ERRATA to FDA Briefing Document
Cardiovascular and Renal Drugs Advisory Committee Meeting
Supplemental new drug application (sNDA) 207620-S18
December 15, 2020

1. **Sections 1, 2, 5, 6.2.4, 7.1**

   Investigator-reported primary and expanded primary composite endpoints are described as post-hoc exploratory analyses.

   The investigator-reported endpoints should be described as follows:

   The investigator-reported endpoint analyses were not specifically listed as exploratory objectives in PARAGON-HF. These analyses were conducted as supplementary/sensitivity analyses and were pre-specified in the statistical analysis plan (SAP). Specifically, the SAP section 9 titled "efficacy evaluation" states that, "o*nly adjudicated and confirmed events will be counted in the primary and secondary analyses. Event information received after the analysis cut-off date will not be included in the primary and secondary efficacy analyses, but they will be included in the investigator reported event analysis*.....*In the analysis, as specified before, only adjudicated events will be utilized if the events included in the analysis are required to be adjudicated. However, in the sensitivity analysis, the investigator reported events may also be used*."

2. **Section 4**

   Sacubitril/valsartan was approved to treat patients with HFrEF based on the PARADIGM-HF study that demonstrated superiority of sacubitril/valsartan 200 mg bid compared to enalapril 10 mg bid in symptomatic patients with HFrEF, defined as HF with LVEF ≤ 40%, changed to ≤ 35% by Protocol Amendment 1 (N 8,442) in reducing the incidence of CV death and HHF.

   Text should read

   Sacubitril/valsartan was approved to treat patients with HFrEF based on the PARADIGM-HF trial. PARADIGM-HF demonstrated superiority of sacubitril/valsartan 200 mg bid compared to enalapril 10 mg bid in symptomatic patients with HFrEF (n=8399) in reducing the incidence of CV death and HHF. In PARADIGM-HF, HFrEF was initially defined as HF with LVEF ≤ 40% and later changed to ≤ 35% by Protocol Amendment 1. Protocol Amendment 1 dated December 15, 2010 was issued after accrual of 39 (1.9%) total primary endpoint events. PARADIGM-HF was initiated on December 8, 2009 and as of December 10, 2010, 1285 patients had been randomized. Based on meeting minutes from the Executive Committee of PARADIGM-HF trial, two reasons for reducing the LVEF criterion to $\underline{\leq}$ 35% were: 1) Patient characteristics whose screening LVEFs were between 35% and 40% appeared to be more similar to patients characterized as HFpEF, compared to those with an LVEF < 30% that had HFrEF. This raised the concern of "EF creep"; and 2) Use of aldosterone antagonists was anticipated to increase over the course of the trial

based on newly published results (EMPHASIS-HF)[1] at that time. This amendment was designed to ensure an adequate accumulation primary endpoint events (CV death and HHF).

3. Sections 5 and 6.2.4

A time to first event analysis of CEC-confirmed HHF demonstrated that the incidence of HHF was 405/2407 (16.83%) versus 433/2389 (18.12%) in the sacubitril/valsartan and valsartan arms, respectively. The HR was 0.90; 95% CI: 0.79, 1.04; p = 0.19. Figure 5 displays the Kaplan-Meier plot of time to first CEC-confirmed HHF in PARAGON-HF.

Additional description of time to first event analyses is as follows:

Note that the p-value of 0.19 is based on log-rank test and p-value of 0.1457 in Figure 5 is based on Cox-regression model.

As PARAGON-HF failed to reject the null hypothesis, p-values for secondary, exploratory, post-hoc or sensitivity analyses are difficult to interpret. Hence, details of methodologies used to analyze various endpoints are discussed only when relevant to the issue(s) under consideration.

4. Section 6.2.3

A total of 12 (0.50%) and 14 (0.58%) patients in sacubitril/valsartan and valsartan arms, respectively were excluded from the full analysis set because of protocol deviations for GCP reasons (drug supply issues).

The text should read:

A total of 12 (0.50%) and 14 (0.58%) patients in sacubitril/valsartan and valsartan arms, respectively were excluded from the full analysis set because of significant GCP deviations, which affected data integrity, not due to drug supply issues.

[1] Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011 Jan 6;364(1):11-21. doi: 10.1056/NEJMoa1009492. Epub 2010 Nov 14. PMID: 21073363.

5. **Section 6.2.5**

Table 10. Endpoint Results for First Events in PARAGON-HF

	Events/N Sacubitril/valsartan	Valsartan	HR (95% CI)
Primary Composite	526 / 2407	557 / 2389	0.92 (0.81, 1.03)
CV Death	204 / 2407	212 / 2389	0.95 (0.79, 1.16)
HHF	405 / 2407	433 / 2389	0.90 (0.79, 1.04)
HHF or Urgent HF Visit	422 / 2407	462 / 2389	0.88 (0.77, 1.00)
Expanded Composite	542 / 2407	585 / 2389	0.90 (0.80, 1.01)
Inv. Reported Primary	587 / 2407	624 / 2389	0.91 (0.81, 1.02)
Inv. Reported HHF	587 / 2407	624 / 2389	0.91 (0.81, 1.02)
Inv. Reported HHF or Visit	573 / 2407	620 / 2389	0.88 (0.79, 0.99)
Inv. Reported Expanded Composite	573 / 2407	620 / 2389	0.88 (0.79, 0.99)

Corrected Table 10 is as follows:

	Events/N Sacubitril/Valsartan	Valsartan	HR (95% CI)
Primary Composite	526 / 2407	557 / 2389	0.92 (0.81, 1.03)
CV Death	204 / 2407	212 / 2389	0.95 (0.79, 1.16)
HHF	405 / 2407	433 / 2389	0.90 (0.79, 1.04)
HHF or Urgent HF Visit	422 / 2407	462 / 2389	0.88 (0.77, 1.00)
Expanded Composite	542 / 2407	585 / 2389	0.90 (0.80, 1.01)
Inv. Reported Primary	587 / 2407	624 / 2389	0.91 (0.81, 1.02)
Inv. Reported HHF	515 / 2407	550 / 2389	0.90 (0.80, 1.02)
Inv. Reported HHF or Urgent HF Visit	573 / 2407	620 / 2389	0.88 (0.79, 0.99)
Inv. Reported Expanded Composite	641 / 2407	692 / 2389	0.89 (0.80, 0.99)

6. **Section 7.2**

Table 14 and Figure 10 display the distribution of patients by treatment arm by LVEF categories in full analysis set in PARAGON-HF.

Clarification

The LVEF categories are displayed in increments of 5. Each category is inclusive of the upper range number, for example LVEF category of 45-50 includes patients with LVEF >45 and ≤50.

7. **Section 7.2**

In PARAGON-HF, 70% (3371/4796) of the patients had an LVEF of < 60%.

Text should read:

In PARAGON-HF, 70% (3371/4796) of the patients had an LVEF of ≤ 60%.

8. Conclusion

In PARAGON-HF, 70% of the patients had an LVEF < 60% (Table 14), which is considered to be a reduced LVEF by echocardiography.

Text should read:

In PARAGON-HF, 25 and 46% of the patients had an LVEF ≤ 50 and 55%, respectively (Table 14) which may be considered reduced LVEF by echocardiography, depending on gender.