Food and Drug Administration

Center for Drug Evaluation and Research

FDA Briefing Document

Antimicrobial Drugs Advisory Committee Meeting

October 7, 2021

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the data submitted by the Applicant in support of their New Drug Application (NDA) for maribavir for treatment of resistant or refractory CMV infection and disease in transplant recipients to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1. Introduction and Charge to the Committee

Cytomegalovirus (CMV) infection in the post-transplant setting, although one of the most common infectious complications in post-transplant recipients, is a rare disease overall, and patients with resistant or refractory CMV infection or disease make up a subset of that population, depending on transplant type (Khawaja et al. 2019). There are currently no antiviral drugs specifically approved for treatment of post-transplant CMV infection and disease, including resistant or refractory CMV, and the available CMV antiviral drugs, including ganciclovir, valganciclovir, foscarnet and cidofovir, which were approved for other indications, all have significant toxicities. When patients develop CMV infection that is resistant or refractory to treatment, it is generally because they remain severely immunocompromised and have received prolonged (or multiple) courses of antiviral therapy. These patients may develop CMV disease (i.e., tissue-invasive CMV disease such as pneumonitis, colitis, hepatitis), and may have a higher mortality rate than those without resistant or refractory CMV infection (Avery et al. 2016; Fisher et al. 2017).). Few options exist for treatment of these patients, but generally, these options include switching from oral valganciclovir to intravenous ganciclovir, increasing to higher dose ganciclovir, or switching to foscarnet or cidofovir. Thus, there remains a significant unmet need for new antiviral therapies in this population.

This Advisory Committee background document summarizes the data submitted from two clinical trials to support the proposed indication for the antiviral drug, maribavir, for treatment of resistant or refractory CMV infection in both solid organ transplant (SOT) recipients and hematopoietic stem cell transplant (HSCT) recipients. As noted below, both trials have significant limitations, yet there is considerable unmet need for antiviral drugs for treatment of CMV infection and disease which is resistant or refractory to treatment with currently available therapies. There are no drugs currently approved for treatment of CMV resistant or refractory to currently available therapies, ganciclovir, valganciclovir, foscarnet and cidofovir. The charge to the committee is to advise whether data from these trials support the use of maribavir for treatment of resistant or refractory CMV infection and disease. If the data are not deemed adequate to support the proposed indication, the FDA asks the Advisory Committee to provide input on what additional studies or trials may be needed.

2. Background

a. CMV Infection and Disease in Transplant Recipients

Cytomegalovirus (CMV) is a member of the beta-herpes virus group that causes infection worldwide. Primary infection occurs in CMV seronegative hosts and is usually acquired during the first decades of life. In most cases, primary infection is benign and self-limited. However, in patients with immature or compromised immune systems (e.g., transplant recipients, congenitally infected newborns, or patients with acquired immunodeficiency syndrome (AIDS)), primary CMV infection is often symptomatic and is associated with increased morbidity and mortality.

As with all herpes viruses, CMV establishes lifelong latency after primary infection; thereafter, intermittent viral shedding and disease reactivation can occur, particularly in hosts with compromised immune systems (Ramanan and Razonable 2013).

CMV is the single most frequent opportunistic pathogen in transplant recipients. The incidence of CMV infection and disease in this population depends on a number of factors, such as transplant type, donor and recipient CMV serostatus, and the level of immunosuppression (Ramanan and Razonable 2013).

The clinical manifestations of CMV infection in transplant patients range from asymptomatic CMV viremia to tissue-invasive CMV disease. Any organ can be affected by CMV; however, before the adoption of pre-emptive therapy, CMV pneumonia was the most serious manifestation of CMV infection in hematopoietic stem cell transplant (HSCT) recipients and has been associated with high mortality (Ljungman et al. 2010). CMV in solid organ transplant (SOT) recipients has a predilection to replicate in the allograft, leading to increased morbidity and graft rejection (Razonable et al. 2013). In general, because of the increased morbidity and mortality associated with CMV disease in transplant recipients, preventing CMV disease is recognized as a better strategy than treating established CMV disease. Prophylactic therapy and preemptive therapy are the two strategies used for prevention (Boeckh and Ljungman 2009; Kotton et al. 2018; Hakki et al. 2021). Both strategies have been shown to be effective for preventing CMV disease in HSCT and SOT recipients. For prophylaxis, an anti-CMV drug is administered to patients at risk for CMV infection who have no evidence of CMV viremia (DNAemia) or disease. In the pre-emptive strategy, antiviral therapy is initiated when CMV DNAemia is detected above a prespecified threshold and before the development of any symptoms. Established CMV infection and disease, particularly in patients with CMV infection or disease resistant or refractory to available antiviral drugs is of greatest concern because of the higher rate of morbidity and mortality in this patient population (Avery et al. 2016; Fisher et al. 2017).

Currently, limited therapeutic options for treating or preventing CMV disease in transplant recipients are available. As of September 2021, only five drugs are FDA approved for systemic use for treating or preventing CMV disease: letermovir, ganciclovir and valganciclovir, foscarnet, and cidofovir. Letermovir is approved for CMV prophylaxis in CMV seropositive HSCT recipients; ganciclovir and valganciclovir are approved for preventing CMV disease in transplant recipients and for treating CMV retinitis in immunocompromised patients, including patients with AIDS. Foscarnet and cidofovir have received approval for treating CMV retinitis in AIDS patients. Moreover, most of these drugs (ganciclovir, valganciclovir, foscarnet, and cidofovir) are associated with significant toxicities. It is noteworthy, that no drugs are FDA-approved for the treatment of asymptomatic CMV viremia or for the treatment of resistant or refractory CMV infection and disease.

Risk factors associated with resistant or refractory CMV infection include the prolonged use of antiviral drugs, high CMV viral load, subtherapeutic drug exposure, more intensive immunosuppression, and lack of prior immunity. In SOT, resistant and refractory CMV infections have been reported more often in intestinal, multivisceral, and lung transplant recipients (Kotton et al. 2018; Razonable and Humar 2019). Management of patients with resistant or refractory CMV infection or disease is very challenging due to the absence of controlled clinical trials to help select the best alternate therapy. Existing algorithms are based on consensus expert opinion. Briefly, when drug resistance is suspected, the first step, if possible, is to decrease the immunosuppressive regimen and test for genotypic resistance. If severe CMV disease is present, most experts recommend the addition of or switching to foscarnet; if disease is not severe, most experts recommend full or high dose ganciclovir. Definitive antiviral therapy is based on genotypic resistance testing and clinical response. If no resistance-associated substitutions are detected, treatment with ganciclovir is generally continued and emphasis is given to optimization of drug dosing and immunomodulators rather than switching antiviral agents. If resistance-associated substitutions are identified, treatment is modified based on the substitutions (UL97 or UL54) and whether these substitutions confer high or low resistance to ganciclovir (Kotton et al. 2018; Razonable and Humar 2019). The Applicant believes that maribavir with its novel mechanism of action and the relatively benign safety profile will contribute to fulfillment of this unmet medical need.

b. Virology Data for Maribavir

Mechanism of Action

Cytomegaloviruses are members of the Herpesviridae family, which contain large, linear, double-stranded DNA genomes, and are capable of causing a variety of acute, latent, and recurrent infections in humans and animals. Human CMV (HCMV), also designated as the human herpesvirus 5, is the prototype for the betaherpesvirus group (Roizman et al., 1981). Like other herpesviruses, HCMV is able to establish latent infections, which can subsequently recur to an active infection state. HCMV replicates in endothelial cells, epithelial cells, smooth muscle cells, and fibroblasts. Latency occurs in cells of the myeloid lineage.

Maribavir was initially identified in a screen for compounds that inhibit the pUL97 serine protein kinase of HCMV. Maribavir inhibited wild-type pUL97 protein kinase in a biochemical assay with an IC_{50} value of 3 nM. In contrast, the IC_{50} value of maribavir against the pUL97 kinase with the L397R amino acid substitution from the 2916rA resistant virus was increased 20,000-fold to 60 µM, consistent with the maribavir resistance profile.

The activity of maribavir as well as the 5'-mono- and 5'-triphosphate derivatives of maribavir against HCMV DNA polymerase and human polymerase, delta, were also evaluated in biochemical assays. Enzyme activity was measured by incorporation of ^{3}H-deoxynucleotide triphosphates ([dNTPs], namely dATP, dCTP, dGTP, and dTTP) into activated calf thymus DNA. Maribavir and its 5′-mono- and 5′-triphosphate derivatives at 100 µM had no significant

effect on the incorporation of deoxynucleoside triphosphates for both HCMV DNA polymerase and human polymerase, delta.

Antiviral Activity in Cell Culture

The cell culture antiviral activity of maribavir has been evaluated against HCMV (strain AD169; gB2 genotype) using various cell lines and assays. The EC_{50} values ranged from 0.03 to 2.2 μM depending on the cell line and assay endpoint. The cell culture antiviral activity of maribavir has also been evaluated against HCMV clinical isolates. The median EC_{50} values were 0.1 μM (n=10, range 0.04-0.13 μM) and 0.28 μM (n=10, range 0.12-0.56 μM) using DNA hybridization and plaque reduction assays, respectively. The antiviral activity of maribavir in a plaque reduction assay was similar for different gB genotypes with median EC_{50} values of 0.33 μM (n=2, range 0.28-0.38 μM), 0.51 μM (n=1), 0.44 μM (n=4, range 0.34-0.45 μM), and 0.35 μM (n=1) against gB1, gB2, gB3, and gB4 isolates, respectively. The distribution of gB genotypes in the US population was reported to be 26-50%, 18-40%, 23-28%, and 4-8% for gB1, gB2, gB3, and gB4, respectively (Bale et al., 2000; Zipeto et al., 1998).

Combination Antiviral Activity of Maribavir with Approved Drugs for HCMV in Cell Culture

Maribavir in combination with cidofovir, ganciclovir, foscarnet, letermovir, and the mTOR inhibitor rapamycin was evaluated in a checkerboard cell culture assay. The combination of maribavir and ganciclovir at the drugs EC_{50} values was antagonistic. This result was anticipated given that ganciclovir needs to initially be phosphorylated by the pUL97 for its antiviral activity; and this phosphorylation would be inhibited by maribavir. Maribavir in combination with cidofovir, foscarnet, and letermovir was not antagonistic at the EC_{50} values for these drugs.

Resistance Development in Cell Culture and Reported in Previous Clinical Studies

Amino acid substitutions pUL97 L337M, V353A, L397R, T409M, and H411L/N/Y have been selected by maribavir in cell culture (Chou et al., 2007, Chou et al., 2012, Chou et al., 2013; Chou et al. 2019; Chou and Marousek, 2008) and pUL97 F342Y, T409M, H411L/N/Y, and C480F have been observed as treatment-emergent resistance-associated substitutions (RAS) in subjects who were considered clinical failures on maribavir therapy. The reductions in susceptibility for these maribavir RAS ranged from 3.4-fold to >200-fold. Furthermore, HCMV carrying the substitutions that confer decreased sensitivity to maribavir do not affect the growth of recombinant HCMV in cell culture, indicating that these pUL97 substitutions do not significantly impact the fitness of virus (Chou et al., 2020). The pUL97 substitutions F342Y and C480F have been observed as treatment-emergent RAS in the current sponsor's clinical studies, but enrichment by valganciclovir/ganciclovir cannot be ruled out (i.e., not detected at baseline due to levels being too low) given that these substitutions were observed only in subjects who had previously been treated with valganciclovir/ganciclovir.

Resistance to maribavir can also occur as a result of amino acid substitutions in pUL27, a viral encoded protein found in the nucleus and of unknown function. pUL27 E22stop, W153R, L193F, C218del, R233S, A269T, 301-311del, L335P, V353E, W362R, W362stop, L426F, and the combination of A406V and C415stop were selected in cell culture (Chou et al., 2004, Chou et al., 2009; Chou et al., 2012; Komazin et al., 2003). The reductions in susceptibility for these range from 1.7-fold to 23-fold. HCMV carrying pUL27 substitutions that confer decreased susceptibility

to maribavir do not affect the growth of recombinant HCMV in cell culture, indicating that these substitutions do not significantly impact the fitness of virus (Chou et al., 2009). Additionally, resistant virus with amino acid substitutions in both pUL27 and pUL97 have been reported (pUL27 R233S + pUL97 S337M, 7.2-fold reduction in susceptibility; pUL27 R233S + pUL97 S353A, 27-fold reduction in susceptibility; Chou et al., 2012).

Cross-resistance

Several pUL97 substitutions selected by valganciclovir/ganciclovir or investigational methylenecyclopropane analogues confer reduced susceptibility to maribavir. These include pUL97 substitutions F342S/Y, K355del, V356G, D456N, V466G, C480R, P521L, and Y617del, each reducing susceptibility to maribavir > 4.5-fold. Other valganciclovir/ganciclovir resistance pathways have not been evaluated for cross-resistance to maribavir. pUL54 DNA polymerase substitutions conferring resistance to valganciclovir/ganciclovir, foscarnet, or cidofovir remained susceptible to maribavir (Drew et al., 2006).

Substitutions pUL97 F342Y and C480F are maribavir treatment-emergent resistance-associated substitutions that confer >1.5-fold reduced susceptibility to valganciclovir/ganciclovir, a fold reduction that is associated with phenotypic resistance to valganciclovir/ganciclovir. The clinical significance of this cross-resistance to valganciclovir/ganciclovir for these substitutions has not been determined. Maribavir resistant virus remains susceptible to cidofovir and foscarnet (Chou and Marousek, 2008; Drew et al., 2006). Additionally, there are no reports of any pUL27 maribavir resistance-associated substitutions evaluated for valganciclovir/ganciclovir, cidofovir, or foscarnet cross-resistance. However, cross-resistance is not expected for pUL27 substitutions based on the different mechanisms of action.

c. Regulatory Background

i. Prophylaxis trials

Discussions with FDA regarding the development of maribavir for prophylaxis or treatment of CMV infections in transplant patients were initiated almost two decades ago. An initial phase 2 trial (1263-200) was conducted between 2004 and 2006 for CMV prophylaxis in CMV seropositive HSCT recipients.

Phase 2 trial 1263-200: This was a randomized, placebo-controlled, dose-ranging trial comparing maribavir (100 mg BID, 400 mg QD, and 400 mg BID) administered orally for up to 12 weeks post-transplantation against placebo for the prevention of CMV disease in allogeneic stem cell transplant recipients. The trial showed a lower incidence of CMV infection and disease within 100 days post-transplantation in each of the maribavir dose groups compared to placebo. No significant differences in the incidence of CMV infection and disease were observed among the three maribavir dosing regimens (see Appendix 1 for a table with efficacy results) (Winston et al. 2008). Based on the results of this trial, the lowest dose (100 mg BID) that showed efficacy and with the most favorable safety profile (dysgeusia and nausea) was selected for further evaluation in two phase 3 CMV prophylaxis trials; one in HSCT recipients (1263-300) and one in liver transplant recipients at high risk (1263-301).

Phase 3 Trial 1263-300: This was a multicenter, randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of maribavir used prophylactically for the prevention of CMV disease in adult allogeneic stem cell transplant recipients. After transplantation and engraftment, eligible subjects were randomized in a 2:1 ratio to receive either maribavir 100 mg BID or placebo for up to a maximum of 12 weeks. The primary endpoint of the study was the incidence of CMV disease confirmed by an endpoint committee within 6 months post-transplantation. Major pre-specified secondary endpoints included the incidence and time to onset of CMV infection and start of treatment against CMV viremia as pre-emptive therapy or as treatment of CMV disease. Efficacy results demonstrated no difference in the primary and key secondary endpoints between the maribavir and the placebo groups (see Appendix II for a table with efficacy results) (Marty et al 2011).

Phase 3 Trial 1263-301: This was a multicenter, randomized, double-blind study designed to assess the efficacy and safety of prophylactic use of maribavir versus ganciclovir for the prevention of CMV disease in adult orthotopic liver transplant recipients. Following transplantation, eligible subjects were stratified by receipt of induction antilymphocyte antibodies and randomized in a 1:1 ratio to receive treatment with either maribavir (100 mg b.i.d) with oral acyclovir (400 mg b.i.d.) or oral ganciclovir alone (1000 mg t.i.d.) for up to 14 weeks. Acyclovir was added to the maribavir group because maribavir lacks activity against herpes simplex virus and varicella zoster virus, while ganciclovir has activity against both viruses. The primary endpoint of the study was the incidence of CMV disease (either CMV syndrome or CMV tissue-invasive disease) confirmed by the endpoint committee within 6 months of transplantation. The study did not meet the non-inferiority comparison to oral ganciclovir for prevention of CMV disease. In addition, the trial demonstrated statistical significance favoring ganciclovir for key secondary endpoints (see Appendix III for a table with efficacy results) (Winston et al. 2012)

ii. Treatment trials

The Applicant considered the selected dose (100 mg BID) as a possible explanation for why the two phase 3 prophylaxis trials did not meet their primary and secondary endpoints. The Applicant conducted two new phase 2 treatment trials (Trial SHP620-202 (202) in post-transplant HSCT or SOT recipients with resistant/refractory CMV infection and Trial SHP620-203 (203) in post-transplant HSCT or SOT recipients with asymptomatic CMV viremia) with higher maribavir doses (400 mg BID, 800 mg BID, and 1200 mg BID). Based on encouraging results from the two new phase 2 trials, the 400 mg BID dose of maribavir was selected for further evaluation in the following two phase 3 treatment trials:

Phase 3 Trial SHP620-303 (303): A multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir treatment compared to investigator-assigned

treatment (IAT) in HSCT or SOT transplant recipients with CMV infections that were resistant or refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir.

Phase 3 Trial SHP620-302(302): A multicenter, randomized, double-blind, double-dummy, active-controlled non-inferiority trial to assess the efficacy and safety of maribavir compared to valganciclovir for the treatment of HSCT recipients with asymptomatic CMV viremia (trial ongoing).

It should be noted that although the selected dose (100 mg BID) was considered a possible explanation for the failure to demonstrate benefit in the phase 3 prophylaxis trials, no evidence for this hypothesis has ever been provided by the Applicant. In fact, in the phase 2 trial 1263-200, efficacy results were similar between the 100 mg BID and the 400 mg BID doses. Further, no dose response was observed in the phase 2 treatment trials (Trials 202 and 203).

3. Data to Support Treatment of Resistant and Refractory CMV Infection and Disease

The Applicant's request for approval of maribavir for the treatment of post-transplant CMV infection and disease resistant or refractory to ganciclovir, valganciclovir, cidofovir or foscarnet is based on data from the phase 3 trial 303, and supportive data from the phase 2 trial, 202.

Phase 3 Trial SHP620-303 (303)

Trial 303 was a phase 3, multicenter, randomized, open-label, active-controlled trial designed to assess the efficacy and safety of maribavir compared to investigator-assigned treatment (IAT) for the treatment of post-transplant CMV infections in HSCT and SOT transplant recipients which were resistant or refractory to treatment with ganciclovir, valganciclovir, foscarnet or cidofovir. Subjects fulfilling the entry criteria were randomized in a 2:1 ratio to receive either maribavir 400 mg b.i.d. or the IAT for 8 weeks. Upon completion of the treatment period, enrolled subjects entered a 12-week follow-up period. To be eligible for the trial, subjects had to have documented CMV infection resistant or refractory to anti-CMV drugs with a screening CMV DNA value ≥ 910 IU/mL in plasma (or ≥ 2730 IU/mL in whole blood) in two consecutive assessments separated by at least 24 hours, as determined by the local or central lab quantitative PCR (qPCR) testing. Both samples were to be taken within 14 days before randomization with the 2nd sample obtained within 5 days before randomization. Results from the same laboratory and same type of blood sample (plasma or whole blood) were to be used for the randomization. For the purposes of this trial, resistant and refractory CMV were defined as follows:

<u>Resistant CMV:</u>

- Documented failure to achieve > 1 $\log_{10}$ decline in CMV DNA level in whole blood or plasma after an interval of 2 or more weeks of treatment with IV ganciclovir, oral valganciclovir, IV foscarnet or IV cidofovir; ***and***

- Documentation of one or more CMV resistance-associated amino acid substitutions to ganciclovir/valganciclovir, foscarnet or cidofovir

Refractory CMV:

- Documented failure to achieve > 1 $\log_{10}$ decline in CMV DNA level in whole blood or plasma after an interval of 2 or more weeks of treatment with IV ganciclovir, oral valganciclovir, IV foscarnet or IV cidofovir; ***and***
- Absence of any known resistance-associated amino acid substitutions to ganciclovir/ valganciclovir, foscarnet or cidofovir.

The documentation of resistance during screening was based on the local laboratory genotypic analysis. However, the final determination about the presence of resistance-associated substitutions was based on the results from the central laboratory. Similarly, CMV DNA levels based on central laboratory results were used for data analysis.

Subject enrollment was monitored to achieve an approximate target of 60% subjects with resistant CMV infection whereas the remaining subjects had refractory CMV infection.

Eligible subjects were stratified by transplant type (HSCT or SOT) and baseline CMV viral load as determined by the most recent local or central laboratory qPCR results available at the time of randomization:

- High viral load (≥ 91000 IU/mL in plasma or ≥ 273000 IU/mL in whole plasma)
- Intermediate viral load (≥ 9100 IU/mL to < 91000 IU/mL in plasma or ≥ 27300 IU/mL to < 273000 IU/ml in whole blood)
- Low viral load (≥ 910 IU/mL to < 9100 IU/mL in plasma or ≥ 2730 IU/mL to < 27300 IU/mL in whole blood)

At the time of enrollment, subjects randomized to the maribavir arm discontinued their current anti-CMV drugs . For subjects in the IAT arm, the investigators were able to start on one or two anti-CMV agents among ganciclovir, valganciclovir, foscarnet or cidofovir. Subjects who were started on two antiviral agents could have one of the agents withdrawn. Changes between intravenous ganciclovir and oral valganciclovir were permissible as well as changes in dosing or dosing regimen. However, once the anti-CMV regimen was initiated, patients in the IAT arm were not allowed to add or switch to another agent other than between ganciclovir and valganciclovir. Subjects who switched to prohibited ani-CMV agents were considered failures for the primary analysis.

Subjects in the investigator-assigned treatment arm were eligible to switch to maribavir after at least 3 weeks of treatment if any of the following criteria were met:

- Increased CMV viral load ≥ 1 $\log_{10}$ IU/mL

- Subjects with tissue invasive CMV disease who had decrease viral load < 1 $\log_{10}$ IU/mL but whose symptoms did not improve or worsened
- No CMV viremia clearance was achieved, and the subject demonstrated intolerance to the IAT drug (e.g., neutropenia, increased creatinine)

Subjects who took maribavir as rescue therapy were considered as failures for the primary efficacy analysis.

The primary endpoint of the trial was confirmed CMV viremia clearance, defined as the proportion of subjects with CMV DNA levels less than the lower limit of quantification (< LLOQ) at the end of 8 weeks of treatment (2 consecutive samples separated by at least 5 days with DNA levels < LLOQ (i.e., < 137 IU/mL)). Subjects with missing data at Week 7 and 8 who achieved confirmed viremia clearance at the time of early discontinuation were considered as failures for the primary analysis (examples are shown in Appendix IV).

The main secondary endpoint was the proportion of subjects who maintained CMV viremia clearance after 8 weeks of treatment through Study Week 16 (i.e., 8 weeks after study drug discontinuation). It is noteworthy that a cohort of the enrolled subjects had tissue-invasive CMV disease or CMV syndrome at baseline. These subjects were also assessed for the improvement or resolution of the symptoms of CMV disease or CMV syndrome. Other important secondary endpoints included the proportion of subjects with confirmed CMV viremia clearance and control of CMV disease symptoms after 8 weeks of treatment through Study Week 12 (4 weeks after study drug discontinuation) and Study Week 20 (12 weeks after study drug discontinuation); recurrences during the treatment phase and during the follow-up period; all-cause mortality; new onset symptomatic CMV disease; and maribavir resistance profile.

Trial 303 Results

Baseline Demographics and Disease Characteristics

A total of 352 subjects were randomized into Trial 303; 235 subjects in the maribavir arm and 117 subjects in the IAT arm. The mean age of trial subjects was 53 years, and most subjects were male (61%), white (76%) and not Hispanic or Latino (83%). In general, baseline characteristics across the two treatment arms were similar. The most common treatment used in the IAT arm was foscarnet which was administered in 47 (41%) subjects, followed by ganciclovir and valganciclovir, each administered in 28 (24%) subjects. Cidofovir was administered in 6 subjects, the combination of foscarnet and valganciclovir in 4 subjects, and the combination of foscarnet and ganciclovir in 3 subjects. The disease characteristics at baseline are summarized in Table 1. Approximately 60% of subjects in each arm had SOT. Among subjects with SOT, kidney was the most common transplant type (50%), followed by lung transplant (29%) and heart transplant (11%). In both the maribavir and the IAT treatment arms, most subjects had baseline viral load less than 9100 IU/mL (65% and 73%, respectively); and most did not have

symptomatic CMV disease at baseline (91% and 93%, respectively). . Further, most of the subjects had resistance-associated substitutions to at least one of the IAT drugs (52% and 59%, respectively).

Table 1. Disease Characteristics at Baseline in Trial 303

Characteristic	**Maribavir N=235 n (%)**	**IAT N=117 n (%)**
Transplant type		
HSCT	93 (40)	48 (41)
SOT	142 (60)	69 (59)
Kidney	74 (52)	32 (46)
Lung	40 (28)	22 (32)
Heart	14 (10)	9 (13)
Other (multiple, liver, pancreas, intestine)	14 (10)	6 (9)
CMV DNA levels (IU/mL in plasma)		
Low (< 9,100)	153 (65)	85 (73)
Intermediate (≥ 9,100 and < 91,000)	68 (29)	25 (21)
High (≥ 91000)	14 (6)	7 (6)
Symptomatic CMV infection		
No	214 (91)	109 (93)
Yes:	21 (9)	8 (7)
CMV syndrome	9 (43)	7 (88)
Tissue-invasive disease	12 (57)[a]	1 (13)
Genotypic resistance to other anti-CMV agents	121 (52)	69 (59)
Yes (resistant)	96 (41)	34 (29)
No (refractory)	17 (7)	13 (11)
Unable to genotype		

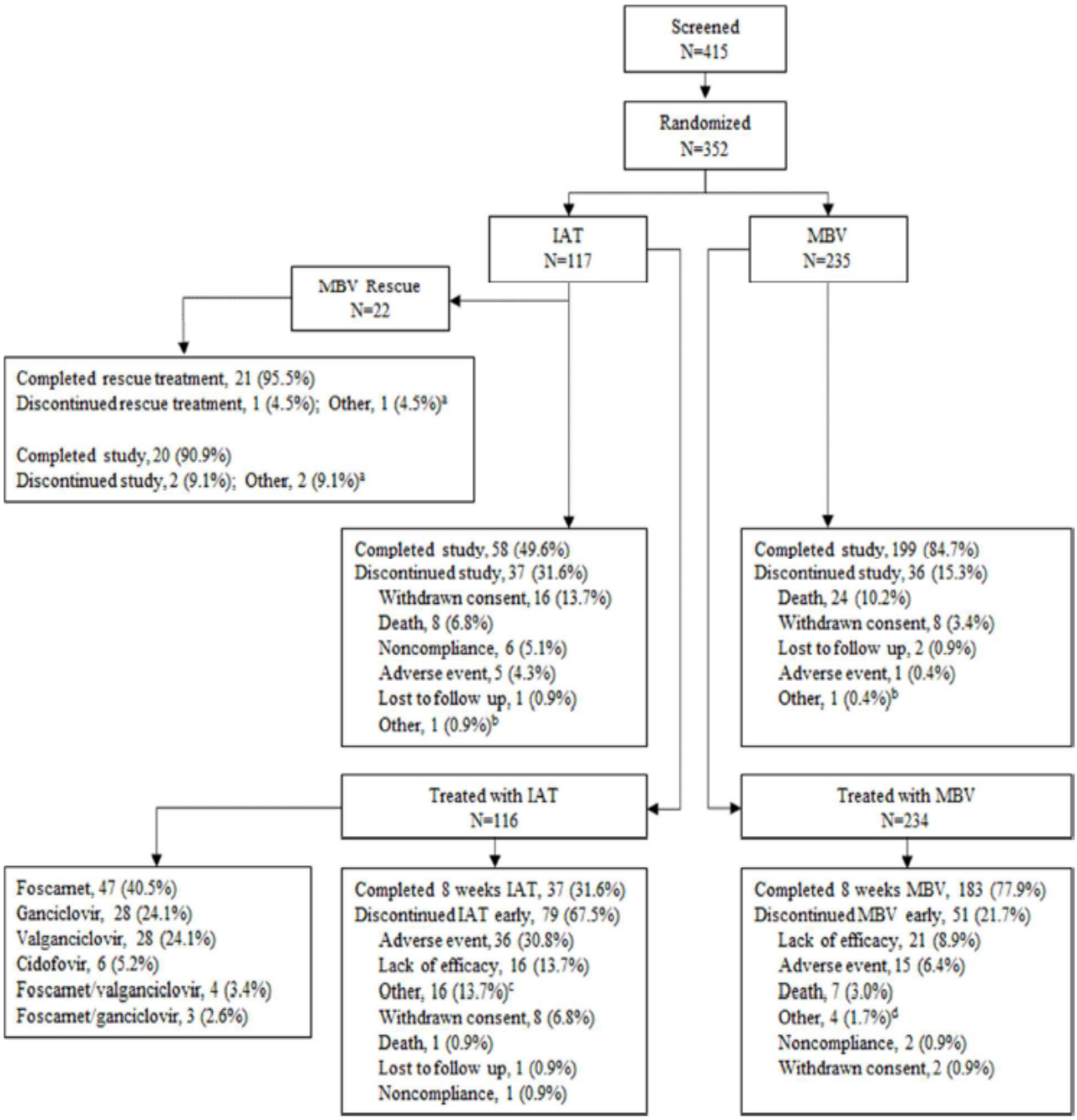
[a]One of the subjects had both CMV syndrome and CMV disease but was counted for CMV disease only
[b]Modified randomized set (Maribavir: N=234; IAT: N=116)

Subject disposition

A total of 352 subjects from 94 sites in 12 countries who met the inclusion criteria were enrolled in this trial (235 subjects in the maribavir group and 117 subjects in the IAT group). Sites in North America accounted for 58% of the randomized subjects. Sites in Europe randomized 39% of subjects and sites in Asia contributed for 3% of randomized subjects.

It is noteworthy that only 37 out of the 116 subjects (32%) treated with IAT completed 8 weeks of treatment. The major reason for drug discontinuation in the IAT arm was due to adverse events (36 subjects out of 116, 31%) In the maribavir arm, 183 out of the 234 subjects (78%) completed the 8-week treatment. Lack of efficacy (21 subjects, 9%) was the major reason for drug discontinuation in the maribavir arm. Disposition of subjects is summarized in the following figure, as provided in the Applicant's submission.

Figure 1. Diagram of Subject Disposition in Trial 303



[a] One subject discontinued rescue treatment and the study due to sponsor decision. One subject discontinued the study due to hospitalization in a different city (unable to complete follow-up visits)
[b]Other reasons for study discontinuation included PI discretion to discontinue 1 subject before dosing with maribavir and no efficacy with IAT for a subject who was not eligible for rescue therapy.
[c] Other reasons for treatment discontinuation in the IAT group fell into the general categories of low viral load/CMV clearance (with concern of toxicity with continued administration of IAT) (9 subjects), subject safety (3 subjects), subject/PI request (2 subjects), no efficacy and subject ineligible for rescue therapy (1 subject), and peripherally inserted central catheter issues (1 subject).
[d] Other reasons for treatment discontinuation in the maribavir group included PI decision to switch to letermovir (1 subject), CMV detected in cerebrospinal fluid (1 subject), nothing-by-mouth status with mental status change with risk for aspiration (1 subject), and disease progression (1 subject).

Efficacy results

Primary efficacy endpoint: The primary endpoint of the trial was the proportion of subjects with CMV DNA clearance at Week 8 (end of treatment). The results are summarized in Table 2.

Table 2. Primary Efficacy Analysis: Confirmed CMV Viremia Clearance at Week 8 (Randomized Patients)

CMV Viremia Clearance	**Maribavir N=235 n(%)**	**IAT N=117 N (%)**
Responders	131 (56)	28 (24)
Adjusted difference in proportion of responders (95% CI)[a]	33 (23, 43)	
P-value: adjusted[a]	< 0.001	

[a]Mantel-Haenszel weighted average approach was used for the adjusted difference in proportions (maribavir-IAT), the corresponding 95% CI, and the p-value, adjusting for the transplant type and baseline CMV DNA level. Only those with both stratification factors were included in this computation.

The proportion of subjects with undetectable CMV DNA levels at Week 8 was significantly higher in the maribavir group (56%) compared to the IAT group (24%; $p < 0.001$). However, the proportion of subjects with undetectable CMV DNA at Week 8 in the IAT arm appears to be lower than that observed in clinical practice (Avery et al. 2016). To provide an explanation for these differences, we conducted a further analysis of the failures of the primary efficacy endpoint. In addition, we investigated whether subjects were responding at the time of discontinuation. These results are summarized in the following table.

Table 3. Analysis of Primary Efficacy Endpoint Failures

Outcome at Week 8	**Maribavir N=235 n (%)**	**IAT N=117 n (%)**
Non-responders at Week 8	**104 (44)**	**89 (76)**
• **Due to no virological response on treatment:**	**80 (34)**	**42 (36)**
o CMV DNA never < LLOQ[a]	48 (20)	35 (30)
o CMV DNA breakthrough[b]	32 (14)	7 (6)
• **Due to drug/study discontinuation**	**24 (10)**	**47 (40)**
o Discontinued or switched treatment due to AE and not responding at the time of discontinuation or switch	8 (3) 10 (4)	26 (22) 3 (3)
o Death and not responding	1 (<1)	9 (8)
o Withdrawal of consent	2 (1)	6 (5)
o Other reasons[c]	3 (1)	3(3)
o Missing		

[a] LLOQ=137 IU/mL; [b] CMV DNA breakthrough=achieved viral load < LLOQ and subsequently became detectable; [c]Other reasons=other reasons not including AEs, deaths, non-compliance, and withdrawal of consent

The analysis of the failures of the primary endpoint indicates that the superiority of maribavir against IAT was due to drug discontinuation due to adverse events or other reasons. The proportion of virologic non-responders at week 8 was similar for the two arms, 34% and 36% for maribavir and IAT, respectively; while discontinuations or switches due to adverse events, was more frequent in the IAT arm (26% in IAT arm and 24% in maribavir arm), and discontinuation was considered failure in the primary efficacy endpoint analysis, regardless of whether there was a virologic response at the time of discontinuation.

Sensitivity analyses of the primary endpoint

To investigate the robustness of the results of the analysis of the primary efficacy endpoint, additional analyses of the primary endpoint were conducted based on alternate definitions of response.

1. Sensitivity analysis including subjects who met the criteria of CMV viremia clearance at the time of early discontinuation

Table 4. Sensitivity Analysis Including Subjects who Had CMV Viremia Clearance at the Time of Early Discontinuation

Analysis	Number of Subjects (%)		Risk Difference (95% CI)	Adjusted p-value
	Maribavir 400mg BID N=235 n (%)	IAT N=117 n (%)		
Responders[a, b]	141 (60)	51 (44)	18% (7%, 29%)	0.001

[a] Response was assessed regardless of whether the study randomized treatment was discontinued before the end of the stipulated 8-week therapy; [b] CMV DNA assessments after starting prohibited anti-CMV treatment or maribavir rescue therapy were not evaluable for the assessment of response.

The results indicate that the proportion of subjects with undetectable CMV DNA at Week 8 remains significantly higher in the maribavir group than in the IAT group (60% versus 44%, p=0.001) when subjects who met the criteria of CMV viremia clearance at the time of discontinuation were included as responders in the analysis.

2. Sensitivity analysis including subjects who met the criteria of confirmed CMV viremia clearance at Week 8 regardless of whether subject received prohibited anti-CMV treatment or maribavir rescue therapy.

Table 5. Sensitivity Analysis Including Subjects Who Met the Criteria of Confirmed CMV Viremia Clearance at Week 8 Regardless of whether Subject Received Prohibited anti-CMV Treatment or Maribavir Rescue Therapy.

Analysis	Number of Subjects (%)		Risk Difference (95% CI)	Adjusted p-value
	Maribavir 400mg BID N=235 n (%)	IAT N=117 n (%)		
Responders[a]	139 (59)	50 (43)	18% (7%, 28%)	< 0.001

[a] Response was assessed regardless of whether the study randomized treatment was discontinued before the end of the stipulated 8-week therapy.

The results of this sensitivity analysis of the primary endpoint indicate that the proportion of subjects with undetectable CMV DNA at Week 8 in the maribavir treatment arm remains significantly higher than in the IAT group (59% vs. 43%, $p < 0.001$) when subjects who received prohibited anti-CMV treatment or maribavir rescue therapy were included as responders in the analysis.

Subgroup analyses of the primary endpoint

Efficacy results were consistent across transplant type. The proportion of subjects with confirmed CMV viremia clearance at week 8 was significantly higher for both the SOT and HSCT recipients treated with maribavir compared to those treated with IAT (Table 6).

Table 6. Subgroup Analysis of the Primary Endpoint by Transplant type

Transplant type	**Maribavir 400 mg BID N=235 n (%)**	**IAT N=117 n (%)**	**Risk Difference (95% CI) Adjusted p-value**
SOT	79/142 (56)	18/69 (26)	30 (17, 44) < 0.001
HSCT	52/93 (56)	10/48 (21)	36 (21, 51) < 0.001

SOT= Solid Organ Transplant; HSCT= Hematopoietic Stem Cell Transplant

Efficacy was also consistent across type of solid organ transplant and age groups, including patients ≥ 65 years of age. With regards to subjects without CMV syndrome or disease at baseline, subgroup analysis showed that higher proportion of subjects treated with maribavir had CMV viremia clearance at Week 8 compared to those treated with IAT. Subjects with CMV syndrome or disease at baseline responded better with maribavir than subjects treated in the IAT group although the response was not as good as in subjects without CMV syndrome or disease. The subgroup analysis of the primary endpoint based on the presence or absence of CMV syndrome or disease at baseline is summarized in the following table.

Table 7. Subgroup Analysis of the Primary Endpoint based the Presence of CMV Syndrome or Disease at Baseline

CMV syndrome or disease at baseline	**Maribavir 400 N=235 n (%)**	**IAT N=117 n(%)**	**Risk Difference (95% CI) p-value**
No	121/214 (57)	27/109 (25)	33 (22, 43) < 0.001
Yes	10/21 (48)	1/8 (13)	30 (-2, +62) 0.07

With regard to the subgroup analysis based on the evidence of genotypic resistance at baseline, the analysis showed that a higher proportion of subjects with evidence of genotypic resistance who were treated with maribavir had confirmed CMV viremia clearance at Week 8 compared to those treated with IAT (maribavir 63% vs. IAT 20%; $p < 0.001$). The difference between the two groups in subjects without evidence of genotypic resistance at baseline (refractory) was not statistically significant (maribavir 44% vs. IAT 32%; p=0.17), although there was a trend favoring maribavir. In the absence of documented resistance, it is not clear why response rates were lower in the refractory subgroup for maribavir than in

the resistant subgroup or in the overall study population unless a host factor (such as level of immune suppression, return of CMV cell-mediated immunity, etc.) also had an important role in CMV clearance. In the refractory subgroup, response to maribavir was numerically better than in IAT group, noting, however, that total duration of treatment was longer in maribavir than the IAT arm.

Table 8. Proportion of Responders by Genotypic Resistance to Other Anti-CMV Drugs[a]

Genotypic resistance to other anti-CMV agents	**Maribavir 400 mg BID N=235 n (%)**	**IAT N=117 n (%)**	**Risk Difference (95% CI) p-value**
Yes (resistant)	76/121 (63)	14/69 (20)	44 (31, 57) < 0.001
No (refractory)	42/96 (44)	11/34 (32)	13 (-5, +31) 0.17

p-value for Breslow-Day interaction test=0.03, adjusting for the transplant type and baseline CMV DNA level concentration

[a]Ganciclovir, valganciclovir, foscarnet, or cidofovir

Subgroup analysis based on baseline CMV DNA levels showed that the higher the CMV DNA levels, the lower the efficacy of maribavir. Virologic response to maribavir decreased significantly with higher CMV DNA levels at baseline, particularly for subjects with CMV DNA levels ≥ 20,000 IU/mL. The following table shows that the effect of maribavir was mainly driven by subjects with CMV DNA levels (e.g. < 2000 IU/mL and < 20,000 IU/mL.

Table 9. Analysis of Primary Endpoint by Baseline CMV DNA Levels

Baseline CMV DNA levels (IU/mL)	**Maribavir N=235 n/N (%)**	**IAT N=117 n/N (%)**
< 2000[a]	61/88 (69)	13/45 (29)
≥2000 and < 20000	53/101 (52)	9/48 (19)
≥20000 and <50000	10/23 (43)	3/12 (25)
≥50000	7/23 (30)	3/12 (25)

[a] Although a minimum baseline CMV viral load ≥ 910 IU/mL was an inclusion criterion, approximately 20% of subjects in each treatment arm had lower levels

Subgroup analysis including only subjects who received 8 weeks of treatment is shown in the following table.

Table 10. Confirmed CMV Viremia Clearance at Week 8 for Subjects Who Received 8 Weeks of Treatment

CMV viremia Clearance	**Maribavir N=235 n (%)**	**IAT N=117 n (%)**

Subjects who received 8 weeks of study assigned treatment, n	183	37
Responders	129 (70)	22 (59)
Non-responders	54 (30)	15 (41)
Adjusted difference in proportion of responders (95% CI)[a]	10.2 (-7.01, 27.41)	
p-value adjusted[a]	0.245	

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

These results showed that 70% of subjects in the maribavir arm who completed the 8-week treatment had undetectable CMV DNA levels at Week 8. The proportion of subjects in the IAT arm who completed the treatment and had CMV viremia clearance at week 8 was 59%. The difference between the two arms is not statistically significant (p=0.245), although the proportion of subjects who were responders is numerically higher for maribavir. This subgroup analysis of the primary endpoint reflects an unlikely scenario in that in practice it would be unlikely for all patients who receive IAT drugs, to complete 8-weeks of treatment, particularly for those who receive foscarnet or cidofovir.

Secondary efficacy endpoint analyses

Maintenance of CMV Viremia Clearance and Control of Symptoms of CMV Disease From Study Week 8 Through Week 16

The main secondary endpoint of the trial was the proportion of subjects who maintained CMV viremia clearance and control of CMV disease symptoms after 8 weeks of treatment through Study Week 16 (i.e., 8 weeks after study drug discontinuation). Although the difference between the two treatment arms in the proportion of subjects who maintained the CMV viremia clearance and controlled CMV symptoms through Week 16 remained statistically significant (p=0.013) favoring the maribavir group, the majority of patients in both arms did not maintain virologic clearance after stopping treatment. Of the 131 responders at Week 8 in the maribavir group, only 44 subjects had undetectable CMV DNA at Study Week 16. In the IAT group, of the 28 subjects who were responders at Week 8, only 12 maintained CMV viremia clearance at 8 weeks post-treatment. These results are shown in Table 11.

Table 11. Maintenance of CMV Viremia Clearance and Control of CMV Disease Symptoms From Study Week 8 through Week 16

CMV viremia clearance	**Maribavir 400 mg BID N=235 n (%)**	**IAT N=117 n (%)**
Responders at Week 8 (end of treatment, primary endpoint)	131 (56)	28 (24)

Responders at Week 8 with maintenance through Week 16 (8 weeks post-treatment)	44 (19)	12 (10)
Adjusted difference in proportion of responders (95% CI)[a]	33 (23, 43)	
P-value: adjusted[a]	0.013	

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

It should be noted that most of the failures occurred during the first 4 weeks after treatment discontinuation (study Week 12). Between Week 16 and Week 20 there were only two failures, one in each treatment arm. Most of the failures during the follow-up period were due to CMV viremia relapses; 75% in the maribavir group and 69% in the IAT group.

New Onset Symptomatic CMV Disease

During the entire study, a similar percentage of subjects in each treatment group developed new onset symptomatic CMV infection (maribavir 6% [14/235]; IAT 6% [7/113]).

All-cause mortality

A similar percentage of subjects in each treatment arm died during the trial (maribavir 11% [27/235]; IAT 11% [13/117]).

Central Laboratory Viral Load Assay Issue in Trial 303

The central laboratory used the United States Food and Drug Administration (FDA)-approved COBAS® AmpliPrep/COBAS® TaqMan® CMV Test (CAP/CTM) (https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160041B.pdf). The local laboratories could use any quantitative polymerase chain reaction or comparable quantitative HCMV deoxyribonucleic acid (DNA) test. Randomized subjects had a baseline HCMV viral load performed immediately prior to the start of treatment. HCMV DNA quantification for the baseline and all subsequent on-study samples was performed at the central specialty laboratory using the CAP/CTM assay according to the study schedule of assessments. Upon review of subject baseline viral loads, the sponsor noted that 23% (82/352) of randomized subjects had a screening viral load ≥910 IU/mL in 2 consecutive assessments as assessed at the local laboratory, but had a baseline central laboratory result <910 IU/mL, and in some cases less than the lower limit of quantification (<LLOQ).

As the assessment of the primary efficacy endpoint, i.e. virologic clearance at Week 8, is based on central laboratory results, if unaddressed, it may be problematic to adjudicate the viral load outcomes in some of these subjects. To address the issue of assessing virologic outcomes for this ~20% subset of randomized subjects with qualifying screening HCMV viral load, but a baseline viral load <910 IU/mL using CAP/CTM at the central laboratory, the sponsor proposed to retest the baseline samples using the FDA-approved Abbott Realtime CMV assay (https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160044B.pdf). The FDA-approved Abbott Realtime CMV (Abbott) assay aims to mitigate the risk of not detecting or under-quantifying virus due to substitutions in the regions of the viral genome covered by the primers and/or probes by

using two small targets. The Abbott amplicons are in pUL34, 95 bp, and pUL80.5, 105 bp, whereas the CAP/CTM assay uses one large 340 bp amplicon that targets the DNA polymerase (pUL54). Of note, the primers of the CAP/CTM assay do not map to regions previously identified as encoding valganciclovir/ganciclovir resistance-associated substitutions ruling out primer mismatch as an explanation for low values in the COBAS® AmpliPrep/COBAS® TaqMan® CMV Test. The Abbott assay is reported to have a limit of detection (LOD) value of 31 IU/mL (for genotypes gB1 to gB4) and LLOQ value of 50 IU/ml.

Of the 82 subjects who had a baseline central laboratory result <910 IU/mL, the sponsor has retested 62 subject samples using the Abbott Realtime CMV assay. The median difference was ~5.4-fold (range 0.88-fold to 176-fold) lower in the COBAS® AmpliPrep/COBAS® TaqMan® CMV Test compared to the Abbott Realtime CMV assay. Eighty-five percent (17/20) and 71% (30/42) of subjects in the placebo and maribavir treatment arms, respectively, were confirmed to have a baseline viral load >910 IU/mL consistent with the findings at the local lab. Among these subjects with available baseline genotypic data, 42% (5/12) and 26% (7/27) had valganciclovir/ganciclovir resistance-associated substitutions at baseline in the control and maribavir treatment arms, respectively. Of the subjects with a baseline viral load <910 IU/mL using the Abbott test, five percent (1/20) and 21% (9/42) of subjects in the placebo and maribavir treatment arms, respectively, had a viral load <910 IU/mL but >455 IU/mL. Amongst these subjects, none (0/1) and 22% (2/9) had a valganciclovir/ganciclovir resistance-associated substitution at baseline in the control and maribavir treatment arms, respectively.

Given that the sponsor has not submitted all of the quality control data for the comparison between the CAP/CTM and the Abbott's assay, the primary endpoint was reassessed after censoring the 82 subjects who had a baseline viral load >910 IU/mL at screening from the local lab and <910 IU/mL at the central lab on or before first dose of study drug. Maribavir remained superior to IAT in achieving confirmed HCMV DNAemia <LLOQ at the end of Week 8 in transplant recipients with resistant/refractory HCMV infection (with or without resistance). Fifty-two percent (94/182) and 25% (22/88) of subjects achieved confirmed HCMV DNAemia <LLOQ at the end of Week 8 in the maribavir and IAT arms, respectively ($p<0.0001$).

Impact of Baseline Valganciclovir/Ganciclovir/Cidofovir/FoscarnetResistance-associated Substitutions - Trial 303

The impact of baseline valganciclovir/ganciclovir/cidofovir/foscarnet resistance-associated substitutions was evaluated to determine if any of these substitutions were predictive of nonresponse. Valganciclovir/ganciclovir resistance-associated substitutions pUL97 M460I/V, H520Q, C592G, A594P/S/T/V, L595F/S/W, C603W and del597-599 were present at baseline. The percentage of subjects meeting the primary endpoint in the maribavir arm for those subjects with pUL97 A594P/T, L595W, and del597-599 substitutions was ≤45% (i.e., >10% lower than the overall efficacy). The reductions in susceptibility to maribavir for these substitutions have not been determined. The other valganciclovir/ganciclovir pUL97 resistance-associated substitutions, i.e. M460I/V, H520Q, C592G, A594S/V, L595F/S, and C603W, did not appear to have a significant impact on the efficacy of maribavir. The reductions in susceptibility to maribavir for these are <2.5 fold, with the exceptions of M460I, L595F, and C603W for which the reductions in susceptibility have not been determined. It should be noted that the number of subjects for each of the pUL97 A594P/T and L595W substitutions and the del597-599 was small and subjects with

other amino acids substituted at these positions responded (e.g. pUL97 A594S/V and L595F/S) so no definitive conclusions with respect to the impact of these substitutions on the response to maribavir can be made. The reductions in susceptibility for maribavir treatment-emergent resistance-associated substitutions range from 4.5-81. These ranges indicate that the minimum fold-shift associated with treatment failure due to cross-resistance is in the 2.6-4.5 fold-change range and may explain the variable response for pUL97 A594P (40%; 2/5)/T(33.3%; 1/3), L595W (0%; 0/2), or del 597-599 (0%; 0/2).

Study 303: Treatment-emergent resistance analysis
There were 118 total paired sequences (n=80 and 38 in the maribavir and IAT arms, respectively) for the treatment-emergent resistance analysis. Among these paired sequences, 46 and 32 in the maribavir and IAT arms, respectively, had one or more valganciclovir/ganciclovir RAS at baseline. The majority of the virologic failures were on-treatment failures.

In the virologic failures from the maribavir treated arm, maribavir resistance-associated pUL97 amino acid substitutions identified in cell culture selection experiments as well as in the sponsor's Phase 2 studies 202 and 203 were frequently observed (n=42 subjects): F342Y [n=3; 4.5-fold reduction in susceptibility to maribavir], T409M [n=24; 81-fold reduction], H411L [n=1; 69-fold reduction], H411N [n=2; 9-fold reduction], H411Y [n=14; 12-fold reduction], and C480F [n=13; 224-fold reduction]. T409M and H411L/N/Y are maribavir specific resistance-associated substitutions. F342 (6-fold reduction to valganciclovir/ganciclovir) and C480 (2.3-fold reduction to valganciclovir/ganciclovir) may have been enriched by valganciclovir/ganciclovir to levels below the detection of the Sanger nucleotide sequence assay and therefore their association with maribavir resistance is unclear.

As stated above, 118 paired sequences (80 and 38 in the maribavir and IAT arms, respectively) were available for the treatment-emergent resistance analysis. Among the 80 virologic failures in the maribavir arm, 42 had one or more of the treatment-emergent pUL97 maribavir resistance-associated substitutions. Among the 42, 13 subjects had two maribavir resistance-associated substitutions (pUL97 F342Y+H411Y [n=1], pUL97 F342Y+T409M [n=1], pUL97 H411Y+C480F [n=1], pUL97 H411Y+C480F [n=1], pUL97 T409M+C480F [n=3], and pUL97 T409M+H411Y [n=7]). Of note, 41 of these were observed in subjects who were on-treatment failure while only 1 was from a subject who experienced a relapse. These resistance data further support the antiviral activity of maribavir.

In the pUL27, there were no treatment-emergent pUL27 resistance-associated substitutions that have been previously reported to confer resistance to maribavir.

Safety Results

In general, maribavir was relatively well tolerated. A higher proportion of subjects treated with maribavir in Trial 303 remained on treatment longer than subjects treated with IAT. As a result, the mean duration of exposure to maribavir was approximately 50% longer than IAT (52.5 days vs. 36 days)

An overview of the adverse events observed in Trial 303 are summarized in the following table.

Table 12. Overview of Adverse Events in Trial 303

Category	Maribavir[a] N=234 n (%)	IAT[a] N=116 n (%)
Any AE	228 (97)	106 (91)
Any treatment-related AE	141 (60)	57 (49)
Any serious adverse event (SAE)	90 (38)	43 (37)
Any treatment-related SAE	12 (5)	17 (14)
Any severe AE	75 (32)	44 (38)
Any treatment-related severe AE	9 (4)	24 (21)
Any AE leading to discontinuation of study-assigned treatment	31 (13)	37 (32)
Any treatment-related AE leading to discontinuation of study-assigned treatment	11 (5)	27 (23)

[a]Two randomized subjects, one in each treatment arm, were discontinued before dosing with study drugs.

Almost all patients in each group experienced at least one adverse event. This is not unexpected considering the underlying disease and associated treatment. However, a higher percentage of patients in the maribavir arm experienced an adverse event considered related to study drug (maribavir 60%, IAT 49%). This difference was mainly due to taste disturbance, an adverse event known to be related to maribavir from previous studies. The most common adverse event reported in subjects who received maribavir was taste disturbance (47%) followed by nausea (21%) and diarrhea (19%). Table 13 below summarizes the adverse events that were reported in ≥ 10% of patients who received maribavir in Trial 303

Table 13. Adverse Events (All Grades) Reported in ≥10% of Subjects in Maribavir Group in Trial 303

Adverse Event	Maribavir N=234 (%)	IAT N=116 (%)
Taste disturbance[a]	47	4
Nausea	21	22
Diarrhea	19	21
Vomiting	14	16
Fatigue	12	9
Pyrexia	10	15
CMV viremia	10	5

[a] Includes the following reported preferred terms: ageusia, dysgeusia, hypogeusia, and taste disorder

Serious adverse events (SAEs)

Similar proportions of subjects in the maribavir and IAT groups experienced SAEs (38% in the maribavir group and 37% in the IAT group). The most common SAE in both treatment groups occurred in the Infections and infestations system organ class (SOC) (maribavir 23%; IAT 15%) with CMV infection and disease being the most common in both groups.

SAEs in the SOC of Blood and lymphatic system disorders were reported in 6% of IAT-treated subjects compared to 4% of maribavir-treated subjects. SAEs in the SOC of Renal and urinary disorders were reported in 5% of subjects in the IAT group and 4% of subjects in the maribavir group.

Although the incidence of SAEs was similar between the two treatment groups, SAEs considered related to study drugs occurred more frequently in the IAT group compared to the maribavir group (15% and 5%, respectively) which raises concerns of potential open-label bias. Neutropenia and febrile neutropenia were the major contributors to this difference.

Adverse events leading to drug discontinuation

Adverse events leading to study drug discontinuation were reported more frequently in the IAT group (32%) compared to the maribavir group (13%). Blood and lymphatic system disorders were the leading cause (IAT 11%) followed by renal and urinary disorders (IAT 10%). Table 14 below summarizes the adverse events leading to study drug discontinuation.

Table 14. Most Common Adverse Events Leading to Study Drug Discontinuation

Adverse events leading to study drug discontinuation	**Maribavir N=234 n (%)**	**IAT N=116 n (%)**
Any adverse event leading to drug discontinuation	31 (13)	37 (32)
Blood and lymphatic system disorder (i.e., neutropenia, thrombocytopenia)	0	13 (11)
Renal and urinary disorders (i.e., acute kidney injury)	0	11 (10)
Infections and infestations (mainly CMV infections)	17 (7)	8 (7)
Gastrointestinal disorders (e.g., diarrhea, nausea)	4 (2)	3 (3)

Selected laboratory abnormalities of special interest

Table 15 summarizes selected laboratory abnormalities of special interest (using central and local lab data)

Table 15. Selected Laboratory Abnormalities[a]

Laboratory test	**Maribavir (N=234) n (%)**	**IAT (N=116) n (%)**
Neutrophils decreased Grade 3	17 (7)	13 (11)

Grade 4	4 (2)	4 (3)
Hemoglobin decreased		
Grade 3	37 (16)	25 (22)
Grade 4	0	0
Platelets decreased		
Grade 3	27 (12)	10 (9)
Grade 4	11 (5)	6 (5)
Creatinine increased		
Grade 3	6 (3)	2 (2)
Grade 4	0	0

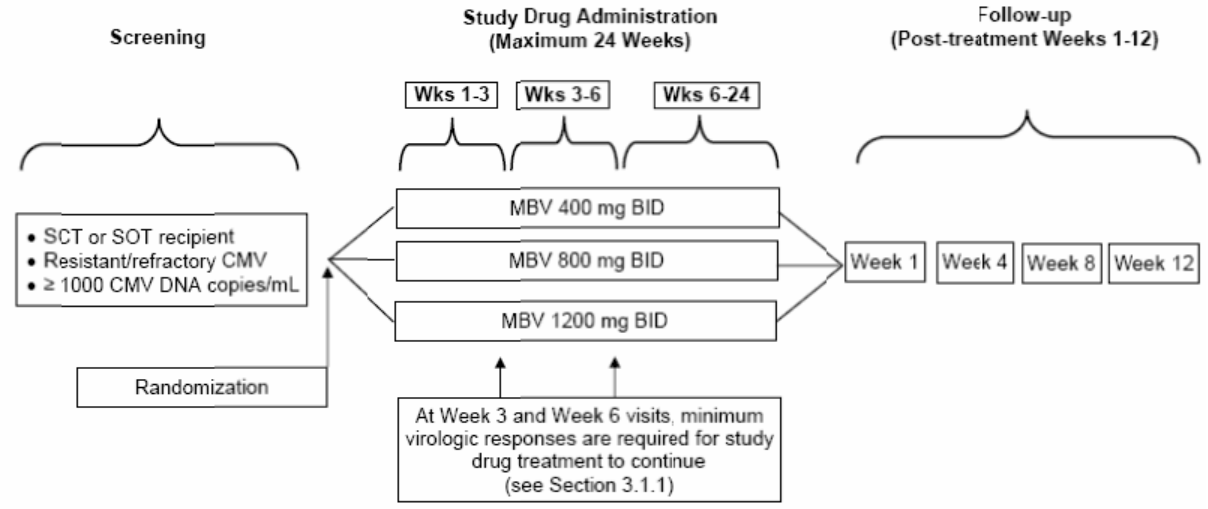
[a]Based on central and local laboratory tests.

No significant differences were observed between the two treatment groups. Further, these findings are not consistent with the high percentages of blood and lymphatic system disorders and renal and urinary disorders which led to discontinuation of the assigned IAT drug.

Phase 2 Trial 202

Trial 202, was a phase 2, randomized, dose-ranging trial in subjects ≥ 12 years of age who had undergone HSCT or SOT and had CMV infection which was resistant or refractory to treatment with ganciclovir/valganciclovir or foscarnet. Eligible subjects were stratified by transplant type (HSCT or SOT) and were randomized in a 1:1:1 ratio to receive oral maribavir 400 mg BID, 800 mg BID or 1200 mg BID. All subjects received maribavir, but subjects and investigators were blinded to maribavir dose. At the Week 3 visit, and based on the Week 2 CMV test results, subjects who had demonstrated any decrease in CMV DNA levels were allowed to continue study drug at the discretion of the investigator. Subjects still receiving study drug through Week 6 continued treatment with study drug if the Week 5 CMV test results demonstrated a ≥ 2 $\log_{10}$ decrease from baseline or undetectable CMV DNA levels. For subjects who continued dosing after the Week 6 visit, dosing was continued at the discretion of the investigator through a maximum of 24 weeks in an attempt to decrease CMV DNA to undetectable and/or to maintain undetectable CMV DNA levels. An overview of the study is shown in the following figure taken from the Applicant's submission.

Figure 2. Trial 202 Design



The definition of resistant and refractory CMV infection used in this phase 2 trial was the same as the one previously described for the phase 3 trial.

Primary efficacy endpoint: Proportion of subjects with undetectable plasma CMV DNA levels (< 200 copies/mL) in 2 consecutive samples separated by at least 5 days within the first 6 weeks of treatment.

Major secondary efficacy endpoint: Proportion of subjects with CMV recurrence during the study period. It was defined as achievement of undetectable CMV DNA (central laboratory) at any time after Day 1 (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. Plasma CMV DNA PCR values ≥ 200 copies/mL were considered detectable.

Trial 202 Results

Baseline demographics and disease characteristics

A total of 120 subjects were randomized into the trial (40 subjects in each treatment group) and received at least one dose of study drug. The percentage of subjects who completed 24 weeks of treatment was very low, but similar among the three treatment groups (400 mg BID: 9/40 [23%]; 800 mg BID 18% [7/40]; and 1200 mg BID 28% [11/40]). The decision for the duration of treatment was based on the minimum virologic response at Weeks 3 and 6 and it was based at the discretion of the investigators. The major reasons for not completing the study were adverse events, recovery from CMV infection as judged by investigators, and lack of efficacy.

The median age was 55 years, and most subjects were male (58%), white (79%) and not Hispanic or Latino (93%), with similar distribution across the three treatment groups. Among the 120 randomized subjects, 73 had SOT (61%) and 47 had HSCT (39%). Acute myeloid leukemia was the most common primary underlying disease (13%), followed by non-Hodgkin's lymphoma (8%), idiopathic pulmonary fibrosis (7%), and acute lymphocytic leukemia (5%).

Efficacy results

Primary efficacy endpoint: Table 16 below summarizes the results of the primary endpoint. Overall, 67% of subjects had confirmed undetectable plasma CMV DNA levels within 6 weeks after starting treatment with maribavir. The proportion of subjects with undetectable plasma CMV DNA was comparable among the three treatment groups with the highest proportion (70%) in the 400 mg BID group followed by 68% in the 1200 mg BID group, and 63% in the 800 mg BID group. It should be noted that in the phase 3 trial (303) the primary endpoint was defined as CMV viremia (DNAemia) clearance at the end of the 8-week treatment. However, in this phase 2 trial the primary endpoint was defined as undetectable CMV DNAemia at any time within the 6-week treatment period. This means that a subject who became undetectable, but then detectable within the 6-week timeframe was considered a responder.

Table 16. Confirmed Plasma CMV DNA Clearance Within 6 Weeks (Trial 202, ITT-S Population[a])

	Maribavir 400 mg BID N=40	Maribavir 800 mg BID N=40	Maribavir 1200 mg BID N=40	Maribavir All doses N=120
Subjects with confirmed undetectable plasma CMV DNA:				
Yes	28 (70)	25 (63)	27 (68	80 (67)
No	12 (30)	15 (38)	11 (28)	38 (32)
Subjects with missing data, n (%)	0	0	2 (5)	2 (2)

[a] The Intention-to-Treat-Safety (ITT-S) population consisted of all subjects who took any dose of study-assigned treatment. Subjects were analyzed according to the treatment actually received.

Subgroup analyses of the primary endpoint

The numbers and percentages of subjects who achieved undetectable plasma CMV DNA within 6 weeks of treatment by subgroups of special interest are summarized in Table 17.

Table 17. Confirmed Undetectable Plasma CMV DNA Within 6 Weeks by Subgroups of Interest, Trial 202

	Maribavir 400 mg BID N=40	**Maribavir 800 mg BID N=40**	**Maribavir 1200 mg BID N=40**	**Maribavir All doses N=120**
Baseline plasma CMV DNA				
< 10,000 copies/mL	19/23 (83%)	18/21 (86%)	18/23 (78%)	55/67 (82%)
≥ 10,000 copies/mL	8/16 (50%)	7/19 (37%)	8/16 (50%)	23/51 (45%)
Transplantation type				
HSCT	11/16 (69%)	11/16 (69%)	11/15 (73%)	33/47 (70%)
SOT	17/24 (71%)	14/24 (58%)	16/25 (64%)	47/73 (64%)

Baseline categorization of CMV infection:				
Asymptomatic CMV	17/24 (71%)	18/26 (69%)	22/27 ((81%)	57/77 (74%)
Symptomatic CMV infection or CMV tissue-invasive disease	11/16 (69%)	7/14 (50%)	5/13 (38%)	23/43 (53%)

The major findings were as follows:

- A higher percentage of subjects with low baseline viral load (< 10,000 copies/mL) achieved undetectable plasma CMV DNA compared with subjects with viral load ≥ 10,000 copies/mL (82% vs. 45%). This trend was similar across the three maribavir treatment groups. This observation is similar to that observed in the phase 3 trial.
- A similar proportion of SOT and HSCT recipients had virologic response within 6 weeks of treatment (64% vs. 70%).
- A higher percentage of subjects with asymptomatic CMV infection achieved undetectable CMV DNA within 6 weeks of treatment compared with those with symptomatic or tissue-invasive CMV disease (74% vs. 53%). This trend was similar across the three maribavir treatment groups.
- The Applicant also reported that a lower percentage of subjects with baseline CMV genetic substitutions associated with ganciclovir/valganciclovir or foscarnet resistance achieved undetectable CMV DNA within 6 weeks of treatment compared with subjects without associated resistance substitutions (61% versus 76%). This trend was similar across the three maribavir treatment groups. However, no conclusion could be made regarding this issue because baseline resistance was poorly defined by the central laboratory and, therefore, for most subjects it is not possible to differentiate resistant or refractory CMV infection.

Major secondary efficacy endpoint analysis

CMV recurrence: After becoming undetectable, a significant number of subjects (35%) experienced CMV recurrence during the study. The 400 mg group had lower percentage of recurrences (24% compared to subjects in the 800 mg BID group (41%) and the 1200 mg BID group (40%). These results are summarized in Table 18.

Table 18: CMV recurrence at any time during Trial 202 (ITT-S Population[a])

	Maribavir 400 mg BID N=40	Maribavir 800 mg BID N=40	Maribavir 1200 mg BID N=40	Maribavir All doses N=120
Number of subjects achieving confirmed undetectable CMV DNA[b]	29	27[e]	30[e]	86
Subjects with CMV recurrence, n (%)				
Yes[c]	7 (24)	11 (41)	12 (40)	30 (35)
No[d]	22 (76)	14 (59)	17 (60)	53 (65)

[a] The Intention-to-Treat-Safety (ITT-S) population consisted of all subjects who took any dose of study-assigned treatment. Subjects were analyzed according to the treatment actually received.
[b] Number of subjects with at least 2 consecutive undetectable plasma CMV DNA results separated by at least 5 days, including early withdrawn qualified subjects.
[c] Any recurrence during the study, including early withdrawn subjects who had recurrence before withdrawal from study.
[d] Did not have recurrence during the study, including early withdrawn subjects who did not have recurrence before withdrawal from study.
[e]There were missing data from two subjects in the 800 mg BID group and one subject in the 1200 mg BID group. These three subjects discontinued from study after they achieved undetectable CMV DNA levels.

Of note, 24 of the 30 subjects with CMV recurrence had recurrence while on study drug (all doses of maribavir). Further, 13 of these 24 subjects with CMV recurrence while on study drug (4 subjects who received 400 mg bid maribavir, 6 subjects who received 800 mg bid, and 3 subjects who received 1200 mg bid) developed UL97 substitutions previously described as conferring resistance to maribavir.

Safety Results

The safety profile of maribavir observed in this phase 2 trial is similar to that observed in phase 3 trial 303. No appreciable differences in safety were observed among the three maribavir treatment groups.

Study 202: Treatment-emergent resistance analysis

While the preliminary data from this study were encouraging in that maribavir appears to have antiviral activity, there were issues with the sponsor's resistance analyses needed to support the resistance indication the sponsor is seeking. Briefly, valganciclovir/ganciclovir resistance-associated substitutions in baseline isolates from a majority of the 120 subjects enrolled in Study SHP620-202 were not detected based on analyses conducted at the central laboratory. Resistance analyses results from the central laboratory found that baseline isolates from only 3 subjects had pUL97 valganciclovir/ganciclovir resistance-associated substitutions and isolates from 9 subjects had pUL54 substitutions associated with resistance to valganciclovir/ganciclovir, foscarnet, or cidofovir. Genotyping at the central laboratory only covered pUL97 codons 288-468 and did not cover the ganciclovir resistance loci at codons 520 or 590-607. The sponsor would likely have captured the resistance-associated substitutions that were missed by the central laboratory had they genotyped these regions as was done by several of the local laboratories. In comparison, pUL97 valganciclovir/ganciclovir resistance-associated substitutions were found in 62 subjects and pUL54 substitutions associated with resistance to valganciclovir/ganciclovir, foscarnet, or cidofovir were found in 16 subjects based on the local laboratory results.

Additionally, the resistance analyses for study SHP620-202 are limited due to genotyping at the central laboratory (pUL97 codons 288-468) that did not cover the ganciclovir resistance loci at codons 520 or 590-607 nor the maribavir resistance-associated codons (e.g. pUL97 C480F, which was observed in 16% [13/80] virologic failures in the Phase 3 study). Given these issues, a detailed resistance analysis including rates of emergence or identifying new resistance-associated codons could not be conducted. Similar to the Phase 3 study, treatment-emergent maribavir resistance-associated substitutions at codons F342, T409, and H411 were frequently observed. T409 and

H411 substitutions were observed in 19 on-treatment failures across all treatment arms and in one of those who experienced a relapse (T409M=14; H411L=1; H411Y=5). These maribavir specific resistance-associated substitutions do not confer cross-resistance to valganciclovir/ganciclovir. Additionally, no known resistance-associated substitutions in the pUL27 were seen. However, there were 3 subjects who had a treatment-emergent pUL27 M418I substitution. Two of these subjects were paired with a treatment-emergent pUL97 T409M resistance-associated substitution. This substitution has not been phenotypically characterized in cell culture to-date. These data further support the antiviral activity of maribavir.

3. Overall Summary

The Applicant submitted a phase 2 and phase 3 trial, which evaluated the efficacy of maribavir for treatment of resistant or refractory CMV infection or disease in solid organ and stem cell transplant recipients. The phase 3 trial, 303, demonstrated that maribavir was statistically superior to IAT for the primary endpoint, clearance of CMV DNA from plasma in a population which had refractory CMV (all were phenotypically resistant), and some of whom had genotypic CMV resistance. However, these results appeared to be driven by treatment discontinuation in the IAT group (discontinuation was considered treatment failure in the primary analysis). Several sensitivity analyses of the primary endpoint, however, showed that maribavir remained statistically superior to IAT for the primary endpoint, and thus the treatment effect remains robust. In addition, in important subgroup analyses, maribavir remained superior to IAT for the primary endpoint with the exception of the "refractory" subgroup and for the subgroup of patients with CMV disease. In these cases, although there was a trend favoring maribavir over IAT, statistical significance was not demonstrated (although the trial was not powered for subgroup analyses).

In trial 303, one of our major concerns was the potential for bias due to the open-label design of the trial. Although bias is suggested by the demonstration of more discontinuations in the IAT arm than in the maribavir arm, bias cannot be definitively demonstrated or ruled out, particularly because of the known safety profile of the drugs in the IAT arm. We note that Grade 3 and Grade 4 hematologic laboratory abnormalities and abnormal creatinine values were similar in the maribavir and IAT arms.

Maribavir provides some advantages over currently available therapies, i.e., it appears to have a better safety profile, with taste disturbance being the most common adverse reaction associated with its use. In these trials, most subjects did not discontinue maribavir due to taste disturbance or other adverse reactions. Additionally, maribavir is available as an oral tablet (as is valganciclovir), providing ease of administration.

One of maribavir's disadvantages is its low barrier to resistance and potential cross-resistance to valganciclovir or ganciclovir. In trial 303, the frequency of virologic failures was similar in both treatment arms. Most of maribavir virologic failures (on treatment) had developed treatment-emergent resistance-associated substitutions to maribavir. In both treatment arms, CMV relapse

after stopping treatment occurred frequently in both arms. Most relapses (off-treatment) in the maribavir arm, however, were not associated with maribavir resistance, so re-treatment after relapse may be possible, although this was not evaluated.

Trial 202 was an open-label dose-ranging trial of maribavir without an active comparator arm in post-transplant patients resistant or refractory to CMV. In this trial, 65-70% subjects across maribavir treatment arms achieved clearance of CMV viremia, similar to what was shown in Trial 303. No dose-response was demonstrated for achieving the primary endpoint. In addition, in subjects with virologic failure, treatment-emergent resistance-associated substitutions were demonstrated, confirming the antiviral activity of maribavir in this population. One of the main issues with this trial, however, was insufficient characterization of resistance at baseline. In fact, only 10 of 71 (14 %) subjects had confirmed valganciclovir/ganciclovir resistance by the central laboratory, compared to 71 subjects using local laboratory results. This was likely due to use of an assay that did include the entire CMV UL97 and UL54 genes for assessment of resistance. Unfortunately, information on validation of the assays used by the local laboratories was not available, so although, these data may provide support for treatment of CMV resistant to valganciclovir/ganciclovir (in those with resistance associated substitutions detected), if resistance-associated substitutions were not detected, that may have been due to the assay, and subjects with "refractory" CMV cannot be definitively identified. This trial can be considered supportive in that antiviral activity was demonstrated among those with documented CMV resistance.

4. Points for Advisory Committee Consideration

1. Is the overall benefit-risk assessment favorable for the use of maribavir for the treatment of resistant CMV infection and disease in post-transplant patients?

    a. If not, what additional information would be needed for the benefit-risk assessment to be favorable for the use of maribavir in this population?

        i. If a new clinical trial is recommended, please comment on trial design.

2. Is the overall benefit-risk assessment favorable for the use of maribavir for the treatment of refractory CMV infection and disease in post-transplant patients?

    a. If not, what additional information would be needed for the benefit-risk assessment to be favorable for the use of maribavir in this population?

        i. If a new clinical trial is recommended, please comment on trial design.

References

Avery, RK, R Aarav-Boger, KA Marr, E Kraus, S Shoham, L Lees, B Trollinger, P Shah, R Ambinder, D Neofytos, D Ostrander, M Forman, and A Valsamakis, 2016, Outcomes in Transplant Recipients Treated With Foscarnet for Ganciclovir-Resistant or Refractory Cytomegalovirus Infection, Transplantation 100 (10):e74-80.

Bale, J.F., Jr., JR Murph,, GJ Demmler, J Dawson., JE Miller, and SJ Petheram, 2000, Intrauterine Cytomegalovirus Infection and Glycoprotein B Genotypes, J Infect Dis 182:933-936.

Chou, S, GI Marousek, AE Senters, MG Davis, and KK Biron, 2004, Mutations in the human cytomegalovirus UL27 gene that confer resistance to maribavir, J Virol 78:7124-7130.

Chou, S., GI Marousek, LC Van Wechel, S Li, and A Weinberg, 2007, Growth and Drug Resistance Phenotypes Resulting from Cytomegalovirus DNA Polymerase Region III Mutations Observed in Clinical Specimens, Antimicrob Agents Chemother 51:4160-4162.

Chou, S., and GI Marousek, 2008, Accelerated Evolution of Maribavir Resistance in a Cytomegalovirus Exonuclease Domain II Mutant, J Virol 82:246-253.

Chou, S, 2009, Diverse Cytomegalovirus UL27 Mutations Adapt to Loss of Viral UL97 Kinase Activity under Maribavir, Antimicrob Agents Chemother 53:81-85.

Chou, S, M Hakki, and S Villano, 2012, Effects on Maribavir Susceptibility of Cytomegalovirus UL97 Kinase ATP Binding Region Mutations Detected After Drug Exposure In Vitro and In Vivo, Antiviral Res 95:88-92.

Chou, S, RJ Ercolani, G Marousek, and TL Bowlin, 2013, Cytomegalovirus UL97 Kinase Catalytic Domain Mutations that Confer Multidrug Resistance, Antimicrob Agents Chemother 57:3375-3379.

Chou, S., J Wu, K Song, and T Bo, 2019, Novel UL97 Drug Resistance Mutations Identified at Baseline in a Clinical Trial of Maribavir for Resistant or Refractory Cytomegalovirus Infection. Antiviral Res 172: 104616.

Chou, S., K Song, J Wu, T Bo, and C Crumpacker, 2020, Drug Resistance Mutations and Associated Phenotypes Detected in Clinical Trials of Maribavir for Treatment of Cytomegalovirus Infection, J Infect Dis (online ahead of print)

Drew, WL, RC Miner, GL Marousek, and S Chou, 2006, Maribavir Sensitivity of Cytomegalovirus Isolates Resistant to Ganciclovir, Cidofovir or Foscarnet. J Clin Virol 37:124-127.

Fisher, CE, JL Knudsen, ED Lease, KR Jerome, RM Rakita, M Boeckh, and Limaye AP, 2017, Risk Factors and Outcomes of Ganciclovir-Resistant Cytomegalovirus Infection in Solid Organ Transplant Recipients, Clin Infect Dis, 65(1):57-63.

Hakki, M, SL Aitken, L Danziger-Isakov, MG Michaels, PA Carpenter, RF Chemaly, GA Papanicolaou, M Boeckh, and FM Marty, 2021, American Society for Transplantation and Cellular Therapy Series: #3-Prevention of Cytomegalovirus Infection and Disease After Hematopoietic Cell Transplantation, Transplant Cell Ther, 27(9): 707-719.

Khawaja, F, MV Batista, L El Haddad, and RF Chemaly, 2019, Resistant or Refractory Cytomegalovirus Infections after hematopoietic cell transplantation: diagnosis and management, Curr Opin Infect Dis, 32(6):565-574.

Komazin, G, RG Ptak, BT Emmer, LB Townsend, and JC Drach, 2003 Resistance of Human Cytomegalovirus to D- and L-Ribosyl Benzimidazoles as a Tool to Identify Potential Targets for Antiviral Drugs. Nucleosides Nucleotides Nucleic Acids 22:1725-1727.

Kotton, CM, D Kumar, AM Caliendo, S Huprikar, S Chou, L Danziger-Isakov, A Humar; on behalf of the Transplantation Society International CMV Consensus Group, 2018, The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation, Transplantation, 102(6):900–931.

Ljungman, P, M Hakki, and M Boeckh, 2010, Cytomegalovirus in Hematopoietic Stem Cell Transplant Recipients, Infect Dis Clin N Am, 24:319-337.

Marty, FM, P Ljungman, GA Papanicolaou, DJ Winston, RF Chemaly, L Strasfeld, T Rodriguez, J Maertens, M Schmitt, H Einsele, A Ferrant, JH Lipton, SA Villano, H Chen, and M Boeckh; Maribavir 1263-300 Clinical Study Group, 2011, Maribavir Prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: A Phase 3 double-blind, placebo-controlled, randomized trial, Lancet Infect Dis, 11(4):284–292.

Ramanan, P and RR Razonable, 2013, Cytomegalovirus Infections in Solid Organ Transplantation: A Review, Infect Chemother, 45(3):260–271.

Razonable, RR, A Humar, and AST Infectious Diseases Community of Practice, 2013, Cytomegalovirus in Solid Organ Transplantation, Am J Transplant, 13(Suppl 4):93–106.Razonable, RR and A Humar, 2019, Cytomegalovirus in Solid Organ Transplant Recipients – Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice, Clin Transplant, 33(9):e1352.

Roizman, B, LE Carmichael, F Deinhardt, G de-The, AJ Nahmias, W Plowright, F Rapp, P Sheldrick, M Takahashi, and K Wolf, 1981, Herpesviridae. Definition, Provisional Nomenclature, and Taxonomy. The Herpesvirus Study Group, the International Committee on Taxonomy of Viruses. Intervirology 16:201-217.

Winston DJ, JA Young, V Pullarkat, GA Papanicolaou, R Vij, E Vance, GJ Alangaden, RF Chemaly, F Petersen, N Chao, J Klein J, K Sprague, SA Villano , and M Boeckh, 2008, Maribavir Prophylaxis for Prevention of Cytomegalovirus Infection in Allogeneic Stem Cell Transplant Recipients: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study, Blood, 111(11):5403-5410.

Winston DJ, F Saliba, E Blumberg, M Abouljoud, JB Garcia-Diaz, JA Goss, L Clough, R Avery, AP Limaye, BG Ericzon, M Navasa, RI Troisi, H Chen, SA Villano, and ME Uknis ME; 1263-301 Clinical Study Group, 2012, Efficacy and Safety of Maribavir Dosed at 100 mg Orally Twice Daily for the Prevention of Cytomegalovirus Disease in Liver Transplant Recipients: A Randomized, Double-Blind, Multicenter Controlled Trial, Am J Transplant, 12(11):3021-3030.

Zipeto, D., C Hong, G Gerna, M Zavattoni, D Katzenstein, TC Merigan, and L Rasmussen, 1998, Geographic and Demographic Differences in the Frequency of Human Cytomegalovirus gB Genotypes 1-4 in Immunocompromised Patients. AIDS Res Hum Retroviruses 14:533-536.

APPENDIX 1.

The table below summarizes the efficacy results from the phase 2 prophylaxis trial, 1263-200.

Trial 1263-200: Incidence of CMV infection or disease within 100 days post-transplant.

	Placebo	Maribavir dose group		
		100 mg BID	400 mg QD	400 mg BID
ITT population	28	28	28	27
ITT evaluable	28	27	27	26
CMV infection or disease				
With infection assessed by pp65 antigenemia	11 (39%)	4 (15%) p=0.046	5 (19%) p=0.116	4 (15%) p=0.053
With infection assessed by plasma CMV DNA PCR assay	13 (46%)	2 (7%) p=0.001	3 (11%) p=0.007	5 (19%) p=0.038
With infection assessed by initiation of anti-CMV therapy	16 (57%)	4 (15%) p=0.001	8 (30%) p=0.051	4 (15%) p=0.002
CMV disease only	3 (11%)	0 p=0.089	0 p=0.084	0 p=0.091

Source: Applicant's clinical study report for Protocol 1263-200 (IND 51001/SD-130)

APPENDIX II

Efficacy results from the phase 3 prophylaxis trial in HSCT recipients (Trial 1263-300).

	Post-transplant:								
Assessment Period:	**100 Days**			**6 Months**			**12 Months**		
	PBO	**MBV**	**P-value**	**PBO**	**MBV**	**P-value**	**PBO**	**MBV**	**P-value**
ITT Population, N:	227	454		227	454		227	454	
CMV Disease:									
EC-confirmed disease	6 (3%)	11 (2%)	0.860	11 (5%)	20 (4%)	0.789	13 (6%)	22 (5%)	0.617
Investigator-determined disease	6 (3%)	16 (4%)	0.542	11 (5%)	26 (6%)	0.637	13 (6%)	28 (6%)	0.825
CMV Infection or EC-confirmed Disease; Infection Assessed by (Central or Local Labs):									
pp65 antigenemia assay	79 (35%)	120 (26%)	0.022	88 (39%)	143 (31%)	0.056	--	--	--
CMV DNA PCR assay	69 (30%)	126 (28%)	0.468	77 (34%)	152 (33%)	0.904	--	--	--
pp65 antigenemia assay or CMV DNA PCR assay	92 (41%)	157 (35%)	0.125	101 (44%)	183 (40%)	0.289	--	--	--
Initiation of anti-CMV therapy	85 (37%)	139 (31%)	0.069	92 (41%)	172 (38%)	0.493	--	--	--

Source: Applicant's clinical study report for Protocol 1263-300 (IND 51001/SD-316)

PBO=placebo; MBV=maribavir 100 mg BID; -- = not assessed; EC=Endpoint Committee

NOTE: p-value is from the Cochran-Mantel-Haenszel test, adjusting for recipient CMV serostatus (R+ or R-) and transplant type (myeloablative or non-myeloablative/reduced intensity).

APPENDIX III

Efficacy results from the phase 3 prophylaxis trial in liver transplant recipients at high risk (Trial 1263-301).

Assessment Period:	100 Days Post-Transplant			6 Months Post-Transplant		
	Ganciclovir 1000 mg TID	Maribavir 100 mg BID		Ganciclovir 1000 mg TID	Maribavir 100 mg BID	
ITT-M Population, N:	120	113	P-value	120	113	P-value
CMV Disease:						
EC-confirmed CMV disease	0	10 (9%)	0.0007	10 (8%)	14 (12%)	0.2754
Investigator-determined CMV disease	3 (3%)	17 (15%)	0.0008	18 (15%)	22 (19%)	0.3742
CMV Infection or EC-confirmed Disease; Infection Assessed By (Central or Local Labs):						
pp65 antigenemia assay	19 (16%)	49 (43%)	<0.0001	49 (41%)	63 (56%)	0.0283
CMV DNA PCR assay	18 (15%)	59 (52%)	<0.0001	52 (43%)	72 (64%)	0.0024
pp65 antigenemia or CMV DNA PCR assay	24 (20%)	68 (60%)	<0.0001	64 (53%)	81 (72%)	0.0053
Initiation of anti-CMV therapy	5 (4%)	37 (33%)	<0.0001	39 (33%)	46 (41%)	0.2339

Source: Applicant's clinical study report for Protocol 1263-301 (IND 51001/SD-316)

APPENDIX IV

Examples of virologic responses for the primary efficacy endpoint in Trial 303

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

NA = *not available for evaluation of study drug effect*; reason could be not assessable by lab, or starting alternative anti-CMV treatment, withdrawal from study, etc.

*Week 9 data only to be used if Week 8 data are unavailable or missing.

Notes: Scenarios in the table above are provided as examples and may not be all-inclusive of all possibilities.

Only CMV DNA data evaluable for assessment of effect of study drug will be included (ie, prior to the start of alternative anti-CMV treatment if any).

"-" = CMV DNA concentration <LLOQ (<137 IU/mL)

"+" = CMV DNA concentration ≥LLOQ (ie, quantifiable)

Confirmed clearance of plasma CMV DNA (CMV viremia clearance) = 2 consecutive postbaseline assessments of CMV DNA target <LLOQ, separated by at least 5 days.

Source: Table 3 in statistical analysis plan for IND 51001/SD-486