HEART FAILURE TRIALISTS WORKSHOP
Learning from Recent Trials and Shaping the Future of Heart Failure

Japanese Regulatory Viewpoint

Yuki ANDO
Senior Scientist for Biostatistics
Biostatistics Group/Center for Product Evaluation
Pharmaceuticals and Medical Devices Agency
Disclosure & Disclaimer

• Disclosure
  – I have no potential conflicts of interest to report.

• Disclaimer
  – This is not an official PMDA guidance or policy statement.
  – No official support or endorsement by the PMDA is intended or should be inferred.
Clinical development in Japan

• Transition of Japanese drug development
  – From: domestic clinical development in Japan
  – To: global drug development

• Three major types of clinical development strategies in Japan or multiple countries including Japan
  – Single-country development
  – Bridging development to which foreign clinical trial data are extrapolated
  – Global development with confirmatory global clinical trials

• Optimal strategy should be employed in consideration of ethnic factors in disease characteristics and clinical environment.
Development of HF drug in Japan

• Difference between Japan and western countries
  – Underlying disease in heart failure
    • Ischemic heart disease (West) or dilated cardiomyopathy (J)
  – Dosage of drugs for heart failure and underlying disease
    • E.g., β-blocker, ARB (lower dose in Japan)

• Clinical data for efficacy and safety of heart failure drugs in Japanese patients should be sufficient.
  – Especially for the recommended dose for Japanese

• Ethnic difference is associated with difficulty in using foreign data and participating global clinical trials.
Japanese guidance document

- Guideline on clinical evaluation of heart failure drugs
  - Publication: 29 March 2011
  - Enforcement: 1 April 2012
- Background
  - Necessity of reflecting the latest knowledge of pharmaceutical medicine
  - Further understanding of HF and transition of purpose of treatment for HF to “improvement of survival and QOL of patients”
  - Necessity of providing trial endpoints for HF clinical trials in Japan, based on different background from western countries
Acute heart failure

• Purpose of treatment
  – Improvement of short-term prognosis, subjective and objective symptoms, hemodynamics, and QOL

• Trial endpoint
  – Primary endpoint: success of rescue, mortality and morbidity, subjective symptoms
  – Secondary endpoint: improvement of hemodynamics, QOL, etc.
  – Importance of investigation of not only short-term mortality but long term mortality (not worsen, more than 6 months)

• Possibility of conducting domestic confirmatory clinical trials in Japan
  – Trial size will be relatively small for investigating short-term outcome and follow-up period is also relatively short.
Chronic heart failure

• Purpose of treatment
  – Improvement of mortality, morbidity, and QOL

• Trial endpoint
  – Primary endpoint: mortality, morbidity (for Japanese study, in light of lower mortality from HF in Japan) in most cases, and subjective symptoms
  – Secondary endpoint: QOL, exercise tolerance, hemodynamics, etc.

• Possibility of participating in global clinical trials for investigating mortality
  – It is difficult to conduct large-scale confirmatory trial for mortality in Japan.
  – Careful consideration of ethnic difference and recommended dose for Japanese patients is needed.
Endpoint of HF clinical trial

• Importance of improvement of symptom such as relief of dyspnea or improvement of QOL in HF patients are well-recognized in Japan.
  – Drug for improvement of symptoms may possibly be useful unless it worsen mortality.

• So far it is difficult to reach consensus on how to measure and evaluate subjective endpoint.
  – Collected clinical trial data with possible variables may be potential evidence for validation but need careful review.

• Seeking possible surrogate endpoints is also a consideration.
  – E.g., biomarkers such as BNP, diagnostic imaging, improvement of serious arrhythmia or fluid volume
Thank you for your attention.

• Information
  – Email: ando-yuki@pmda.go.jp
  – PMDA Homepage (English)
    • http://www.pmda.go.jp/english/index.html