Clinical trial design WGs: pooling and combo Rx

Michelle Long, MD, MSc
International Medical VP
Liver, Obesity and Devices
NovoNordisk A/S

Disclosures

- Employed by Novo Nordisk
- Shareholder Novo Nordisk

An alternative approach for phase 3 NASH drug development presented by the FDA**

Study 1 in F4c*:
Clinical endpoint using composite liver outcome events

Large & long due to low event rate
5150 patients followed for up to 8 years

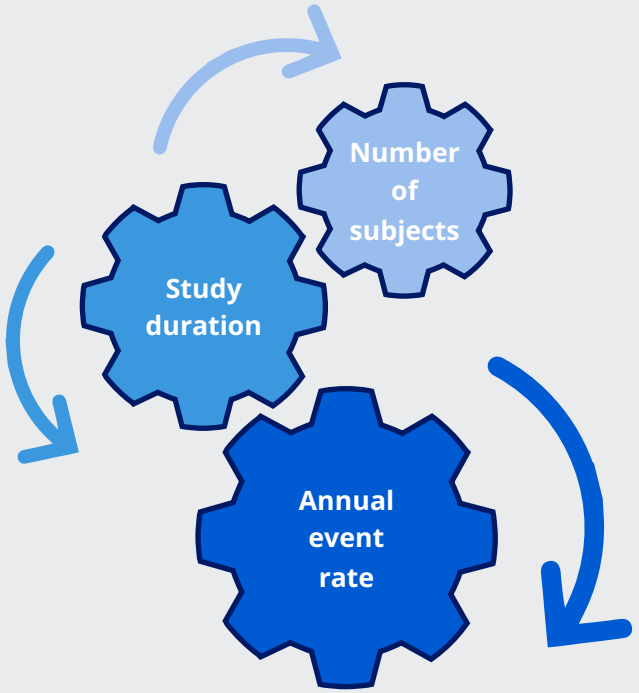
Study 2 in non-cirrhotic:
Surrogate endpoint using histology, i.e., no clinical events

Small & fast
1000 patients all followed for 1.5 years

Submission of marketing application for accelerated / conditional approval in non-cirrhotic

Submission of marketing application for full approval in non-cirrhotic & F4c

Accumulation of the required number of events depends on *three* things:

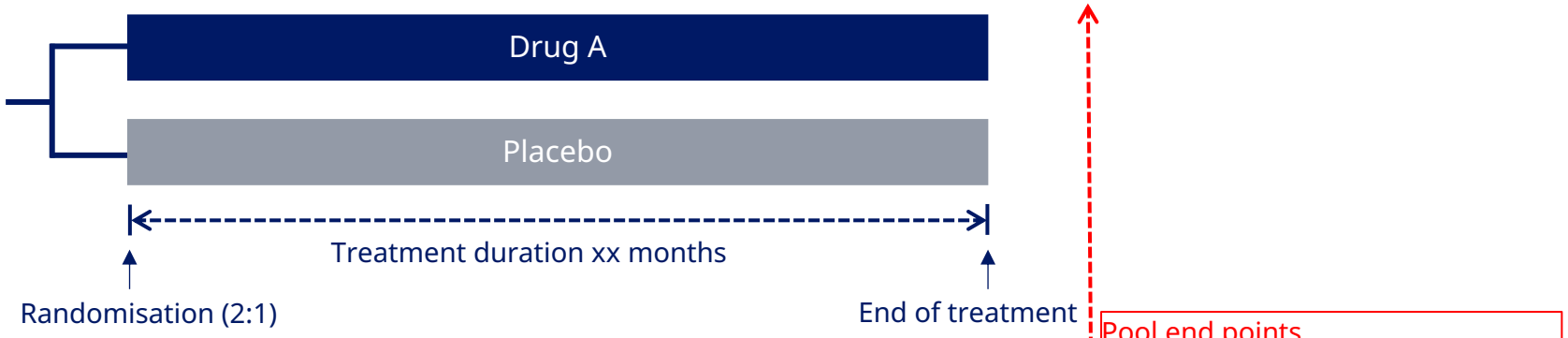


*Study 1: 5150 patients followed for 8 years is based on: a hazard ratio of 0.8 (20% risk reduction), an annual event rate of 3%

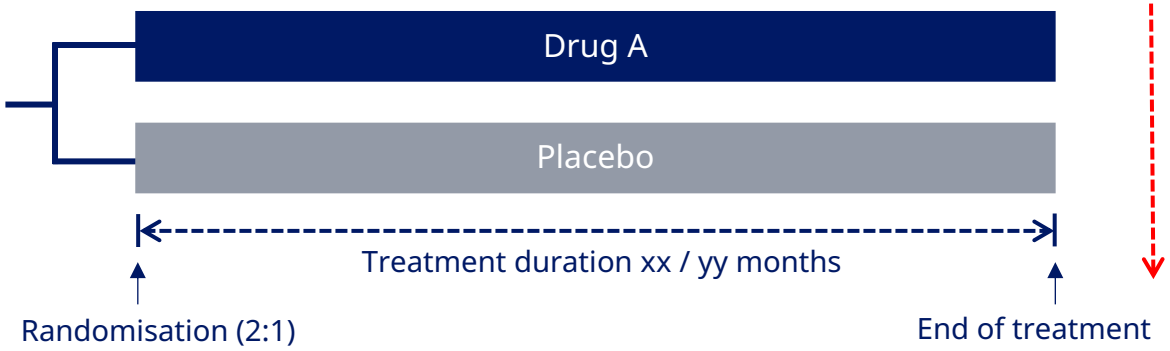
***FDA. Matsubayashi T. Drug Development for Nonalcoholic Steatohepatitis (NASH) with Fibrosis: A Regulatory perspective. 2021. Available from NASH-Webinar-January-2021.pdf (sbiaevents.com)*

If we pool separate F3 and F4 studies?

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



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

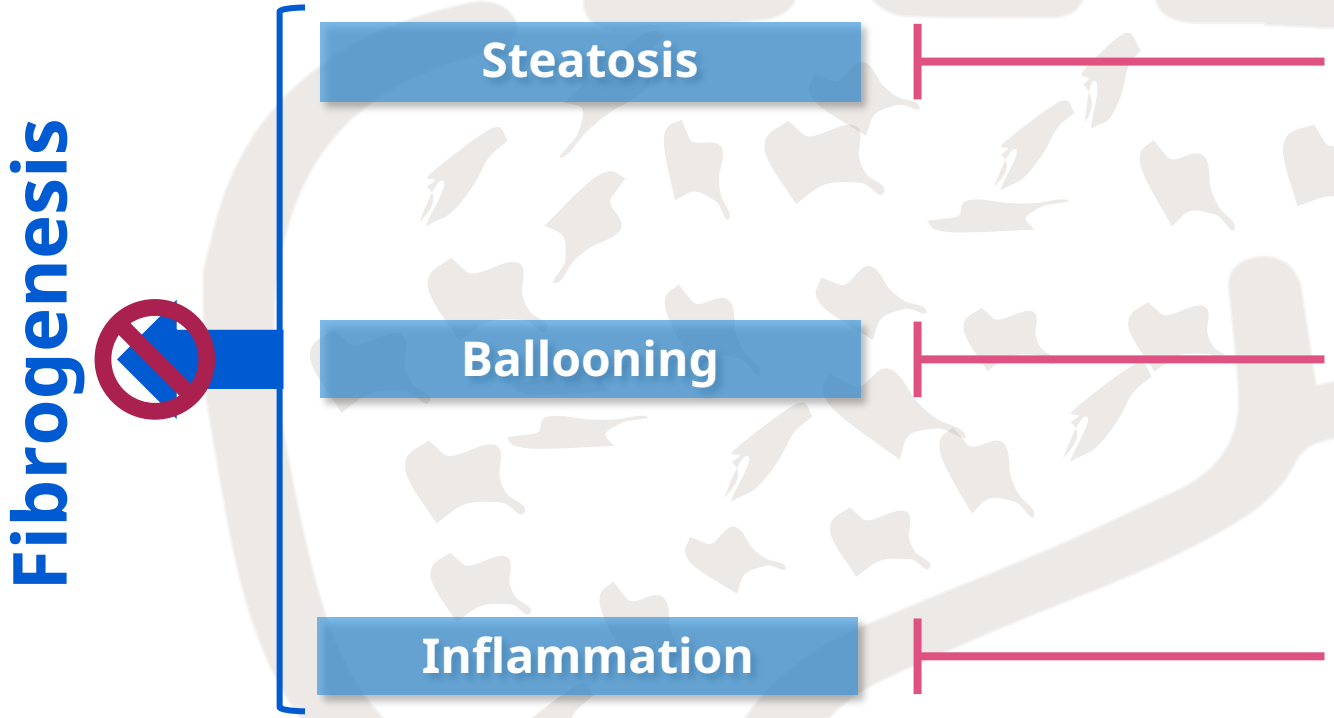


Aspects to deliberate in the working group

Co-Chairs: Sharat Varma (Novo Nordisk) and Jasmohan Bajaj (VCU)

Pros	Points to consider and discuss
• Simultaneous F3+F4 trial • Impact on required persons in trial • Comprehensive approval • No repeated biopsy in F4c	• What end points to pool ? • Longer time to approval (event-driven) • Defining duration of both trials • How to power studies individually according to outcomes? • Statistical Vs Numerical superiority

Pathophysiology of NASH and combination therapies



Given the complexity of the pathophysiology of NASH, it may take the engagement of **several targets** to **obtain clinically meaningful improvements**, especially in more advanced stages of the disease

Purpose:

Develop **combination therapies** to address multiple drivers of liver dysfunction and cardiometabolic disease in patients with NASH

Specific considerations in NASH studies

- Liver histology requirements balanced with need to minimize risk burden on patients
- Minimize patients receiving placebo or less effective therapy during clincial trial given lack of available therapies
- Consider trial design for new therapies vs standard of care or other investigational therapies

Can we remove one or more monotherapy arms in Phase 3?

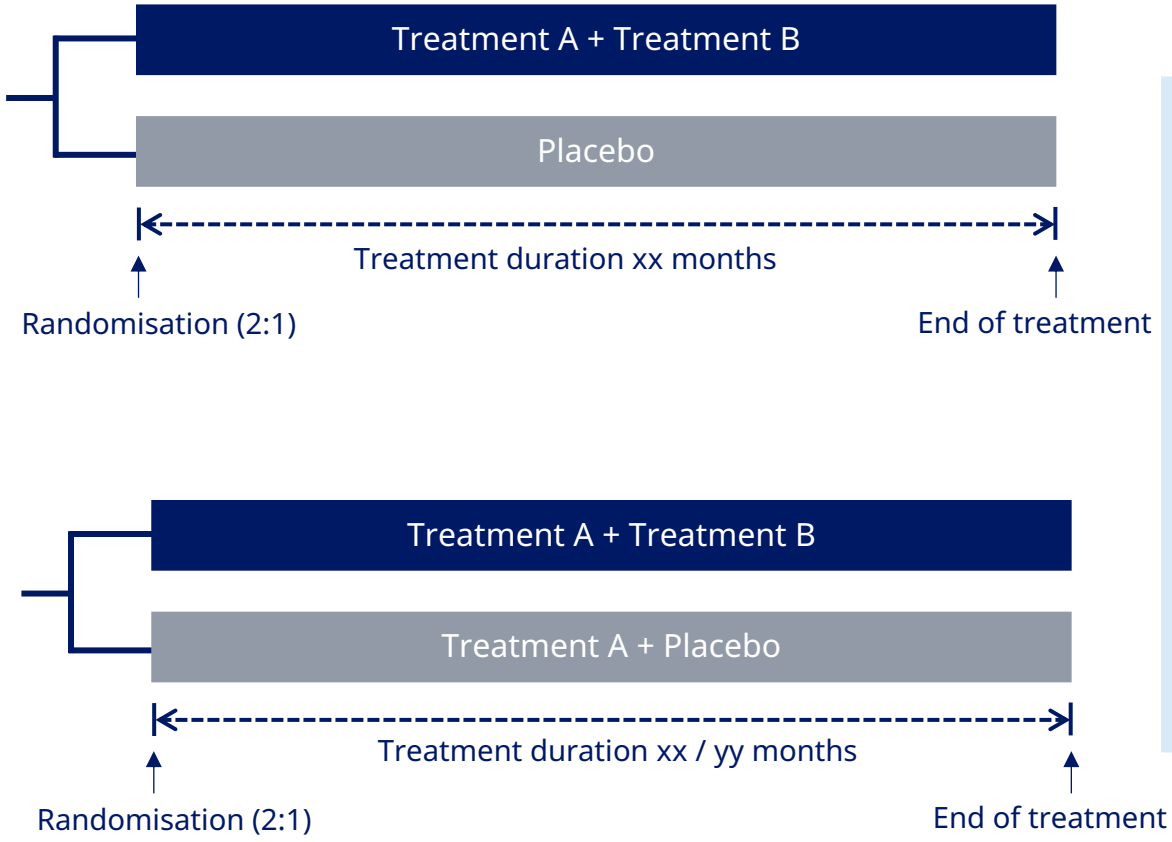
Trial 1

- Time driven by biopsy/histology
- Non-cirrhotic NASH

OR

Trial 2

- Time driven by biopsy/histology
- Non-cirrhotic NASH



How to minimize monotherapy arms?

- Can we extrapolate from historical studies using same or similar molecules for diseases with overlapping phenotypes?
- Can we extrapolate from phase 2 data?
- Can we consider non-histologic surrogates/NITs for monotherapy arms?

Aspects to deliberate in the working group

Co-Chairs: Michelle Long (Novo Nordisk) and Alina Allen (Mayo)

Pros	Points to consider and discuss
• Less complicated study design • Less burdensome on patients • Fewer patients needed on study to reach study objectives • Builds on design of phase 2 study	• Impact on drug approval pathway (for NASH and beyond) • Use of historical information and/or phase 2 results in phase 3 design • What other data sources can be considered to eliminate the need for monotherapy arms? • What use of NITs will be acceptable for monotherapy arm? • True placebo vs monotherapy as placebo?


We need
YOU!