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

Cardiovascular and Renal Drugs Advisory Committee (CRDAC) Meeting
December 16, 2020

QUESTIONS

The study supporting this indication is TOPCAT, 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 for heart failure was approved 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 PCI 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. In TOPCAT, there are reasons to question the applicability of results obtained in some parts of the world. Although not detailed in the review, the review team devoted a considerable effort to look for criteria for the inclusion or exclusion of sites based on baseline data; none seem as compelling as "region."

Although exclusion of a region is exceptional, exclusion of a site is not rare, and this approach has been taken when there have been good reasons to question the validity of the data from a site.

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 the TOPCAT trial provide sufficient evidence to support ANY indication?

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

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