# **WORKING GROUP REPORT:** Disease Definitions for NAFLD

Liver Forum Meeting

Barcelona

# BACKGROUND

- NAFLD is a heterogeneous entity with lack of consensus definition
- Multiple histological classification
- Limited guidance regarding biomarker and diagnostics development

# OVERALL GOAL

- To improve the efficiency of regulatory approval, the Disease Definitions Working groups were convened to clarify stages of NAFLD for future clinical trials using both histological and non-invasive methods

# METHODOLOGY

- The Disease Definition Working groups consisted of representatives from
  - Regulatory agencies (FDA and EMA)
  - Professional societies (AASLD and EASL)
  - Pharmaceutical and diagnostic industry
  - Academia
- Seven sub-groups were identified

# Seven Sub-Groups

1. Isolated Hepatic Steatosis (Manal Abdelmalek)
2. Indeterminate NASH (Stephen Harrison)
3. Definite NASH without fibrosis (Quentin Anstee)
4. NASH with early fibrosis (Vlad Ratziu)
5. NASH with bridging fibrosis (Laurent Castera)
6. NASH with compensated cirrhosis (Scott Friedman)
7. NASH with decompensated cirrhosis (Brent Tetri)

# METHODOLOGY

- Each group group tasked with defining
  - Histology (grade, activity, stage)
  - Clinical phenotype
  - Non-invasive biomarkers
- Subgroups reconvened for further consensus building

# RESULTS

- Disease states consolidated
  - **NAFL** (Isolated hepatic steatosis, indeterminate NASH)
  - **NASH** (NASH without fibrosis, NASH with early fibrosis, and NASH with bridging fibrosis
  - **NASH cirrhosis** (compensated and decompensated)

# NAFL

- Histological definition: >5% steatosis
  - Can have minimal lobular inflammation
  - No cytological ballooning or fibrosis
- Histological subtypes:
  - Isolated hepatic steatosis
  - Indeterminate NASH
  - Steatofibrosis

# NAFL – Comparison of Histological Scoring Systems

| CRITERIA | NASH-CRN | SAF | GOODMAN |
|---|---|---|---|
| Objective | Yes | Yes | Yes |
| Subjective | No | No | No |
| Quantifiable | Yes | Yes | No |
| Sensitive to Change | Yes | Yes | Unknown |
| Externally validated | Yes | Yes | No |
| Used in clinical trials | Multiple | No | No |

# NAFL-Comparison of Non-Invasive Biomarkers

| CRITERIA | Models | CK-18 | Ultrasound | CAP | MRI/MRS |
|---|---|---|---|---|---|
| Objective | Yes | Yes | Yes | Yes | Yes |
| Subjective | No | No | Yes | No | No |
| Quantifiable (Separation of Steatosis Grade) | No | No | No | No | Yes |
| Inter-observer reliability | N/A | N/A | Moderate | Moderate | High |
| Sensitive to change | Unknown | Unknown | Unknown | Unknown | Yes |
| Externally Validated | No | No | Yes | Yes | Yes |
| Used in clinical Trials | No | No | No | No | Yes |

# NAFL Summary

- Histological definition: >5% steatosis
  - Can have minimal lobular inflammation
  - No cytological ballooning or fibrosis
- NASH-CRN is most validated but SAF is quantifiable and promising
- Non-invasive models are not quantifiable
- MRI/MRS is quantifiable and sensitive to change over time

# NASH Histological Definition

- Histological definition:
  - Steatosis, ballooning, lobular inflammation
  - Cannot have cirrhosis (F4)
- Histological Subtypes:
  - NASH without fibrosis
  - NASH with non-advanced fibrosis (F1-F2)
  - NASH with bridging fibrosis (F3)

# NASH – Comparison of Histological Scoring Systems

| CRITERIA | NASH-CRN | SAF | GOODMAN |
|---|---|---|---|
| Objective/Subjective | Both | Obj. | Obj. |
| Quantifiable | Yes | Yes | No |
| Sensitive to Change | Yes | Yes | Unknown |
| Externally validated | Yes | Yes | No |
| Used in clinical trials | Multiple | None | None |

# NAFL-Comparison of Non-Invasive Biomarkers

| CRITERIA | Models | CK-18 | Ultrasound | VCTE | MRI/MRS |
|---|---|---|---|---|---|
| Able to differentiate NASH vs. NAFL | No | No | No | No | No |
| Quantifiable (Separation of Fibrosis Grade) | Limited | No | No | Limited | Yes |
| Inter-observer reliability | High | High | Moderate | Mod-High | High |
| Sensitive to change | Unknown | Unknown | Unknown | Unknown | Limited |
| Externally Validated | No | No | No | No | Yes |
| Used in clinical Trials | No | No | No | No | Yes |

# NASH Summary

- NASH cannot be distinguished non-invasively
- NASH-CRN criteria is sensitive to change and has been used in clinical trials.
- Although SAF is quantifiable, more data is necessary to determine sensitivity to change
- Fibrosis can be quantified via MRE but more data is necessary
- More data with Fibroscan® and non-invasive biomarkers is needed

# NASH Cirrhosis

- No definitive test
  - Histology may or may not show steatosis or steatohepatitis
  - Cryptogenic cirrhosis + history of features of MetS
  - F4 Fibrosis Stage
- Compensated vs. Decompensated
- May or may not have components of metabolic syndrome

# NASH Cirrhosis

- Non-invasive biomarkers need further validation
- MRE is highly accurate
- HVPG can be utilized
- TE needs further validation

# NASH Cirrhosis Summary

- Diagnosis does not solely rely on histology
- Biopsy is not always required
- MRE and Fibroscan ® can be used to diagnosis cirrhosis but more data is needed
- HVPG can be used to follow portal HTN

# Gaps in Knowledge

- Non-invasive biomarkers
  - Sensitivity to change (grade, activity, stage)
  - Differentiating NASH vs. NAFL
- Natural history of the disease
  - Non-NASH categories
  - Clinical phenotypes of at risk patients