HFSA
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August 27, 2019

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

RE: Docket Number 2019-13800 ; Treatment for Heart Failure: Endpoints for Drug Development, Draft Guidance for Industry

To Whom it May Concern:

The Heart Failure Society of America (HFSA) appreciates the opportunity to comment on the *Food and Drug Administration's (FDA) Draft Guidance for Industry on Treatment for Heart Failure: Endpoints for Drug Development*. HFSA is a multidisciplinary organization working to improve and expand heart failure care through collaboration, education, research, innovation, and advocacy.

HFSA commends the FDA for the approach taken in this draft guidance, recognizing that an effect on symptoms or physical function, with or without a favorable effect on survival or risk of hospitalization, can be a basis for approving drugs to treat heart failure. We believe it is paramount for FDA to ensure the safety of all drugs brought to market. We also believe that, since heart failure is a clinical diagnosis, there is a need for increased consideration of patient-centered metrics such as physical function and quality of life when evaluating the efficacy of pharmacologic therapies. In the following paragraphs, we will try to emphasize the salient considerations regarding end points.

Patient Reported Outcomes (PROs)

Patients' family and providers value improvement in symptoms, functional capacity and activities of daily living and quality of life. Patients with advanced heart failure symptoms and poor prognosis may even consider trading off survival for improvement in symptoms, quality of life and/or function. HFSA supports consideration of validated measures of symptoms, activities of daily living and quality of life, functional capacity measured by the 6 min walk distance, and New York Heart Association functional class as end-points. Specific end-points may depend on the characteristics of the target population and mechanism of the drug. Below we examine three scenarios where these measures could be complementary to mortality and hospitalization outcomes or be stand-alone measures.

1. PRO Improved and Mortality/Morbidity Improved: Demonstration of efficacy in patient reported outcomes with safety and/or efficacy in mortality and or hospitalizations: These measures could be complementary, i.e. in addition to clinical end-points of mortality and hospitalization, when a treatment is considered for lower risk patients with lesser symptom burden and good life expectancy. A combined end-point for such approach would be as an example "days alive, outside the hospital and emergency setting and functional".

2. PRO Improved and Mortality/Morbidity Neutral: Demonstration of efficacy in patient reported outcomes with and established short-term safety, but not efficacy in terms of decreased mortality and or hospitalizations: These measures could be considered for approval in PROs, without the necessity to demonstrate safety or efficacy in mortality and or hospitalizations, especially when therapy is considered for higher risk patients with greater symptom burden and shorter life expectancy.
3. PRO Improved and Mortality/Morbidity Increased: Demonstration of strong efficacy in patient reported outcomes alone with evidence for worsening mortality and hospitalization. These measures could be stand-alone, especially when therapy is considered for sub-group of patients with high symptom burden and limited life expectancy. Shared decision making will likely be needed for such patients.

If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is mild to moderately increased, and the overall risk-benefit analysis supports approval, a post-marketing real-world evidence may be necessary to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is small. If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is small and the overall risk-benefit analysis supports approval, a post-market cardiovascular trial generally may not be necessary.

Mortality and Morbidity

- Cause specific mortality: heart failure studies with favorable outcomes regarding all-cause mortality usually demonstrate improvement in cardiovascular death combined with heart failure hospitalizations. It is also important to note that heart failure studies which did not reach statistical significance for the primary end-point of all-cause mortality may have reached significance for cardiovascular death combined with recurrent heart failure hospitalizations. Recently, diabetes trials with SGLT-2 inhibitors demonstrate reductions in cardiovascular death and heart failure hospitalizations. Thus, cardiovascular mortality combined with heart failure hospitalizations appears to provide adequate power for efficacy in most heart failure trials.

- All-cause mortality: We recognize that in studies where off target effects regarding safety maybe of concern, all-cause mortality may be important.

- We would like to also emphasize that time to first hospitalization should not be considered equivalent to time to death.

Hospitalizations

- We recommend consideration “days alive and outside the hospital and or emergency setting” as a preferred end-point versus the hospitalization rate. Alternatively, measures such as annualized hospital days may be considered. We recognize the challenges in end-point of hospitalizations due to differences in incident versus recurrent hospitalizations, observation stay, urgent care and emergency room visits, length of stay, and mortality. Therefore, we believe days alive and outside the hospital and emergency setting (ER or urgent care) may be the preferred metric.

- Heart failure or cardiovascular specific hospitalizations, emergency care visits, outpatient IV diuretics as a composite are preferred to all-cause hospitalization encounters. We believe, due to the burden of recurrent heart failure hospitalizations or emergency care visits, in patients with heart failure with reduced ejection fraction, differences in heart failure hospitalizations and emergency /urgent care visits, rather than all-cause hospitalizations would be more likely to demonstrate the effectiveness of heart failure therapies. Due to the burden of non-heart failure hospitalizations with comorbidities, in patients with heart failure with preserved ejection fraction, all-cause hospitalizations may be considered as a secondary outcome in addition to heart failure or cardiovascular hospitalizations.

- Recurrent hospitalization: In populations where adherence is not a major problem, recurrent event analysis with recurrent heart failure hospitalizations may help achieve higher event rates and associated power for analysis compared with using a binary readmission outcome (yes/no). It should be kept in mind that patients with recurrent hospitalization may represent a higher-risk group with clustering of comorbidities and or social barriers and with lower disease modifiability. More data and experience should be collected and analyzed.

Adjudication

We recognize the challenges in end-point adjudication and recommend a central end-points committee when cause specific end-points are utilized, when competing diagnoses are very likely, when safety is of concern.

We also recognize the challenges in diagnosis and classification of heart failure, especially heart failure with preserved ejection fraction, specific cardiomyopathies, cardiomyopathy due to systemic illnesses; or assessment of PROs in patients with heart failure and comorbidities such as chronic kidney disease, obesity, lung disease, atrial fibrillation.

Thank you for your consideration of these comments. If you have any questions or require additional information, please contact John Barnes, HFSA CEO, at jbarnes@hfsa.org.

Sincerely,

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