Case Definitions Working Group

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Presenter
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WG Output #1: Manuscript

An evaluation of case definitions for inclusion and analysis of endpoints in clinical trials for non-alcoholic steatohepatitis through the lens of regulatory science

- Siddiqui, Harrison, Abdelmalek, Anstee, Bedossa, Castera, Dimick-Santos, Friedman, Kleiner, Megnien, Neuschander-Tetri, Schabel, Miller, Ratziu, Sanyal *on behalf of WG members*

Submitted to J Hepatology

WG Output # 2: Manuscript

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Defining Improvement in NAFLD for Clinical Trial Endpoints: Recommendations from the Liver Forum

- Work in progress
  - October 2016
  - Several conference calls
- Writing team: Cheung, Harrison, Megnien, Miller, Neuschander-Tetri, Rinella, Sanyal (Amanda Cheung, MD)
- Working Group

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Phase 2 Working Group Members

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Objective

Recommendations from the Liver Forum for clinical trial endpoints for NASH and fibrosis

- Clinical trial endpoints in a regulatory science framework
- Clear definitions for regulatory path and drug development in NASH and Fibrosis
  - Consensus on definitions

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Outline

- Background/introduction
- Severity of disease: NASH and fibrosis
- Biopsy limitations
- Measures of NASH severity
- Measures of Fibrosis severity
- Summary of recommendations/conclusions

Background/Introduction

- Prevalence and progression of NASH
- Current regulatory state for assessment of improvement of disease/Histological endpoints
- Statement of scope: overview of assessments of NASH severity and fibrosis, used in clinical trials
- Liver biopsy limitations

NASH severity and fibrosis severity

- Separate assessments of severity of NASH and severity of fibrosis
  - Current measures
  - Exploratory measures
  - Endpoints
    - Definition
    - Correlation with outcomes
    - Data needed to validate

Points to consider

- Severity of NASH and severity of fibrosis as separate assessments versus global severity of disease
  - Definition of activity of NASH and severity of disease
  - Take into consideration inconsistent improvement/worsening
  - Definition of changes
- NAFLD severity and NASH severity
  - Steatohepatitis for clinical trials
  - Steato-fibrosis in separate discussion
- Early phase and mid to late stage trial endpoints

Recommendations

- List of endpoints
  - Clinical trial stage (Registration, early stage)
  - Population/indication
- Clear consensual Definitions:
  - Precise, quantifiable, and reproducible for clinical trials
  - Acceptable by regulatory agencies
  - Harmonization across trials

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Next Steps

- Manuscript outline
  - Distribution to Working Group
- Draft Manuscript
  - A. Cheung and Writing team