4)	26 (7.4)
Hepatic impairment			
No impairment	218 (92.8)	107 (91.5)	325 (92.3)
Grade 1	9 (3.8)	3 (2.6)	12 (3.4)
Grade 2	4 (1.7)	3 (2.6)	7 (2.0)
Grade 3 or 4	0	0	0
Missing	4 (1.7)	4 (3.4)	8 (2.3)
Karnofsky Scale Performance Status, n	213	108	321
100	37 (15.7)	22 (18.8)	59 (16.8)
90	65 (27.7)	20 (17.1)	85 (24.1)
80	39 (16.6)	29 (24.8)	68 (19.3)
70	43 (18.3)	26 (22.2)	69 (19.6)
60	15 (6.4)	5 (4.3)	20 (5.7)
50	5 (2.1)	1 (0.9)	6 (1.7)
40	6 (2.6)	3 (2.6)	9 (2.6)
30	1 (0.4)	2 (1.7)	3 (0.9)
20	2 (0.9)	0	2 (0.6)
10	0	0	0
0	0	0	0
Missing	22 (9.4)	9 (7.7)	31 (8.8)

BID=twice daily; CMV=cytomegalovirus; GvHD=graft versus host disease; IAT=investigator-assigned anti-CMV treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir);N=number of patients
[a] Includes grafts that failed (5 patients) and 1 patient with stable renal function.
Source: Study 303 CSR, Table 14.1.4.2.1