Moderated Panel Discussion

Moderators:

- **Judith Ertle**, Boehringer Ingelheim
- **Arun Sanyal**, Virginia Commonwealth University
- **Brent Tetri**, Saint Louis University

Panelists:

- **Pierre Bedossa**, LiverPat
- **Cynthia Behling**, University of California San Diego
- **Oscar Cummings**, Indiana University
- **Lara Dimick-Santos**, U.S. Food and Drug Administration, CDER
- **Stephen Harrison**, Oxford University
- **Prakash Jha**, U.S. Food and Drug Administration, CDRH
- **David Kleiner**, NIH National Cancer Institute
- **Massimo Siciliano**, Università Cattolica del Sacro Cuore & external AIFA / EMA expert

How to Improve Trials with Biopsies?

1. Should we classify patients with steatosis (no inflammation and/or ballooning) and fibrosis as NASH patients, especially in trials assessing improvement of fibrosis as primary read-out, as fibrosis is a result/complication of NASH?
    a) How do you think we could reduce the high screen failure rate in NASH clinical trials?
2. Should the follow-up biopsies be read in comparison with the baseline biopsy or independent?
    a) Does it make a difference at all, as the follow-up biopsy is not taken in the same exact spot as the baseline biopsy?
    b) How best to cope with the irregular distribution of NASH and fibrosis in the liver in regards of 2 biopsies taken a year (26-72 weeks) apart?
3. Taking into account issues on repeatability, variability in assessments of biopsies, are we really assessing drug efficacy, or is the efficacy diminished in the “noise”?

How to Improve Histological Scoring?

1. What does a worsening of NAS really mean (e.g. 1-point worsening vs. 3-point worsening), as fibrosis is the prognosis factor in histological features of NASH?
2. Is the categorical assessment of biopsies really the best approach to assess changes due to pharmacological treatment in NASH and fibrosis?
    a) Should we start to discuss if it is time to modify NASH CRN staging of NASH?

How to Improve Technical Aspects?

1. Is there evidence that one way of biopsy reading (i.e., # of readers, sequence of reading) is better than another?
2. What is the minimum core biopsy length (and/or of portal space number) to be considered adequate to assess NAS and stage in clinical trials?
3. How many bridges must be present in the lobule to define stage 3 fibrosis in NAFLD (one or more)?
4. Can a second reading by the same pathologist after a few days enhance biopsy sensitivity?

Additional Trial Design Considerations

1. Should we try to replace biopsies with non-invasive biomarkers (as surrogate for the surrogate), or should we search for biomarkers as surrogate for long-term outcome events?
2. If biopsies are not accepted as surrogate biomarkers for long-term outcomes, do we still have to do biopsies at baseline to confirm NASH and fibrosis diagnosis?
3. In an outcomes trial in cirrhosis or advanced fibrosis, would a not histologically defined cohort be acceptable?
4. Does the biopsy reading plan for a phase 2B have to be identical to phase 3?