Endpoints and Populations and Trial Designs for Clinical Trials in NASH Indications

Lara Dimick-Santos, MD
Food and Drug Administration

The Liver Forum

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Disclaimer

The views presented are mine and do not reflect the official position of the FDA

Populations – Phase 1 & 2

- The Division has been advising:
  - Early phase trials – proof-of-concept
    - Best to use patients with biopsy proven NASH, but acceptable to use patients at high risk for NASH
  - Dose-ranging trials – phase 2
    - Biopsy proven NASH (NAS ≥ 4)
    - Include patients with NASH and liver fibrosis
  - Trials to inform the phase 3 design
    - Best to use patients with NASH and ≥ Fibrosis stage 2

Populations - Phase 3

- The Division has been advising
  - Trials to support a marketing application
    - Patients at greater risk for liver related outcomes
      - Patients with NASH and liver fibrosis ≥ 2
        - » NASH/CRN Brunt/Kleiner stage
    - Practicality - Shorter time to development of clinical benefit endpoints

Surrogate Endpoints that have been used in Drug Development

- Early phase trials
  - Endpoints should be based on mechanism of drug
  - Consider using improvement in NAS (ballooning & inflammation) and/or fibrosis
- Phase 3 trials
  - Complete resolution of steatohepatitis and no worsening of fibrosis – composite endpoint*
  - At least one point improvement in fibrosis with no worsening of steatohepatitis (no increase in steatosis, ballooning or inflammation), composite

*patient must meet both criteria to be a responder

Clinical Benefit Endpoints that have been used for Pre-cirrhotic Populations

- Histopathologic progression to cirrhosis
- Death
- Transplant
- Hepatocellular Carcinoma (HCC)
- Decompensation events
  - Hepatic encephalopathy – West Haven ≥ grade 2
  - Variceal bleeding – requiring hospitalization
  - Ascites - requiring intervention
  - Spontaneous bacteria peritonitis

Clinical Benefit Endpoints that have been used for Compensated Cirrhosis Populations

- Death
- Transplant
- Decompensation Events
- HCC
  - Unknown if risk would be decreased in Tx group – may exclude
- MELD score change by > 2 points or MELD increase to > 15 in population enrolled with ≤ 13

Accelerated Approval with Surrogate Endpoints (Subpart H/E)

- Requires that the drug be studied further to verify and describe its clinical benefit
- Generally these trial(s) should be ongoing at the time of marketing approval

The Division's Approach - as Shared with Sponsors

- Given that the patients studied to establish the treatment effect on the surrogate will continue into the verification trial:
  - The (phase 4) trial design should be acceptable by the FDA along with the design of the phase 3 trial that will support the marketing application
  - The Statistical Analysis Plan (SAP) for both trials should be acceptable to the FDA before phase 3 starts
  - Alpha must be divided between trials
- Guidance for Industry – Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
  - *http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Alternate Trial Designs

- Seamless phase 2/3/4 trial design for Accelerated Approval (Subpart H/E)
  - Advantage of saving time in long run
  - Requires planning entire clinical development plan before phase 2 starts
  - Must submit SAP for review before phase 2 starts

Alternative Trial Designs

- Single Trial to support marketing approval
  - Generally at least two adequate and well-designed trials are required to support a marketing application
  - For the results of a single trial to constitute substantial evidence of efficacy
    - Requires robust and persuasive efficacy data
    - There should be consistent findings across subgroups and study sites
  - Guidance for Industry – Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
    - http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf

Questions?