Clinical trial design pooled or meta -analysis

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

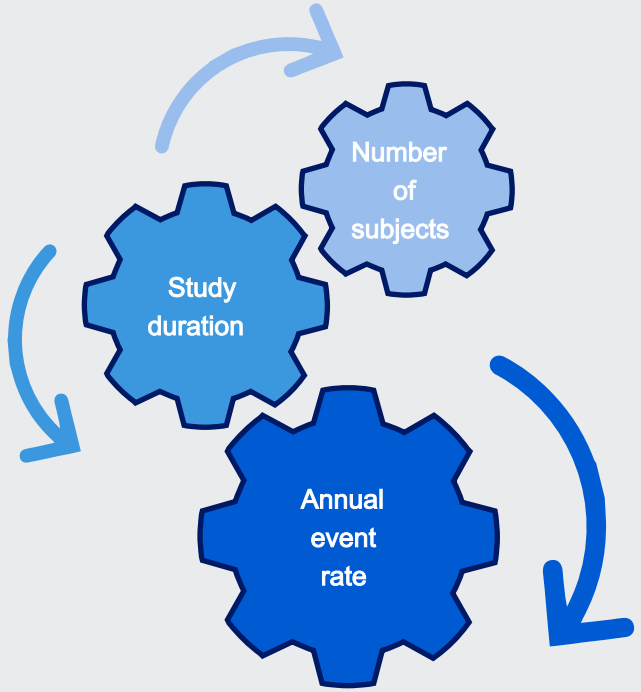
Study 2 in non -cirrhotic:
Surrogate endpoint using histology, i.e., no clincal events

→ **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. 2021Available from NASHWebinar-January-2021.pdf (sbiaevents.com)*

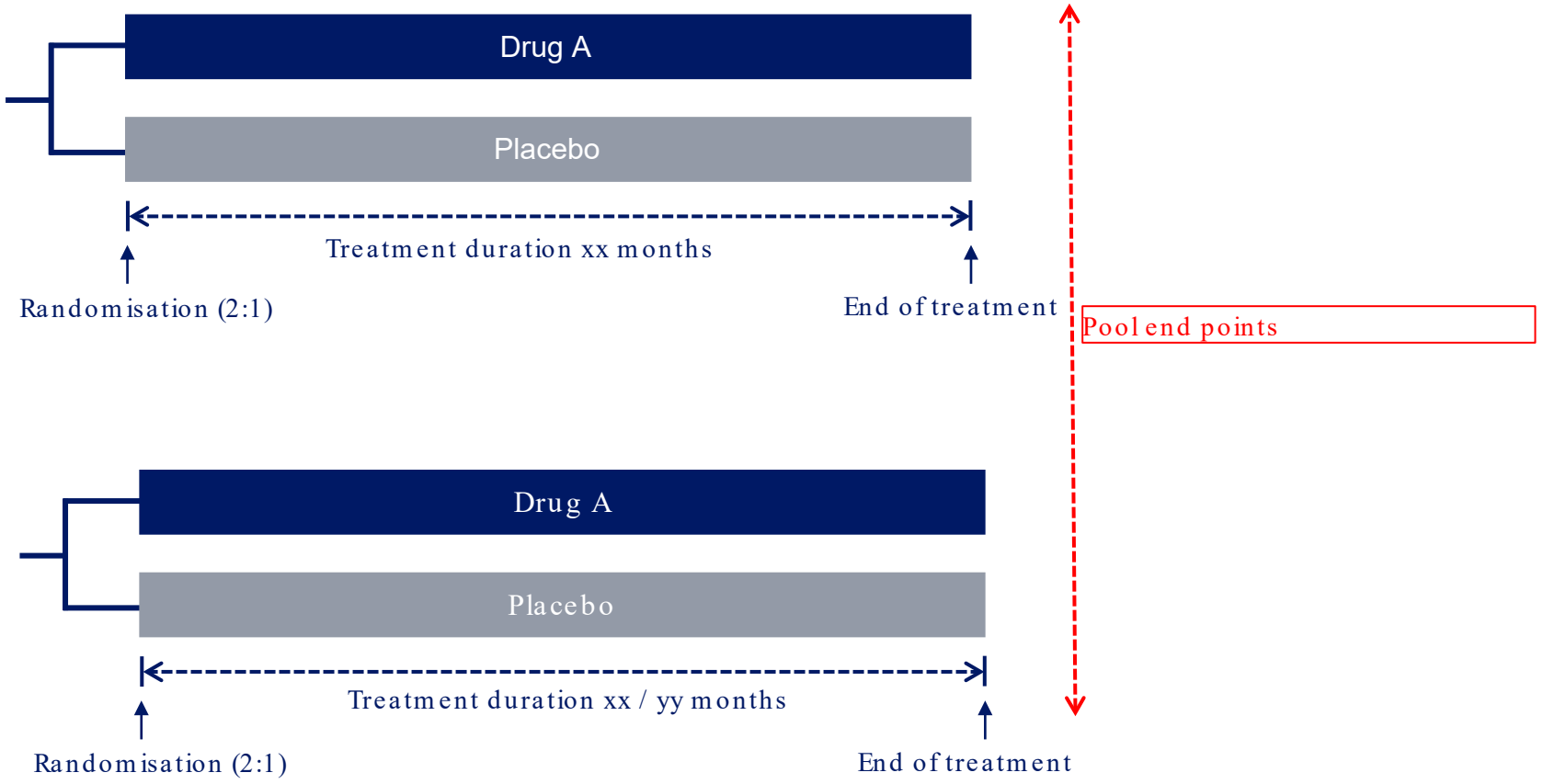
If we pool separate F3 and F4 studies?

Trial 1

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

Trial 2

- Event driven
- NASH with **F4c**



Aspects to deliberate in the working group

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