NDA 215596

Maribavir tablets

Treatment of resistant or refractory cytomegalovirus (CMV) infection and disease in transplant patients

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING
October 7, 2021

Division of Antivirals, Office of Infectious Diseases
Center for Drug Evaluation and Research

CMV Background

- Cytomegalovirus (CMV) is a member of the betaherpesvirus group
- Establishes life-long latency after primary infection
- Frequent opportunistic pathogen in transplant recipients; but considered a rare disease
- Incidence of CMV infection and disease depends on:
  - Transplant type, donor and recipient CMV serostatus, level of immunosuppression
- CMV infection can result in tissue-invasive disease (pneumonitis, colitis, hepatitis, allograft infection), has negative indirect effects such as rejection and is associated with higher mortality post-transplant
- Most transplant patients receive either prophylaxis or preemptive therapy to prevent CMV disease

CMV

- Limited therapeutic options for treating or preventing CMV infection or disease
- The following 5 drugs are approved for treatment or prevention of CMV disease:
  - Letermovir - CMV prophylaxis in HSCT recipients
  - Ganciclovir (IV)- CMV prevention in transplant recipients and treatment of CMV retinitis
  - Valganciclovir - CMV prevention in certain SOT recipients and treatment of CMV retinitis
  - Foscarnet - treatment of CMV retinitis
  - Cidofovir - treatment of CMV retinitis
- No approved therapeutics for treatment of CMV infection or disease in transplant patients

CMV Prevention and Treatment

- Available CMV therapies are associated with significant toxicities
  - Ganciclovir/valganciclovir - hematologic toxicity
  - Foscarnet- nephrotoxicity, severe electrolyte abnormalities, many others
  - Cidofovir – nephrotoxicity

- Some patients will develop CMV infection that is refractory to available therapies, with or without associated genotypic resistance
  - Resistance most commonly occurs after prolonged antiviral treatment in setting of immunosuppressive therapy post transplant
  - Resistant and refractory infections are associated with worse clinical outcomes

- Unmet medical need - No drugs are FDA approved for treatment of resistant or refractory CMV disease in the post-transplant setting

Drug Development for Maribavir

- **Phase 2 and Phase 3 CMV *Prophylaxis* Trials Post-Transplant**
  - **Will not be reviewed in detail today**

- **Phase 2 and Phase 3 CMV *Treatment* Trials Post-Transplant**
  - ✓ **Trial 202** in CMV refractory +/- genotypic resistance patients
  - o **Trial 203** in patients with asymptomatic, non-resistant/non-refractory CMV viremia
  - ✓ **Trial 303** in CMV refractory +/- genotypic resistance patients
  - o **Trial 302** in patients with asymptomatic CMV viremia (an **ongoing** trial comparing maribavir vs. valganciclovir in HSCT patients with asymptomatic CMV viremia)

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Applicant's Proposed Indication:

Maribavir is indicated for the treatment of adults with post-transplant cytomegalovirus infection and/or disease, including infections resistant and/or refractory to ganciclovir, valganciclovir, cidofovir or foscarnet

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- In Trial 303, in addition to the primary and secondary endpoint analyses, several sensitivity analyses were conducted that supported the primary endpoint

- Subgroup analyses were also conducted – e.g., transplant type, refractory without resistance vs. refractory with resistance to other CMV antivirals, presence of CMV syndrome or tissue-invasive disease, baseline viral load

- Additional analyses were important to address potential biases in the open label phase 3 clinical trial in refractory +/- genotypic resistance patients

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Discussion Question 1:

Discuss your evaluation of efficacy in the phase 3 trial SHP620-303, data from the phase 2 trial, SHP620-202, and the overall risk-benefit assessment for maribavir.

Consider:

- **Population – narrow population with unmet medical need**
- **Trial design and limitations, including potential bias**
- **Primary efficacy outcome**
- **Results from the sensitivity and subgroup analyses**
- **Maribavir safety profile**

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Voting Question #2

Is the overall benefit-risk assessment favorable for the use of maribavir for the treatment of transplant recipients with CMV infection and disease refractory to treatment and *with* genotypic resistance to ganciclovir, valganciclovir, cidofovir or foscarnet?

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

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

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Voting Question #3

Is the overall benefit-risk assessment favorable for the use of maribavir for the treatment of transplant recipients with CMV infection and disease refractory to treatment, but *without* genotypic resistance to ganciclovir, valganciclovir, cidofovir or foscarnet?

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

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

Agenda

9:00 a.m.	**Call to Order and Introduction of Committee**	**Lindsey Baden, MD Chair, AMDAC**
9:10 a.m.	Conflict of Interest Statement	**Moon Hee V. Choi, PharmD Acting Designated Federal Officer, AMDAC**
9:15 a.m.	FDA Opening Remarks	**Debra Birnkrant, MD Director, Division of Antivirals**
9:25 a.m.	APPLICANT PRESENTATIONS	**Takeda Pharmaceuticals USA, Inc.**
10:20 a.m.	Clarifying Questions	
10:40 a.m.	BREAK	
10:50 a.m.	FDA PRESENTATIONS	**Andreas Pikis, MD, Senior Medical Officer Takashi Komatsu, PhD, Senior Virology Reviewer**
11:45 a.m.	Clarifying questions for FDA	
12:05p.m.	Lunch Break	
1:00 p.m.	OPEN PUBLIC HEARING	
2:00 p.m.	Charge to the Committee	**Division of Antivirals**
2:05 p.m.	Questions to the Committee/Committee Discussion	
5:00 p.m.	ADJOURNMENT	

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Maribavir tablets

Treatment of post-transplant CMV infection and disease resistant or refractory to ganciclovir, valganciclovir, cidofovir or foscarnet

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING
October 7, 2021

Andreas Pikis, M.D. - Medical Officer
Takashi Komatsu, Ph.D., RAC - Clinical Virologist
Division of Antivirals, Office of Infectious Diseases
Center for Drug Evaluation and Research

Agenda

- Background
- Trials targeted to a limited population:
  - Refractory CMV infection or disease with or without genotypic resistance (resistant/refractory CMV)

Efficacy and safety data:

-Phase 3 trial SHP620-303 (303)

-Phase 2 trial SHP620-202 (202)

Virology data:

- Phase 3 trial SHP620-303 (303)

Background

Drug Development Milestones for Maribavir

- **Phase 2 and Phase 3 CMV *Prophylaxis* Trials Post-Transplant:**
  - **Phase 2 trial (Trial 200):** A randomized, placebo-controlled, dose-ranging trial, comparing maribavir (100 mg BID, 400 mg QD, 400 mg BID) against placebo for CMV prophylaxis in CMV seropositive hematopoietic stem cell transplant (HSCT) recipients.
    - Fewer CMV infections/disease with maribavir compared to placebo, but no dose-response seen; 100 mg BID dose chosen for two phase 3 prophylaxis trials (Trial 300 and 301)
  - **Phase 3 Trials (300 and 301):** The two phase 3 prophylaxis trials, one in HSCT recipients and the other in liver transplant recipients, failed to meet the primary and key secondary endpoints.

Drug Development Milestones for Maribavir (continued)

Phase 2 and Phase 3 CMV *Treatment* Trials Post-Transplant:

The lower dose selected (100 mg BID) was considered a possible explanation for why the two phase 3 prophylaxis trials did not meet their primary and key secondary endpoints.

The Applicant conducted two new **phase 2** trials with higher maribavir doses (400 mg BID, 800 mg BID, and 1200 mg BID):

- **Trial 202** in CMV resistant/refractory patients, and
- **Trial 203** in patients with asymptomatic, non-resistant/non-refractory CMV viremia

Although no dose response was observed in the phase 2 trials, the 400 mg BID dose was selected for further evaluation in two **phase 3** treatment trials:

- **Trial 303** in patients with CMV resistant/refractory
- **Trial 302** in patients with asymptomatic CMV viremia (an ongoing trial comparing maribavir vs. valganciclovir in HSCT patients with CMV viremia)

Efficacy

Phase 3 Trial 303: Trial Design

- **A randomized, open-label, active-controlled trial of maribavir vs. Investigator-Assigned Treatment (IAT) in transplant patients with CMV infections resistant or refractory to treatment with ganciclovir, valganciclovir, foscarnet or cidofovir**
  - Treatment duration: up to 8 weeks
  - Maribavir dose: 400 mg BID
  - IAT dose: based on drug labels (dose adjustment was allowed at the discretion of the investigator)
  - Follow-up period for additional 12 weeks

Investigator-Assigned Treatment (IAT)

Allowed treatment options included:

- Start on one or two of the following agents: ganciclovir, valganciclovir, foscarnet or cidofovir
- Withdrawal of one agent if the patient was started on two anti-CMV agents
- Changes between intravenous ganciclovir and oral valganciclovir
- Changes in dose or dosing regimen

Prohibited treatment (subjects who received prohibited treatment were considered treatment failures):

- Addition of another agent
- Switch to another agent (other than between ganciclovir and valganciclovir)

Trial Design (continued)

Maribavir Rescue Arm: Subjects in the IAT arm were eligible to switch to maribavir after 3 weeks of treatment if any one of the following criteria was met:

- Increased CMV viral load ≥ 1 $\log_{10}$
- Subjects had tissue invasive CMV disease after being on treatment for 3 weeks and met both of the following criteria:
  - Had a decrease in viral load < 1 $\log_{10}$ from baseline, and
  - Symptoms of CMV disease did not improve or worsened
- CMV viremia clearance was not achieved, and the subject demonstrated intolerance to the IAT drug (e.g., neutropenia, increased creatinine)

Subjects who switched to rescue arm were considered failures in the primary analysis.

Trial Design: Definitions of Resistant and Refractory CMV

For the purposes of this trial, resistant and refractory CMV infections were defined as follows:

Resistant:

- 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:

- 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**

Trial Design: Stratification

Stratification was based on:

- Transplant type (HSCT or SOT); and
- Baseline CMV viral load (IU/mL in plasma):
  - Low viral load: ≥ 910 to < 9100
  - Intermediate viral load: ≥ 9100 to < 91000
  - High viral load: ≥ 91000

Trial Design: Population and Endpoints

Population: All subjects had refractory CMV infection *with or without* genotypic resistance.

Primary efficacy endpoint:

- Proportion of subjects with confirmed clearance of plasma CMV DNA (2 consecutive samples separated by at least 5 days with DNA levels < LLOQ (i.e., < 137 IU/mL)) at the end of treatment (Study Week 8).

Key secondary endpoint:

- Confirmed CMV viremia clearance and control of CMV disease symptoms at Study week 8 and maintenance through Study Week 16 (8 weeks off treatment).

Primary analysis population:

- All subjects randomized to the study treatment.

Primary Efficacy Analysis
Confirmed CMV Viremia Clearance at Week 8

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 proportion (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.

Analysis of Failures of Primary Efficacy Endpoint

Outcome at Week 8	Maribavir (N=235) n (%)	IAT (N=117) n (%)
Subjects who met the primary endpoint (CMV DNA < LLOQ)[a]	**131 (56)**	**28 (24)**
Subjects who failed the primary endpoint:	**104 (44)**	**89 (76)**
Due to virologic failure:	**80 (34)**	**42 (36)**
• **CMV DNA never < LLOQ**	48 (20)	35 (30)
• **CMV DNA breakthrough[b]**	32 (14)	7 (6)
Due to drug/study discontinuation:	**21 (9)**	**44 (38)**
• **Adverse events**	8 (3)	26 (22)
• **Deaths**	10 (4)	3 (3)
• **Withdrawal of consent**	1 (< 1)	9 (8)
• **Other reasons[d]**	2 (1)	6 (5)
Due to other reasons but remained on study[d]:	**3 (1)**	**3 (3)**

[a] **LLOQ**=137 IU/mL; [b] **CMV DNA breakthrough** =achieved viral load <LLOQ and subsequently became detectable; [d] **Other reasons**= other reasons not including AEs, deaths deaths and lack of efficacy, withdrawal of consent, and non-compliance; [d] Includes subjects who completed study assigned treatment and were non-responders.

Sensitivity Analyses of the Primary Endpoint

Inclusive of subjects who met the criteria of CMV viremia clearance at the time of early discontinuation

Analysis	Number of Subjects (%)		Risk Difference (95% CI)	Adjusted p-value
	Maribavir N=235 n (%)	IAT N=117 n (%)		
Responders[a]	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 weeks therapy.

Source: Statistics reviewer's analysis

Confirmed CMV viremia clearance at Week 8 regardless of prohibited anti-CMV treatment or maribavir rescue therapy

Analysis	Number of Subjects (%)		Risk Difference (95% CI)	Adjusted p-value
	Maribavir 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 weeks therapy.

Source: Statistics reviewer's analysis

Subgroup Analyses of the Primary Endpoint

Proportion of Responders by Transplant Type

Transplant type	Maribavir 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

Proportion of Responders by Genotypic Resistance to Other Anti-CMV Agents[a]

Genotypic resistance to other anti-CMV agents[b]	Maribavir N=235 n/N (%)	IAT N=117 n/N (%)	Risk Difference (95% CI) Adjusted 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

[a]Ganciclovir, valganciclovir, foscarnet, or cidofovir

[b]Breslow-Day p-value for interaction test=0.02, adjusting for the transplant type and baseline CMV DNA level.

Analysis by Presence of CMV Syndrome or Disease at Baseline

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

Analysis by Baseline Viral Load

Baseline CMV DNA levels (IU/mL)[a]	Maribavir N=235 n(%)	IAT N=117 n(%)
< 5,000[b]	88/132 (67)	18/73 (25)
≥ 5,000 to <20000	26/57 (46)	4/20 (20)
≥ 20,000 to <50,000	10/23 (43)	3/12 (25)
≥ 50,000	7/23 (30)	3/12 (25)

[a] Although a minimum baseline CMV DNA levels ≥ 910 IU/mL was an inclusion criterion, approximately 20% of subjects in each treatment arm had lower levels; [b] Among subjects with baseline CMV DNA levels < 5000 IU/mL, more than 60% in each group had CMV DNA levels < 2000 IU/mL (67% in the maribavir group and 62% in the IAT group).

Virology reviewer's analysis

Confirmed CMV viremia clearance in subjects who received 8 weeks of treatment

CMV Viremia Clearance Response	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 (-7, 27)	
P-value adjusted[a]	0.24	

[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 adjusting for the transplant type and baseline CMV DNA level concentration, as homogeneity was met.

Source: CSR – Table 24

Secondary Efficacy Endpoints Analyses

Secondary Endpoints

Confirmed CMV Viremia Clearance and Control of CMV Disease Symptoms at Study Week 8 and Maintenance Through Week 16*

CMV Viremia Clearance Response	Maribavir N=235 n(%)	IAT N=117 n(%)
Responders at Week 8 with maintenance through Week 16 (8 weeks post-treatment)	44 (19)	12 (10)
Adjusted difference in percentage of responders (95% CI)	9 (2, 17)	
P-value adjusted	0.02	

*Randomized set

Note: Most of the failures in both arms were due to CMV viremia relapses (off treatment); 75% in the maribavir arm and 69% in the IAT arm.

All-cause Mortality and Timing of Deaths

Deaths	Maribavir N=235 n(%)	IAT N=117 n(%)
Reported deaths at any time	27 (11)	13 (11)
Within 8 weeks	14 (6)	5 (4)
Within 20 weeks	25 (11)	11 (9)
After 20 weeks	2 (1)	2 (2)

New Onset Symptomatic CMV Infection

New onset symptomatic CMV disease	Maribavir N=235 n(%)	IAT N=116 n(%)
Reported at any time	14 (6)	7 (6) [a]
Within 8 weeks	7 (3)	5 (4)
Within 16 weeks	13 (6)	7 (6)
Within 20 weeks	14 (6)	7 (6)

[a] One subject had two episodes of new onset symptomatic CMV infection both between Week 8 and Week 16

Phase 2 Trial: 202

Trial Design

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.

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

Primary efficacy results

Confirmed Undetectable Plasma CMV DNA Within 6 Weeks (ITT-S Population)

	Maribavir 400 mg BID N=40 n(%)	Maribavir 800 mg BID N=40 n(%)	Maribavir 1200 mg BID N=40 n(%)	Maribavir All doses N=120 n(%)
Subjects with confirmed undetectable plasma CMV DNA				
Yes	28 (70)	25 (63)	27 (68)	80 (67)
No	12 (30)	15 (36)	11 (28)	38 (32)
Subjects with missing data, n (%)	0	0	2 (5)	2 (2)

Comments:

- No appreciable differences in safety among the three treatment groups
- Significant rate (35%) of CMV viremia breakthrough (on treatment) or relapse (off treatment)

Virology

Maribavir

- Inhibits the protein kinase activity of human CMV enzyme pUL97, which results in inhibition of the phosphorylation of proteins.
- Resistance to maribavir occurs as a result of substitutions in pUL97 and pUL27 (nuclear protein of unknown function).
- Resistance to vGCV/GCV occurs as a result of substitutions in pUL97 and pUL54 (DNA polymerase).
- Cross-resistance can occur between vGCV/GCV and maribavir due to substitutions in pUL97.

vGCV/GCV Resistance Substitutions Conferring Reduced Susceptibility to Maribavir

pUL97	Fold Shift in Susceptibility to GCV	Fold Shift in Susceptibility to MBV
F342S	7.8	18
K355del	16	304
V356G	5.5	108
D456N	12	278
V466G	11	321
C480R	9	243
P521L	17	428–445
Y617del	10	372

Expected to impact maribavir treatment

pUL97	Fold Shift in Susceptibility to GCV	Fold Shift in Susceptibility to MBV
M460V	5.5-7.2	0.4
H520Q	5.2	1.6
C592G	3.9	1.3
A594V	5.8-10.4	1.6-2.1
L595S	5.8-8.6	1.7-2.5

Not expected to impact maribavir treatment

Maribavir Resistance Substitutions and Cross-resistance with vGCV/GCV

pUL97	Fold Shift in Susceptibility to MBV	Fold Shift in Susceptibility to GCV
F342Y*	4.5	6.0
C480F*	224	2.3

Maribavir resistance-associated substitutions expected to confer cross-resistance to vGCV/GCV
*RAS emerged in virologic failures after maribavir treatment in Phase 2 and/or Phase 3 studies.

pUL97	Fold Shift in Susceptibility to MBV	Fold Shift in Susceptibility to GCV
L337M	3.4–3.5	1.02
V353A	10-16	1.0–1.5
L397R	>200	1.6
T409M*	81	0.9
H411L*	69	0.7
H411N*	9	1.0
H411Y*	12	0.5

Maribavir resistance-associated substitutions not expected to confer cross-resistance to vGCV/GCV
*RAS emerged in virologic failures after maribavir treatment in Phase 2 and/or Phase 3 studies.

Summary of Efficacy Based on Baseline vGCV/GCV RAS - Trial 303 (Cross-resistance)

- The presence of known vGCV/GCV pUL97 resistance-associated substitutions M460I/V, H520Q, C592G, A594S/V, L595F/S, and C603W did not appear to have a significant impact on the efficacy of maribavir.
- Maribavir efficacy was lower in those with the pUL97 A594P (40%; 2/5)/T(33.3%; 1/3), L595W (0%; 0/2), or del 597-599 (0%; 0/2); note the numbers were small. Furthermore, we do not have the shift(s) in susceptibility to maribavir for these substitutions.

Summary of Efficacy Based on Baseline vGCV/GCV RAS Trial 303 (Cross-resistance)

- Subjects with vGCV substitutions conferring <2.5-fold reduction in susceptibility to maribavir responded to maribavir therapy
- The reductions in susceptibility for maribavir treatment-emergent resistance-associated substitutions range from 4.5-81.
- These ranges indicate that the minimum fold-shift for maribavir associated with treatment failure due to cross-resistance is in the 2.6-4.5 fold-change 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).
- Of note, there was one subject who had the pUL27 L193F maribavir resistance-associated substitution (2.6-fold reduced susceptibility to maribavir) at baseline. This subject did not meet the primary endpoint.

Substitution pUL97 F342Y Is a Maribavir and vGCV/GCV RAS Trial 303 (Cross-resistance)

- The pUL97 F342Y substitution emerged in vGCV/GCV treatment failures and is selected clinically by maribavir. It confers 4.5-fold and 6.0-fold reduced susceptibility to maribavir and vGCV/GCV, respectively.
- F342Y emerged in 3 subjects who failed maribavir treatment in study 303.
- Three subjects in study 303 had the pUL97 F342Y substitution at baseline. All 3 subjects were initially in the IAT arm. One subject was rolled-over to the maribavir rescue arm. This subject also failed maribavir rescue treatment.
- Additionally, there was one subject in study SHP620-202 who had the pUL97 F342Y substitution at baseline. This subject failed to meet the primary endpoint.

Virologic Response at Week 8 in Trial 303

	MBV % (n/N)	IAT % (n/N)
Viral load <LLOQ at Week 8	56 (131/235)	24 (28/117)
Virologic Failure (>LLOQ at Week 8)	36 (84/235)	44 (51/117)
Other (e.g. discontinuation)	7 (17/235)	30 (35/117)
< 4 day treatment	1 (3/235)	3 (3/117)

- Amongst the 84 virologic failures in the maribavir arm, the applicant provided 76 paired sequences. 62% (47/76) had one or more pUL97 treatment-emergent maribavir RAS. Of note, 47% (22/47) had maribavir RAS that were cross-resistant to GCV.
- In the maribavir arm, 36% (84/235) of treatment failures were virologic failures and 9% (20/235) failed for other reasons.
- By comparison, 44% (51/117) of treatment failures in the IAT arm were virologic failures and 32% (38/117) failed for other reasons (e.g. discontinuation).

Relapse in Subjects Who Were <LLOQ at Week 8 in Trial 303

	MBV % (n/N)	IAT % (n/N)
Viral Load <LLOQ at Week 8	56 (131/235)	24 (28/117)
Relapse post-treatment	50 (65/131)	39 (11/28)
% of Relapsers at Wk 9	40 (26/65)	18 (2/11)
% of Relapsers at Wk 10	25 (16/65)	36 (4/11)
% of Relapsers at Wk 11	20 (13/65)	36 (4/11)
% of Relapsers at Wk 12	5 (3/65)	9 (1/11)
% of Relapsers at Wk 14	3 (2/65)	0 (0/11)
% of Relapsers at Wk 16	6 (4/65)	0 (0/11)
% of Relapsers at Wk 18	2 (1/65)	0 (0/11)

- Most of the relapses occurred during the first 2 weeks off treatment.
- Applicant provided 48 paired sequences amongst the subjects who experienced a relapse. 23% (11/48) had a treatment-emergent maribavir RAS. Of note, 9% (1/11) had maribavir RAS that is cross-resistant to GCV.

Safety

Trial 303: Treatment-emergent AEs During the On-treatment Period

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 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

Adverse Events (all grades) Reported in > 10% in the Maribavir Treatment Group

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

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

Most Common Adverse Events Leading to Permanent Discontinuation of Study Drug

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	4 (2)	3 (3)

Source: CSR –Table 45

Selected Laboratory Abnormalities

Laboratory test	Maribavir N=234 n (%)	IAT N=116 n (%)
Neutrophils (cells /µL)		
< 500	4 (2)	4 (3)
≥ 500 to < 750	7 (3)	7 (6)
≥ 750 to < 1000	10 (4)	6 (5)
Hemoglobin (g/dL)		
< 6.5	3 (1)	1 (1)
≥ 6.5 < 8.0	34 (15)	23 (20)
≥ 8.0 to < 9.5	76 (32)	33 (28)
Platelets (cells /µL)		
< 25000	11 (5)	6 (5)
≥ 25000 to < 50000	27 (12)	10 (9)
≥ 50000 to < 100000	41 (18)	20 (17)
Creatinine (mg/dL)		
> 2.5	16 (7)	12 (10)
> 1.5 to ≤ 2.5	78 (33)	29 (25)

Summary for Trial 303

- **Strengths**
  - Statistically significant treatment effect for maribavir vs. IAT for primary endpoint
  - Sensitivity analyses support primary endpoint
  - Taste disturbance was the most common adverse reaction, but treatment discontinuation due to this event was infrequent

- **Limitations**
  - Open-label design
    - — Potential bias resulting in imbalance in drug/study discontinuations due to AEs, withdrawal of consent or other reasons
    - — Overall treatment effect due to drug/study discontinuation; proportion of virologic failures similar in both arms

Summary
Trial 202 in Resistant/Refractory CMV

- **Strengths**
  - Similar antiviral activity shown with maribavir in the same population (resistant/refractory) as compared to phase 3 trial, 303
  - Similar maribavir safety profile compared to trial 303.
- **Limitations**
  - No comparator arm
  - No dose response was demonstrated
  - Baseline resistance was poorly defined (cannot differentiate resistant or refractory for most subjects)

CONCLUSIONS

CONCLUSIONS

- Trial 303 demonstrated that maribavir was statistically superior to IAT in primary endpoint analysis (56% vs. 24%).
- Sensitivity analyses supported superiority of maribavir over IAT for the primary efficacy endpoint
- Study was limited by open-label design and potential bias
- Analysis of failures for the primary efficacy endpoint demonstrated that virologic failure rates were similar in both arms (34% vs. 36%)
- Overall treatment effect was influenced by imbalance in drug/study discontinuation (13% vs. 32%)
- The treatment effect was consistent across transplant type, age groups, and CMV syndrome/disease at baseline

CONCLUSIONS (continued)

- The treatment effect was lower in subjects without genotypic resistance (refractory CMV) (44% vs. 32%)
- Primary efficacy endpoint results in the maribavir arm were mainly driven by subjects with baseline CMV DNA levels < 5,000 IU/mL; there was an inverse relationship between maribavir efficacy and baseline CMV DNA level
- No difference in mortality or new onset of symptomatic CMV disease
- High rate of maribavir resistance among the on-treatment virologic failures (62%) many of these confer cross resistance to ganciclovir/valganciclovir (47%)
- Relapse (off-treatment) was observed in both arms (50% vs. 39%)

ACKNOWLEDGEMENTS

CHARGE TO THE COMMITTEE

Backup Slides Shown

Trial 303: Grade 3 and Grade 4 of selected laboratory abnormalities

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)	24 (21)
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

Trial 303: Shifts of 3 grades and 4 grades of selected laboratory abnormalities

Laboratory test	Maribavir (N=234) n (%)	IAT (N=116) n (%)
Neutrophils decreased		
Three grades shift	10 (4)	11 (9)
Four grades shift	2 (1)	0
Hemoglobin decreased		
Three grades shift	0	2 (2)
Four grades shift	0	0
Platelets decreased		
Three grades shift	2 (1)	1 (1)
Four grades shift	2 (1)	0
Creatinine increased		
Three grades shift	3 (1)	0
Four grades shift	0	0


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