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Liver Forum 10: NASH regulatory update

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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

Overview

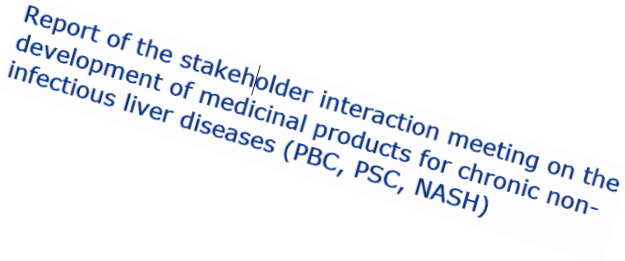
- Current content of the reflection paper regarding trial design
- Regulatory interaction
  - Reflection paper main content/Stakeholder meeting discussion
  - Written Comments on the Reflection Paper
  - Scientific Advice
  - Future perspectives

Content of the EMA reflection paper

Current content with regard to trial design and endpoints:

- Development strategy with „surrogate“ endpoints at intermediate time-points and confirmatory approach post-licensing possible due to unmet medical need; placebo-control recommended.
- Patient population: Either Non-cirrhotic (fibrosis stage 2 and 3) or cirrhotic population; NASH diagnosis by histology (activity), or (cirrhotics) appropriate support of NASH with other factors
- Non-cirrhotic population endpoint: Co-primary of histological evaluations of biopsies: „resolution of NASH without worsening of fibrosis“ and „improvement of fibrosis and no worsening of NASH“. Needs to be confirmed by hard endpoint data.
- Endpoints based on MoA: Possible, but if both co-primary EPs cannot be targeted, additional support needs to be presented (e.g. 2-stage fibrosis improvement in anti-fibrotics).
- Cirrhotic population endpoint: Reversal of cirrhosis. Potentially needs additional support and long-term outcome data. Other endpoints possible (e.g. MELD score improvement; HVPG improvement).
- Cirrhotic population with previous decompensation: Hard outcomes recommended (Decompensation events, LTx, death).
- Fixed duration of trials mentioned (although flexibility allowed)
- Combination treatment: Suitable for non-responder populations and those with high risk.

Regulatory interaction: Stakeholder meeting



Stakeholder meeting Dec 2018:

- Has been presented within the Liver Forum 9 meeting
- Short summary of main points of discussion:
  - The request for co-primary endpoints is a too demanding requirement and one of the components may be important enough from the patient‘s perspective
    - The request for co-primary endpoints is not adequate for certain MoA
    - The disharmonization of FDA and EMA requirements should be avoided
    - May unneccessarily prolong trial duration, and may take false conclusions
  - Requirements for combination therapy too strict
  - Need for development of PRO tools and inclusion of symptoms into trials not sufficiently addressed
  - Extend of CV safety documentation not clear
  - Paediatric issues: Presence of genetic factors, differences to adult disease, need for different endpoints

Regulatory interaction: Written comments overview

Written comments on Reflection paper:

- Total number of comments received: 19
- Total number of comments with regard to NASH parts: 15
- Stakeholder classification with comments on NASH:
    - 9 Industry (single company)
    - 1 Industry (association)
    - 2 Scientific organization/Learned society
    - 1 EU National regulatory agency
    - 1 Patient‘s Advicacy Group/Organization
    - 1 Multistakeholder Organization

Written comments on Reflection paper:

- Comment areas:
  - General:
    - Separate into 2 (or even 3) guidance documents (1 comment)
    - Separate the three disease entities more clearly (2 comments)
    - Separate chapters for non-cirrhotic and cirrhotic populations (1 comment)
    - Separate non-compensated and compensated cirrhotic chapters more clearly (1 comment)

    - Clarify the terms „early and late clinical trials“ (2 comments)
    - Should be mentioned that agents regarded to act on the cause of the disease are more suitable than anti-fibrotics“ (1 comment)
    - Medical need in NASH should be discussed, also more from a CV perspective (1 comment)
    - Classification of fibrosis stages be adapted to AASLD classification (1 comment)
    - Estimand chapters should be more precise (1 comment)
    - Too much emphasis on the need for hard endpoints (1 comment)
    - Non-invasive diagnosis methods favoured/should be more promoted (1 comment)

Written comments on Reflection paper:

- Comment areas:
  - Disease characterization:
    - Oversimplification of pathophysiology should be avoided (1 comment)
  - Inclusion criteria:
    - Consider concomitant medication (and add-on medication during the trial) potentially influencing disease outcome (4 comments)
    - NASH diagnosis requirements based on NAS-requirements (NAS>5 and NAS>4 with additional requirements) too strict (3 comments)
    - Requirement for previously failed dietary treatment should be deleted (1 comment) or clarified/modified (2 comments)
    - Cirrhosis diagnosis should not be histological (but clinical) (2 comments)
    - Criteria for presence of features of the metabolic syndrome should be inclusion criteria (2 comment)
    - Simplify inclusion criteria and separate cirrhotic and non-cirrhotic (1 comment)
    - NASH-cirrhosis diagnosis should be more flexible (1 comment)
    - Severity of cirrhosis should be classified according to established criteria (e.g. Child Pugh) (1 comment)

Written comments on Reflection paper:

- Comment areas:
  - Trial design/Endpoints:
    - The request for co-primary evaluation of the two composites too strict (11 comments)
    - The request for 2-stage improvement of fibrosis in antifibrotics is too strict (6 comments)
    - Symptoms (PROs) and evaluation of QoL should be included (6 comments)
    - The study duration should be given as „flexible“ only (5 comments)
    - Combination therapy requirements too strict (not only 2nd line and „at risk populations“) (5 comments)
    - Requirement for histology in „early“ trials should be deleted (4 comments)
    - Include „manifestation of T2DM“ (1 comment) and CV MACE (3-component) events in the „hard endpoints“ (2 comments)
    - Replace requirement for „MELD>14“ with „MELD>15“ (2 comments)
    - Reversal of cirrhosis should be classified as „hard endpoint“ (1 comment) or be recognized intermediate endpoint without restrictions (3 comments)
    - Manifestation of cirrhosis should be defined as „hard endpoint“ (1 comment)

Written comments on Reflection paper:

- Comment areas:
  - Trial design/Endpoints (continued):
    - Mention the use of special design features (e.g. adaptive design, extrapolation of placebo-control) for development of combination treatments (1 comment)
    - Suitability of MELD for a patient population with CV disease be checked (1 comment)
    - Allow more flexibility with regard to definition of „resolution of NASH“ especially with regard to the ballooning criteria (2 comments) or the steatosis criterion (1 comment)
  - Safety:
    - Clarify/State that CV outcome trials are not required for documentation of safety (3 comments)
    - It should be mentioned that treatments have no detrimental effect on other aspects of the metabolic syndrome (T2DM, obesity, serum lipids)

Written comments on Reflection paper:

- Comment areas:
  - Children:
    - Age cut-off at 10 years proposed (1 comment)
    - Biomarkers should be primary endpoints (1 comment)
    - Histology as endpoint should not be mandatory (1 comment)
    - Histology as endpoint may be needed (1 comment)
    - Different histological features to be taken account of, different scoring system likely be needed (1 comment)
    - Young children (age 6-10) may not be candidates for pharmacological treatment (1 comment)
    - Studies in children (<12 years) should be deferred until more natural history data are available (1 comment)

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EMA reflection paper: Future perspectives

- Schedule for finalization of the reflection paper currently unclear
- EMA still on „business continuity“ and will move to „definite premises“ at the end of the year only.
- Therefore only „rough estimation“ can be given at this point of time:
  - Discussion in the Gastroenterology Drafting Group finalize end of 2019
  - Discussion within relevant EMA groups and CHMP: further 3-4 months
  - Publication of final paper: 2nd-3rd Quarter 2020
  - All comments will be published including acceptance and reasons
- Content to be reflected:
  - Co-primary endpoints to be abandoned? (in consequences also the requirement for 2-stage improvement of fibrosis in anti-fibrotic compounds).
  - 2 separate documents (one for NASH, one for PBC and PSC)

Thank you for your attention!

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