FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Cardiovascular and Renal Drugs Advisory Committee (CRDAC) Meeting
December 15, 2020

QUESTIONS

The study supporting this indication is PARAGON-HF, but this study did not meet its prespecified success criterion for the primary endpoint. Approval under this circumstance is unusual but not unprecedented. Some examples are:

- Enalapril was approved for use in asymptomatic left ventricular dysfunction on the basis of SOLVD-Prevention.
- Digoxin was approved for heart failure on the basis of the DIG study.
- Carvedilol was approved for reduced ejection fraction following myocardial infarction on the basis of the CAPRICORN study.
- Bivalirudin was approved for use after percutaneous coronary intervention on the basis of the post-hoc pooling of the BAT studies.

Like the current case, all of the above involved new indications for approved drugs for relatively common cardiovascular diseases, but the extenuating circumstances were different. For PARAGON-HF, the p-value is only slightly above the 0.05 target. The Division encouraged the applicant to submit the supplementary application for the heart failure with preserved ejection fraction (HFpEF) indication and suggested some of the post-hoc analyses. PARAGON-HF illustrates two issues of long-standing interest to the Division.

- The value of adjudication is questionable in a blinded study with appropriate investigator expertise. In this case, the investigator-determined and adjudicator findings were virtually identical with respect to their risk ratios; inclusion of additional investigator-determined events resulted in a smaller confidence interval and, had the approach been prospectively planned, would have yielded a p-value < 0.05.
- The typical approach in the adjudication of events in cardiovascular trials (followed in PARAGON-HF) is to dichotomize (yes/no) them based on prospectively planned definitions. Regardless of who calls events—investigator or committee—this dichotomization wastes information. Use of strict, narrow definitions will declare "events" with a high degree of confidence, but many cases are adjudicated negatively because of a lack of information (e.g., requirement for the presence of physical examination findings that are not documented in the patient's dossier), or because of alternative practices, and one can be, to varying degrees, confident about them, too. Thus, there is a hierarchy of evidence in favor of the occurrence of an "event." We favor giving "partial credit" to events based on the level of evidence provided, rather than a dichotomous "yes" or "no."

The finding in PARAGON-HF seems mostly driven by subjects with ejection fraction towards the lower end of the range studied, i.e., closer to the range for patients with heart failure with reduced ejection fraction (HFrEF). Had this been anticipated, one could have argued for an alpha level above 0.05 for PARAGON-HF, supported by the data from PARADIGM-HF showing benefit in patients with more reduced ejection fraction. Retrospectively, that still seems relevant.

QUESTIONS (cont.)

1. **DISCUSSION**: Please comment on the various pre-specified and post-hoc analyses. Which ones contribute to the strength of evidence supporting an indication? Which ones do not?

2. **VOTE**: Does PARAGON-HF, perhaps supported by previous studies, provide sufficient evidence to support ANY indication?

3. **DISCUSSION**: If an indication for ENTRESTO were not granted on the basis of available information, what would be necessary to augment the support for approval?

4. **DISCUSSION**: If ENTRESTO warranted an indication, how would you describe the patients in whom such benefit applies?