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PSC Forum Session II: PSC Clinical Trials Design

Comments on the "Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH)" and its potential consequences for Clinical Trials Design

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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
  - Stakeholder meeting
  - Comments on the Reflection Paper
  - Scientific Advice
- Potential consequences for trial design
- Trials without baseline biopsies from the EU regulatory point of view

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.
- Primary endpoint: Histology and ALP reduction
- Co-primary evaluation recommended, both based on responder criteria
- Histological response: 1 stage reduction in fibrosis stage; alternatively „no worsening of fibrosis“ could be used (Nakanuma scoring system recommended).
- Serological response: Reduction of ALP to 1.3xULN, or to 1.5xULN with 40% reduction.
- „Confirmatory“ endpoints: combination of cirrhosis, MELD>14; decompensation events and LTx and death
- Need to have a complete set of non-invasive secondary endpoints (serum biomarkers, imaging), and clinical events (cholangitis, dominant stenosis, cancer, etc.)
- Trial duration: Recommend 2 years for intermediate endpoint; up to 5 years for final evaluation; dependent on mechanism of action, and magnitude of effect

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Regulatory interaction:

Report of the stakeholder interaction meeting on the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH)

Stakeholder meeting Dec 2018:

- Inclusion criteria/population related comments:

  - Population: Should allow occurrence of relevant (clinical) events in the population
  - Diagnosis of disease should be clinical (imaging and biomarkers)
  - Fluctuating biochemistry and cholangitis flares complicate inclusion
  - Trade-off between „too early“ population (ALP not good as biomarker) and „too late“ population with too much interference with dominant stricture and endoscopic treatment
  - Trade-off between patients with advanced fibrosis without relevant bile duct stenosis (which are hard to find) and effect on fibrosis best shown in F3/F4 patients
  - „Enrichment“ by (high) ALP may be a way forward
  - Inclusion of IBD patients should be dependent on mode of action (anti-fibrotics not for active IBD)
  - IBD investigational (or even regular) and other (e.g. antibiotic) co-medication will need to be considered; however, concurrent IBD population encouraged to be included.
  - In early trials a „mixed“ population may be acceptable (e.g. AIH overlap)
  - Stop of UDCA medication should not be required

Stakeholder meeting Dec 2018 (continued):

- <u>Endpoint related comments</u>:
  - ALP is acceptable/proposed as inclusion tool, stratification factor, its role as surrogate needs more clarification
  - Histology could be a robust and acceptable surrogate, and would be acceptable combined with ALP
  - Non-invasive liver stiffness measurement could be an alternative
  - PROs should be part of any trials in PSC (both for adults and children)
  - Data sharing on natural history studies and placebo-treated patients from clinical trials should be encouraged
  - Adequate powering of studies is difficult due to low prevalence and heterogeneity of the disease
  - The „totality of data“ review approach may be the best option
  - Prevention of fibrosis progression/manifestation of cirrhosis (or its reversal) could be a feasible and reasonable surrogate
  - <u>Children</u>: Overlap (e.g. PSC-AIH) more relevant
    - Based on current data GGT response appears to be reasonable surrogate

Written comments on Reflection paper:

- Total number of comments received: 19
- Total number of comments with regard to PSC parts: 11
- Stakeholder classification with comments on PSC:
  - 4 Industry (single company)
  - 1 Industry (association)
  - 2 Scientific organisation/Learned society
  - 1 EU National regulatory agency
  - 2 Patient‘s Advocacy Group/Organisation
  - 2 Multistakeholder Organisation

Sums up to 12; 2 stakeholders have given a joint comment (multistakeholder with patient organisation)

Written comments on Reflection paper:

- Comment areas:
  - General: Divide document into one for PSC/PBC and one for NASH (2 comments)

  - Disease characterisation:
    - Abandon „dominant stricture“ (2 comments)
    - „Small duct disease“ problematic (1 comment)

  - Inclusion criteria:
    - „Compulsory requirement for biopsy“ criticized for not being in accordance with practice guidelines (6 comments)
    - Inclusion of „overlap“ patients problematic (even in exploratory trials) (1 comment)
    - Inclusion of IBD patients encouraged (2 comments)

Written comments on Reflection paper:

- Comment areas:
  - Design and endpoints:
    - Too much focus on ALP and histology; too much focus on IPSCG paper (6 comments)
      - Includes at least 2 comments suggesting abandoning histology
      - Includes also at least one suggestion to abandon ALP
    - Primary endpoints (intermediate) should be more flexible and/or more precise (3 comments)
      - Allow ELF score or MRCP/ERCP/PTC as reasonable surrogate,
      - If histology is included more focus be given to fibrosis development (3 comments)
      - Focus on Nakanuma system should be abandoned (allow other especially when focusing on fibrosis) (2 comments)
      - ALP responder definition arbitrary (3 comments)
    - Development of PROs
      - Evaluation of symptoms should be compulsory (4 comments)
    - Study duration generally too long and demanding (1 comment)

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EMA reflection paper: Future perspectives

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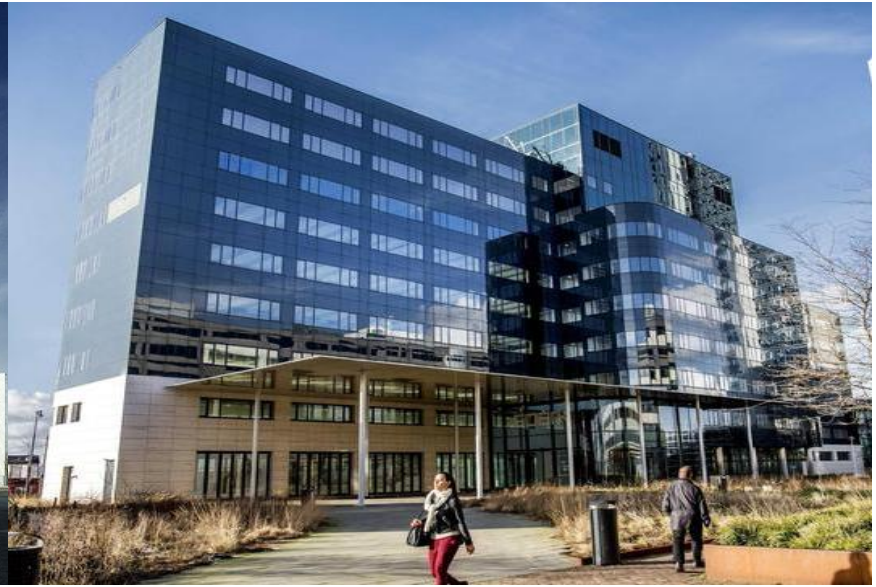
- Schedule for finalization of the reflection paper currently unclear
- EMA still on „business continuity“ and will move to „definite premises“ at the end of the year only.
- Therefore only „rough estimation“ can be given at this point of time:
  - Discussion in the Gastroenterology Drafting Group finalize 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 with comments on acceptance incl. reasons
- Content to be reflected:
  - More flexibility (with regard to endpoints, study duration, etc.?)
  - 2 separate documents (one for NASH, one for PBC and PSC)

Thank you for your attention!



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