Combination Therapy WG

Liver Forum 15 Update
Paris, France

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on behalf of the combination therapy WG

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Working group progress:

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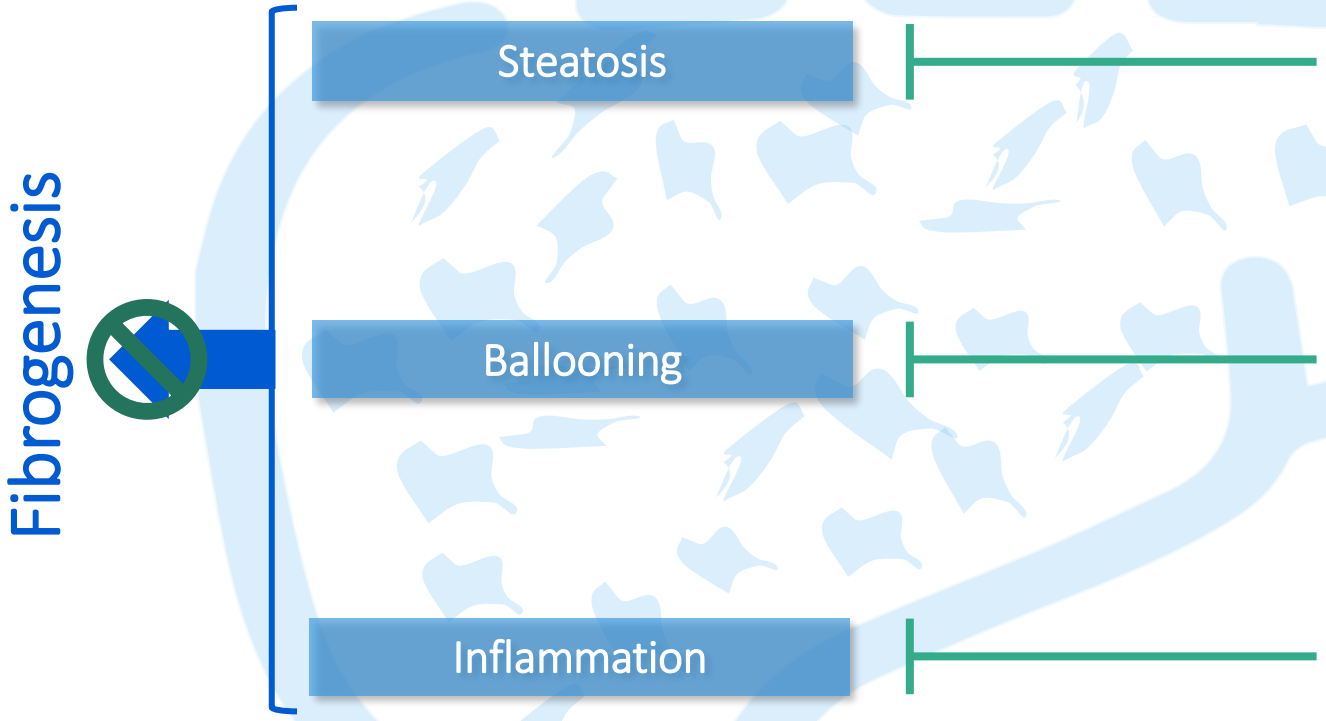
Co-chairs**: Alina Allen** (Mayo) and **Michelle Long** (Novo Nordisk)

Meetings: Monthly, 3 meetings to date

- Alina Allen
- Roberto Calle
- Henry Chang
- Claudia Filozof
- Joanne Imperial
- Madhuri Jerfy
- Sehyr Khan
- Michelle Long
- Libette Luce
- Veronica Miller
- Paul Nitschmann
- Melissa Palmer
- Vlad Ratziu
- Andrea Ribeiro
- Detlef Schuppan
- Abhinav Seth
- Raj Vuppalanchi
- Pam Danagher
- Diogo Ferrinho
- Michael Fuchs
- Azza Karrar
- Sanjay Kumar
- Ruby Mehta
- Mazen Noureddin
- Cathy O'Hare
- Brenda Rodriguez
- Charmaine Stewart
- Pam Young

Combination therapy may most effectively treat MASH



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

How do we approach combination therapy for patients with MASH?

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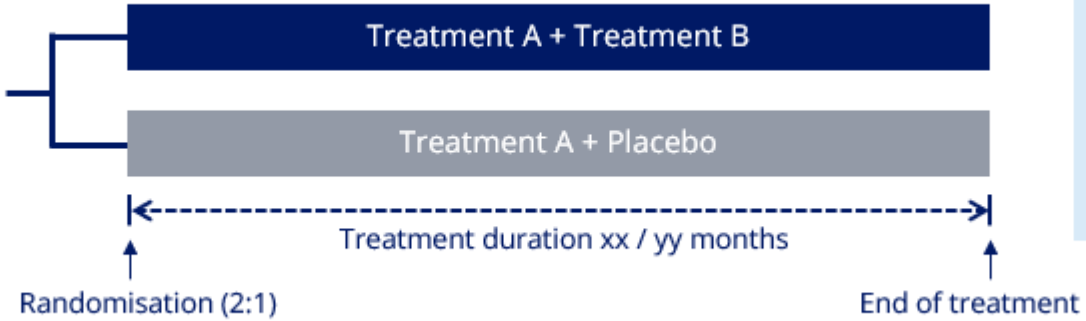
Trial 1
- Time driven by biopsy/histology
- Non-cirrhotic NASH

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?

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2 Identified Workstreams

- 1: Explore the regulatory landscape for combination therapies in MASH
  - Describe current guidance, highlight challenges, describe consensus suggestions which may mitigate challenges
- 2: Consensus statement on combination therapies
  - Consider different MASLD phenotypes (low, mid, high risk of MALO)
  - Mechanistic rationale for combination therapies
  - Inventory of MoA and build consensus around prioritized combinations

Plan: Consensus recommendations on combination drug development

- Aim: combine clinical, drug development and regulatory considerations in single consensus paper
  - Draft outline completed
    - Clinical aspects: Rationale behind combination therapy by MoA, disease severities across MASH spectrum, potential uses of NITs, expected outcomes, PRO and PRE considerations, safety considerations, various treatment strategies
    - Design/regulatory considerations: Consider clinical trial designs and challenges in current regulatory framework, consensus on potential options for mitigation
    - Lessons learned from relevant disease areas
      - Cancer, infectious disease, cardiovascular disease, type 2 diabetes could be considered

Next steps

- Finalize paper outline
  - Continue to add details and build structure to paper outline
  - Form writing group
  - Regularly present sub-sections to larger WG for discussion and sparring
- **Please join us!**