



Regulatory update from Europe: Interim endpoints in phase 3 NASH trials

Elmer Schabel MD

The views expressed in this presentation are primarily those of the author and do not necessarily express those of the BfArM, nor of the EMA





JES AGENCY

Regulatory update from Europe – Interim endpoints in NASH phase 3 trials

 The previously proposed/presented co-primary evaluation of two composes endpoints for the interim has been accepted:



Composite of complete resolution of steatohepatitis (0 for ballooning, 0-1 for inflammation) and no worsening of fibrosis stage



Composite of one point improvement in fibrosis stage (at least 1 stage) and no worsening of steatohepatitis (balloning and inflammation score)

- The endpoint combines different aspects of individual response (the composites) and response at the population level
- Addition in 2017: The intended scenario with conditional licensing/accelerated approval will be more difficult in later development programmes with regard to the fulfillment of the condition/the phase IVI
 - to conclude on a



EUROP SCIENCE

Regulatory update from Europe – Interim endpoints in NASH phase 3 trials

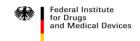
Slide shown Forum A Liver

- (How) can the interim evaluation account for different mechanism of action?
 - E.g. a primary anti-inflammatory agent might not be able to show improvement in fibrosis at interim time-point already
 - The composite of NAS resolution and no worsening of fibrosis not considered sufficient



 Co-primary evaluation of NAS resolution and no worsening of fibrosis would at least be expected in order to show independent effects on fibrosis (in the case prevention of deterioration only can be shown)

Addition 2017: Best: effects should be shown on the individual level (the composite) and at the population level (the co-primary)





Regulatory update from Europe – Interim endpoints in NASH phase 3 trials

- New situation:
- No relevant anti-inflammatory activity, but relevant effects on fibrosis expected
 - Resolution of NASH not an appropriate endpoint (see CENTAUR trial)
 - "Change in character of inflammation" may or may not be demonstrated (immunehistochemistry based evaluation of included cell-types, inflammatory cytokine profiles, etc.)
 - How can a "sufficiently strong" interim endpoint (see above) be established?
 - 1-Stage improvement of fibrosis sufficient in a fibrosis stage 2/3 population?
 - Solution: Composite (at the individual/patient level) of <u>2-stage improvement of fibrosis and no worsening of NASH</u>





Regulatory update from Europe – Interim endpoints in NASH phase 3 trials

- New situation:
- No relevant anti-inflammatory activity, but relevant effects on fibrosis expected
- But also different population intended: Stage 3 and 4 (cirrhosis!)
 - 1-stage reduction for cirrhotic patients (without worsening of inflammation (as composite at the individual level) regarded to be sufficiently strong in cirrhotics!
 - Stage 3 would still need an at least 2-stage reduction of fibrosis (without worsening of fibrosis (as composite at the individual level)

• Consequences: Conduct 2 trials in the two different populations?

However, responder based evaluations could be combined also!

Question unresolved: Is an interim analysis/endpoint necessary for stage 4 patients?





Regulatory update from Europe – Interim endpoints in NASH phase 3 trials

- Can these strong endpoints be met within a realistic timeframe?
- There are measures to increase the chances of success:
 - Good phase 2 data can help to estimate the effect sizes that can be achieved in a certain time frame
 - Prolong the time until interim analysis (=increase the effect size)
 - Increase the number of patients to be included in the interim (= strengthen the statistical basis

Thank you for your attention!





