Errata to the FDA Briefing Document for October 7, 2021 Antimicrobial Drugs Advisory Committee Meeting

Corrections:

1. On page 9, the Title, **Phase 3 Trial SHP620-303 (303),** should read:
   a. **Phase 3 Trial SHP620-303 (303)**

2. On page 11, the second paragraph currently reads:
   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).

   This paragraph should read:

   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 Study Week 8 (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).

3. On page 15, **Table 3** should be replaced with 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 virologic failure:**	**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:**	**21 (9)**	**44 (38)**
o Adverse events	8 (3)	26 (22)
o Deaths	10 (4)	3 (3)
o Withdrawal of consent	1 (<1)	9 (8)
o Other reasons[c]	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; [c] Other reasons=other reasons not including adverse events, deaths, non-compliance, and withdrawal of consent; [d] Includes subjects who completed study assigned treatment and were non-responders.

4. On page 15, the text below Table 3 currently reads:
   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.

   This paragraph should read:

   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, were more frequent in the IAT arm (22% in IAT arm and 3% 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.

5. On page 16, Table 5 should be replaced with the following table:

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.

6. On page 18, Table 8 should be replaced with the following table:

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

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

[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.
[c] In a small number of subjects genotypic analysis of the target genes was not successful due to possible polymorphism(s) within one of the primer binding sites, an insufficient viral load, or PCR inhibitors in the sample.

7. On page 18, the paragraph prior to Table 9 currently reads:

   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.

   This paragraph should read:

   Subgroup analysis based on baseline CMV DNA levels showed that the higher the CMV DNA levels, the lower the efficacy of maribavir. The results were mainly driven by subjects with CMV DNA levels < 5,000 IU/mL. These subjects had a response rate of 67% and accounted for 56% of the randomized subjects in the maribavir group (Table 9).

8. On page 18, **Table 9** should be replaced with the following table:

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

Baseline CMV DNA levels (IU/mL) [a]	Maribavir N=235 n/N (%)	IAT N=117 n/N (%)
< 5,000	88/132 (67)	18/73 (25)
≥5,000 to < 20,000	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 viral load ≥ 910 IU/mL was an inclusion criterion, approximately 20% of subjects in each treatment arm had lower levels.

9. On page 19, Table 11 should be replaced with the following table:

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

CMV viremia clearance	**Maribavir 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]	9 (2, 17)	
P-value: adjusted[a]	0.02	

[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.

10. On page 21, control should be replaced by IAT in the first paragraph.

11. On page 22, text under "Study 303: Treatment-emergent resistance analysis" should be read as follows:

Study 303: Treatment-emergent resistance analysis

There were 196 total paired sequences (n=134 and 62 in the maribavir and IAT arms, respectively) for the treatment-emergent resistance analysis. Among these paired sequences, 77 and 47 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=58 subjects): F342Y [n=3; 4.5-fold reduction in susceptibility to maribavir], T409M [n=29; 81-fold reduction], H411L [n=1; 69-fold reduction], H411N [n=2; 9-fold reduction], H411Y [n=24; 12-fold reduction], and C480F [n=20; 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, 196 paired sequences (134 and 62 in the maribavir and IAT arms, respectively) were available for the treatment-emergent resistance analysis. Among the 134 virologic failures in the maribavir arm, 58 had one or more of the treatment-emergent pUL97 maribavir resistance-associated substitutions. Among the 58, 19 subjects had two or more maribavir resistance-associated substitutions (pUL97 F342Y+H411Y [n=1], pUL97 F342Y+T409M+H411N [n=1], pUL97 H411Y+C480F [n=2], pUL97 H411L+C480F [n=1], pUL97 T409M+C480F [n=6], and pUL97 T409M+H411Y [n=8]). Of note, 47 of these were observed in subjects who had on-treatment failure while only 11 were from subjects 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.

12. On page 25, the Title, **Phase 2 trial 202**, should read:

    b. Phase 2 Trial, SHP620-202 (202)

13. On page 30, the Title**, "3. Overall Summary"**, should read:

    4. Overall Summary

14. On page 31, the section, **4. Points for Advisory Committee Consideration,** has been updated and should read:

5. Points for Advisory Committee Consideration

1) 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, foscarnet or cidofovir?

   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 transplant recipients with CMV infection and disease refractory to treatment but without genotypic resistance to ganciclovir, valganciclovir, foscarnet or cidofovir?

   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.

15. On page 33, the Title, **References**, should read:

6. References