THE FORUM
For Collaborative Research℠

Pooling of Endpoints WG

Liver Forum 16 Update
Washington DC

23 March 2024

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Novo Nordisk, DK
on behalf of the pooling of endpoints WG

Berkeley Public Health

Working group progress:

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Co-chairs**: Jasmohan Bajaj** (VCU) and **Michelle Long**(Novo Nordisk)

Meetings: Approximately Monthly

- Cathy O'Hare
- Arie Regev
- David Shapiro
- Roberto Calle
- Ashish Dhawan
- Diogo Ferrinho
- Claudia Filozof
- Shirin Hemmat
- Massimo Siciliano
- Jörn Schattenberg
- Charmaine Stewart
- Vlad Ratziu
- Brenda Rodriguez
- Toru Matsubayashi
- Mazen Noureddin
- Jose Willemse
- Libette Luce
- Raj Vuppalanchi
- Margot Yann
- Juan Abraldes
- Jasmohan Bajaj
- Azza Karrar
- Sehyr Khan
- Madhuri Jerfy
- Veronica Miller
- Christina Mogenson
- Blue Neustifter
- Melissa Palmer
- Detlef Schuppan
- Radha Seetharam
- Amrik Shah
- Richard Torstenson
- Tram Tran
- Sharat Varma
- Julia Wattacheril
- Pam Young
- Michelle Long

Can we pool endpoints between F3 and F4 studies?

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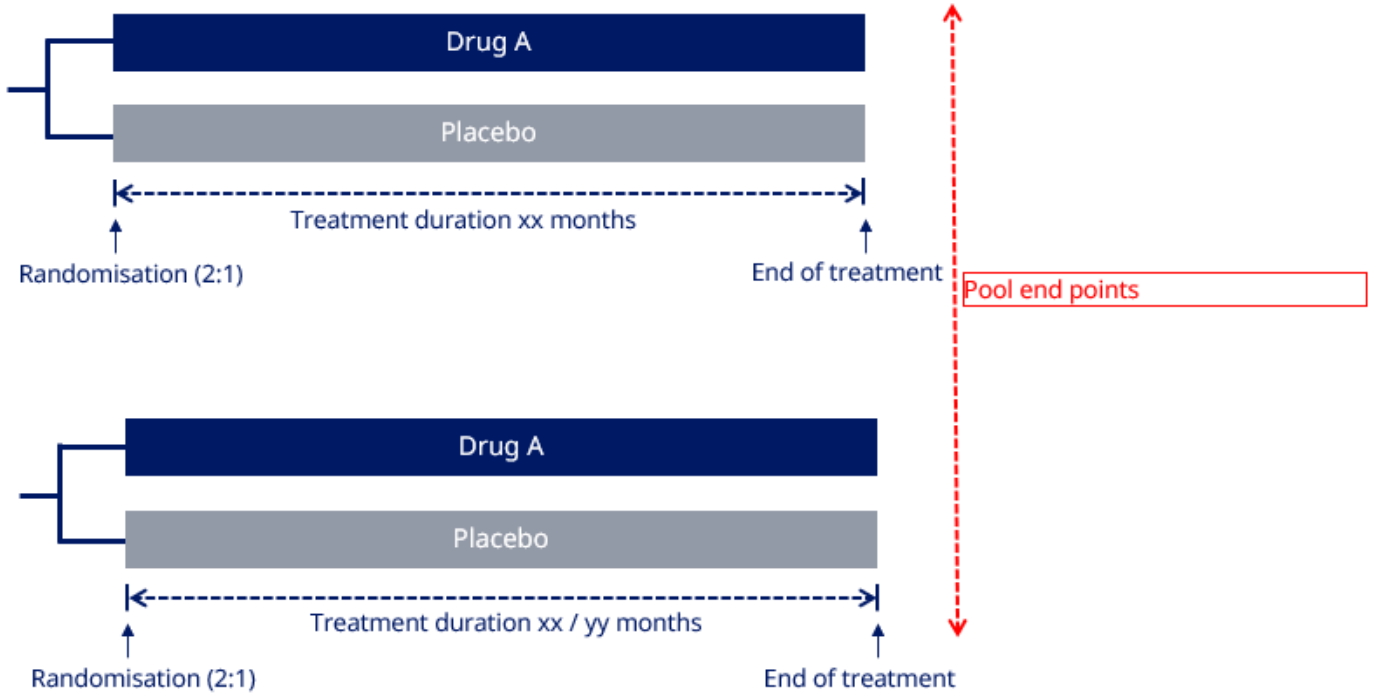
Trial 1
- Time driven by biopsy/histology
- NASH with **F3**



Trial 2
- Event driven
- NASH with **F4c**

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Challenge to pooling endpoints:

- **Pre-cirrhotic MASH**: aim to measure the clinical benefit of a therapeutic on the regression of disease (reduction in fibrosis or resolution of MASH).
  - Time-driven events
- **MASH with compensated cirrhosis**: aim to measure the halting of progression to decompensated cirrhosis.
  - Endpoint-driven events
  - However, there may be some indication that regression of cirrhosis could be an accelerated approval pathway in F4c

Evolving discussion on endpoints

- 1: Pooling patient populations from *distinct trials in F3 and F4 patients* and ranking of endpoints to increase efficiency
  - Consider new, clinically relevant endpoints to add to a composite endpoint
- 2: Incorporate PROs in MASH clinical trials
  - For patients with F3 and F4c fibrosis, with and without signs or symptoms of portal hypertension
- 3: Potential for a *single trial* enrolling F3 and F4 patients
  - With considerations from expert statisticians

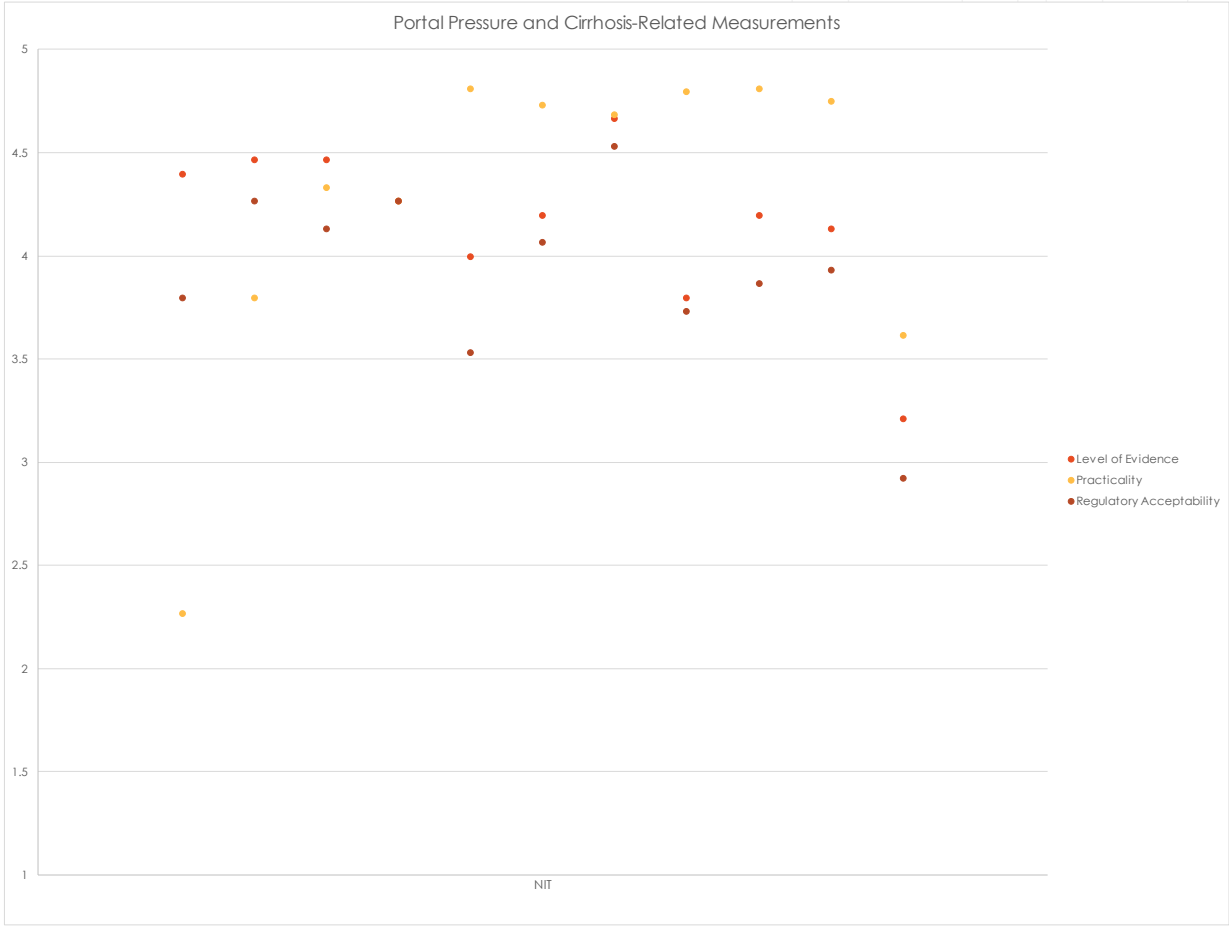
Focus: Workstream 1

- Aim: discuss and recommend a composite endpoint that would allow pooling endpoints in F3 and F4 patients
  - Addresses disease progression, disease stability (no progression, no regression) and disease regression
  - Relates to disease severity strata (F3, F4 with and without portal hypertension)
  - Consider phase 2 and phase 3 CT designs
  - Includes clinical, functional, histological, and non-invasive assessments
    - PROs to be added later (Workstream 1 discussion)
    - Innovative markers are important, but focus will be on considering **endpoints achievable in the near term**

Which measurements should be included in a composite endpoint with F3 and F4 patient populations in mind?

Expanded endpoint survey

- Completed survey of WG members of various endpoints which could be part of a composite endpoint
  - Ranked separately on level of evidence, practicality, and regulatory acceptability
  - Clarified focus is not to get into a discussion on proposing new NIT-based endpoints in the WG



Outline for ongoing discussions

1. Provide an overview of F3 and F4 patient populations and differences in clinical trial design.
    a. Refer to regulatory guidelines in FDA and EMA
    b. Case study from other disease areas?
    c. Outline overlap of F3 and F4 patient populations.
2. Propose a continuum of F3 and F4 patient populations.
    a. Refer to the academic literature suggesting a continuum of cirrhosis in MASH and MASLD populations.
        i. Refer to Mazen Noureddin 2022/2023 paper on cirrhosis risk stratification for clinical trial enrollment.
        ii. MASH and MASLD are not just driven by fibrosis—use of the term compensated advanced chronic liver disease (but this is defined by HVPG)
            1. Consider non HVPG, in advanced compensated

Outline for ongoing discussions

3. Discuss and propose endpoints to characterize the following.
    a. Progression from F3 → F4
    b. Lack of progression within F3 & F4
    c. Regression of cirrhosis (histological cirrhosis) would be relevant to biopsy-driven trials from F4 à F3. Can discuss, movement (89bio)
    d. Discuss pros and cons of the proposed endpoints:
        i. Histology, Ishak Fibrosis Score
        ii. VCTE/Fibroscan
        iii. Development of Varices
            1. Discuss means of grading varices
        iv. define level of evidence, regulatory acceptance, and practicality for all the endpoints above.
        v. Provide rationale based on past/current studies
4. Next steps:
    a. Current limitations; this composite endpoint as an interim solution
    b. proposed clinical trial design for F3 and F4 patient populations.

Next steps

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- Expand discussions on clinical composite (focus on advanced fibrosis)
  - Discuss clinical and laboratory measures that could expand the composite
  - Definitions and standardization of endpoints
- Consider statistical approaches
  - ordinal outcome ranking of composite
- **Please join us!**

- Friday, April 5, 2024 from 11:00 AM- 12:00 PM EDT
- Wednesday, April 24, 2024 from 12:00 PM- 1:00 PM EDT
- Wednesday, May 22, 2024 from 12:00 PM- 1:00 PM EDT

Thank you!