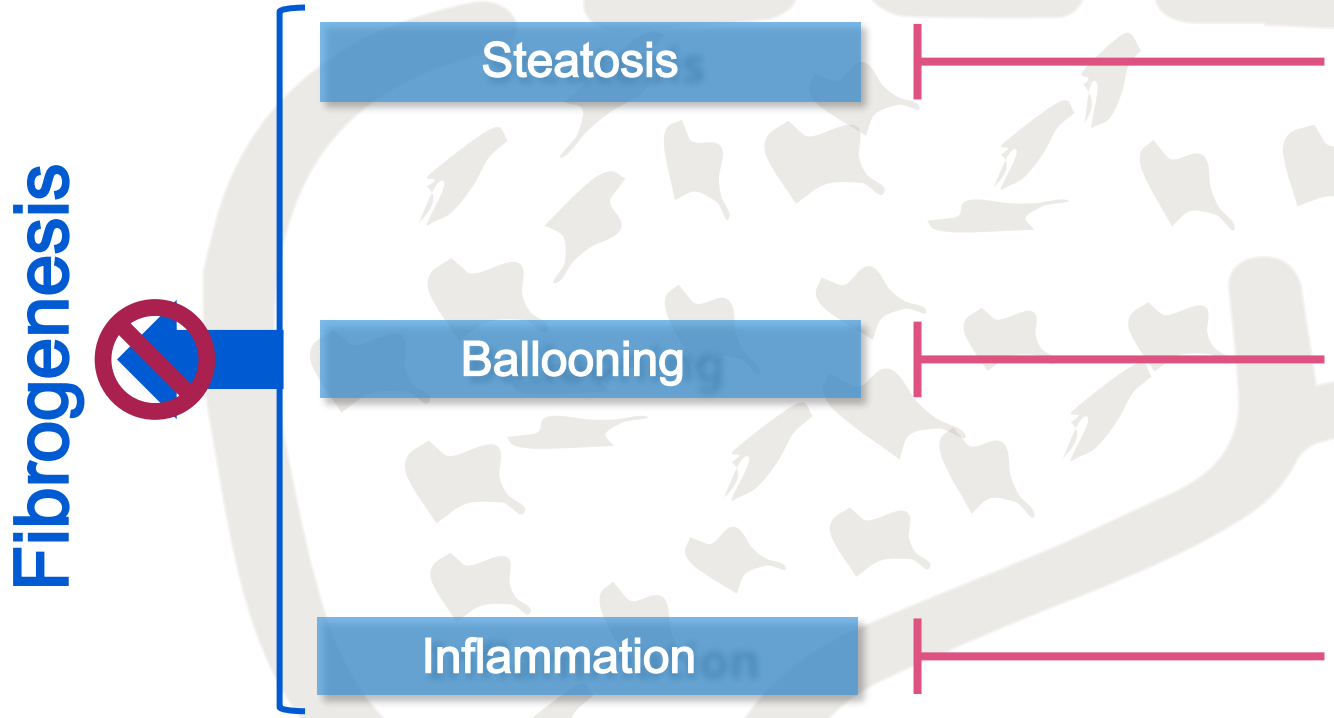
Clinical trial designs for combination therapy

Need for monotherapy arms

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

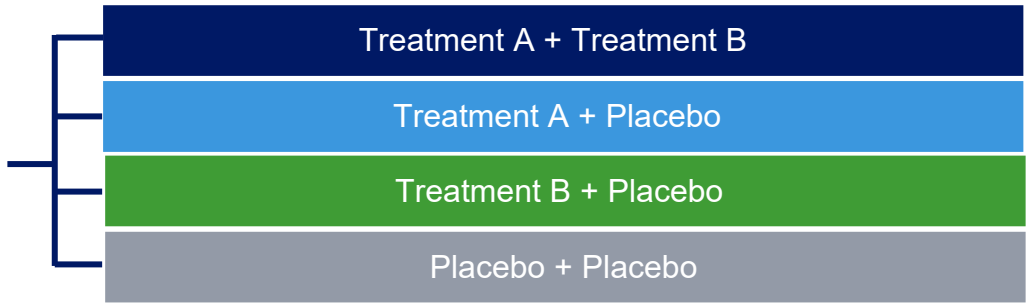
- Liver histology requirements balanced with need to minimize risk burden on patients
- Minimize patients receiving placebo or less effective therapy during clincial trial given lack of available therapies
- Consider trial design for new therapies vs standard of care or other investigational therapies

Trial design: Example in Phase 3

Combination therapy targeting non -cirrhotic NASH

patients

- Non -cirrhotic NASH (histologic criteria)



Trial design

- Duration driven by histology

Key endpoints

- **Primary:** Surrogate endpoints (histologic) demonstrating resolution or improvement in disease

Major Challenges

- High screen failure rate (histology required for enrolment)
- High number of patients needed and receiving placebo
- Treatments may be synergistic and not effective alone
- Higher cost/longer time until drug approval

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

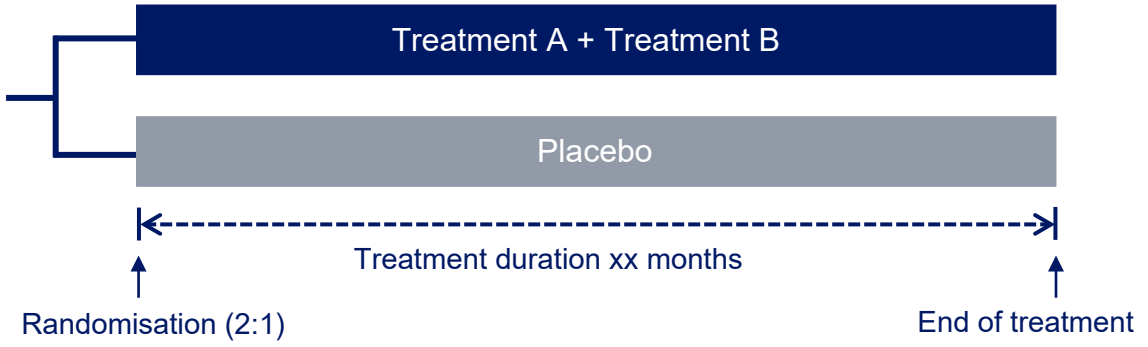
Trial 1

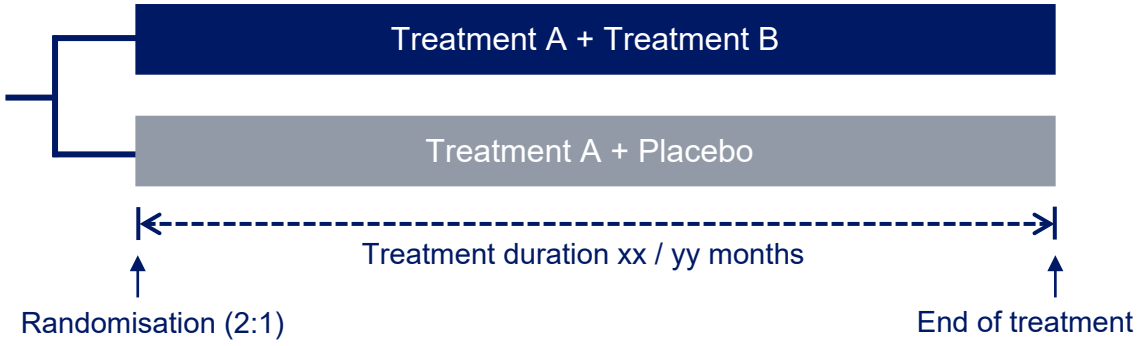
- Time driven by biopsy/histology
- Non-cirrhotic NASH

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

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?