ERRATA to FDA Briefing Document
Cardiovascular and Renal Drugs Advisory Committee Meeting
NDA 22231 (Terlipressin)
July 15, 2020

On June 30, 2020, the Applicant informed FDA of slight differences between the Applicant's analyses and FDA's analyses in the number of subjects in which HRS recurrence could not be excluded, for both the overall population and in the subset of subjects who did not receive a liver transplant. Per the Applicant, there were subjects who were counted as having "verified HRS reversal" per the Case Report Form variable but who did not meet the statistically programmed verified HRS reversal primary endpoint. The analyses below have been recalculated with those subjects removed; the changes are highlighted in yellow.

1. Section 2.2.2. Analysis of Secondary Endpoints, page 21

   "The SAP also prespecified a sensitivity analysis on the secondary endpoint of incidence of verified HRS reversal without HRS recurrence by Day 30 in which all subjects where the investigator could not exclude a recurrence of HRS-1 were treated as having a recurrence (five subjects on terlipressin, zero subjects on placebo). The results were consistent with the results of the corresponding secondary endpoint (22% terlipressin versus 16% placebo, p=0.163)."

   Text should read:
   "The SAP also prespecified a sensitivity analysis on the secondary endpoint of incidence of verified HRS reversal without HRS recurrence by Day 30 in which all subjects where the investigator could not exclude a recurrence of HRS-1 were treated as having a recurrence (three subjects on terlipressin, zero subjects on placebo). The results were consistent with the results of the corresponding secondary endpoint (45/199 (23%) terlipressin versus 16/101 (16%) placebo, p=0.163)."

2. Section 2.3.2. Analyses to Address Durability of Treatment Effect, page 30

   "The clinical protocol prespecified criteria for determination of HRS recurrence by the investigator (see Section 5 in the Appendix of this document for details). Review of the clinical protocol and study report revealed that HRS recurrence was adequately captured during the study. Of the 58 subjects on terlipressin who met the primary endpoint of verified HRS reversal, 10 subjects (17%) met the prespecified criteria for HRS recurrence by Day 30, and HRS recurrence could not be excluded for five subjects (9%). Hence, the proportion of subjects with HRS recurrence may have been as high as 26% in the terlipressin group. None of the 16 placebo arm subjects who met the primary endpoint of verified HRS reversal met criteria for HRS recurrence by Day 30 (see table below)."

Table 1. HRS Recurrence in Subjects With Verified HRS Reversal

n (%)	Terlipressin N=58	Placebo N=16
Met criteria for HRS recurrence by Day 30[1]	10 (17)	0 (0)
Could not exclude HRS recurrence	5 (9)	0 (0)

Source: FDA analysis
[1] HRS recurrence defined as: rapidly progressive worsening in renal function to a SCr at least 2.25 mg/dL and meeting a trajectory for SCr to double over 2 weeks and without sustained improvement in renal function (<20% decrease in SCr and SCr at least 2.25 mg/dL) at least 48 hours after diuretic withdrawal and the beginning of plasma volume expansion with albumin
Abbreviations: HRS, hepatorenal syndrome; SCr, serum creatinine

Text should read:

"The clinical protocol prespecified criteria for determination of HRS recurrence by the investigator (see Section 5 in the Appendix of this document for details). Review of the clinical protocol and study report revealed that HRS recurrence was adequately captured during the study. Of the 58 subjects on terlipressin who met the primary endpoint of verified HRS reversal, 10 subjects (17%) met the prespecified criteria for HRS recurrence by Day 30, and HRS recurrence could not be excluded for three subjects (5%). Hence, the proportion of subjects with HRS recurrence may have been as high as 22% in the terlipressin group. None of the 16 placebo arm subjects who met the primary endpoint of verified HRS reversal met criteria for HRS recurrence by Day 30 (see table below)."

Table 2. HRS Recurrence in Subjects With Verified HRS Reversal

n (%)	Terlipressin N=58	Placebo N=16
Met criteria for HRS recurrence by Day 30[1]	10 (17)	0 (0)
Could not exclude HRS recurrence	3 (5)	0 (0)

Source: FDA analysis
[1] HRS recurrence defined as: rapidly progressive worsening in renal function to a SCr at least 2.25 mg/dL and meeting a trajectory for SCr to double over 2 weeks and without sustained improvement in renal function (<20% decrease in SCr and SCr at least 2.25 mg/dL) at least 48 hours after diuretic withdrawal and the beginning of plasma volume expansion with albumin
Abbreviations: HRS, hepatorenal syndrome; SCr, serum creatinine

3. Section 2.3.2. Analyses to Address Durability of Treatment Effect, page 30

"Of the 44 subjects on terlipressin who met the primary endpoint of verified HRS reversal and did not receive a liver transplant, 10 subjects (23%) either met the prespecified criteria for HRS recurrence by Day 30 or HRS recurrence could not be excluded in those subjects. None of the 11 placebo arm subjects met criteria for HRS recurrence by Day 30 (see Table 18)."

Table 3. HRS Recurrence in Subjects With Verified HRS Reversal in Subpopulation of Subjects Who Did Not Receive a Liver Transplant

n (%)	Terlipressin N=44	Placebo N=11
HRS recurrence by Day 30 (or could not exclude HRS recurrence)	10 (23)	0 (0)

Source: FDA analysis
Abbreviation: HRS, hepatorenal syndrome

Text should read:

"Of the 44 subjects on terlipressin who met the primary endpoint of verified HRS reversal and did not receive a liver transplant, 8 subjects (18%) either met the prespecified criteria for HRS recurrence by Day 30 or HRS recurrence could not be excluded in those subjects. None of the 11 placebo arm subjects met criteria for HRS recurrence by Day 30 (see Table 18)."

Table 4. HRS Recurrence in Subjects With Verified HRS Reversal in Subpopulation of Subjects Who Did Not Receive a Liver Transplant

n (%)	Terlipressin N=44	Placebo N=11
HRS recurrence by Day 30 (or could not exclude HRS recurrence)	8 (18)	0 (0)

Source: FDA analysis
Abbreviation: HRS, hepatorenal syndrome