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Regulatory update from Europe:

Interim endpoints in phase 3 NASH trials

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- The previously proposed/presented co-primary evaluation of two compos… endpoints for the interim has been accepted:
  - Individual level: Composite of complete resolution of steatohepatitis (0 for ballooning, 0-1 for inflammation) and no worsening of fibrosis stage
  - Individual level: 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
- … endpoint is required based on the following:
  - …atory changes and fibrotic changes and their alteration… known
  - The endpoints at the interim… …g to conclude on a positive benefit-risk at the time of the inte… presented later)

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 IV!

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- (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)

At the population level

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

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- 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 2-stage improvement of fibrosis and no worsening of NASH

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- 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?

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- Can these strong endpoints be met within a realistic time-frame?
- 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!

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