Federal Institute
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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory update from Europe:

Study design, population, endpoints and pitfalls of phase 3 trials in NASH

Elmer Schabel MD

Regulatory update from Europe - Overview

- Status of development programmes in NASH from the European perspective
- Current proposals for study design, populations, and endpoints in clinical trials in NASH accepted by CHMP
- Problems identified with regard to
  - Interim endpoint
  - Final endpoint
  - Safety evaluation
  - Statistics

Status of development programmes in NASH from the European perspective

- Current number of development programmes presented to CHMP since 2012: 2!
    - Number of advice procedures higher, because not only phase 3 has been dealt with, but also quality, non-clinical and early clinical development.
- Current number of development programmes presented to the NCA Germany: 1

- There is therefore still very limited experience with regulatory issues in the field!

Current proposals for: Study design

- 2-stage design based on interim analysis with surrogate endpoints and final analysis of „hard outcomes“ generally accepted
- Compliant with European regulation, interim endpoints are suggested to support „conditional approval“, the condition being the final evaluation on „hard endpoints“.
- The high unmet medical need is acknowledged (has to be part of the justificaton!.
- Trials will be ongoing at the time of marketing authorisation (and availability of the medicinal product)
- Currently no proposal has been submitted for a „seamless“ phase 2-4 trial design, but phase 2 data (including dose-finding) have been available in all cases;
- Aspects of dose-finding have been proposed to be included into the phase 3-4 designs (e.g. limited number of different doses) and found to be acceptable. Dropping of dose regarded to be possible at interim.
- The conduct and presentation of a single pivotal trial has generally been accepted by CHMP (caveats see below).

Current proposals for: Patient population

- Proposed and accepted inclusion criteria mainly refer to a population with
  - Active NASH, defined as a NAS score of at least 4
  - Patients with relevant fibrosis (stages 2 and 3) main focus of developments
  - Patients with stage 1 fibrosis can be in- or excluded;
    - stage 1 population should/can be exempted from inclusion into the primary analysis.
    - Exclusion of stage 1 population will have impact on labelling!
    - An acceptable strategy identified has been to limit the inclusion of stage I patient to a certain extent (e.g. 10-15%)
    - Inclusion of stage I patients might be sensible if restricted to those with high inflammatory activity/NAS score
  - Exclusion of stage 4 patients acceptable (reversal of cirrhosis difficult/impossible?)

Current proposals for: Endpoints – Interim endpoint

- The previously proposed/presented co-primary evaluation of two composite 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
- The strength of the endpoint is required based on the following:
  - The interdependence of inflammatory changes and fibrotic changes and their alteration by interventions is at this point unknown
  - The endpoints at the interim analysis have to be sufficiently strong to conclude on a positive benefit-risk at the time of the interim analysis (despite the data to be presented later)

Current proposals for: Endpoints – Final endpoint

A final evaluation based on a composite of

- death, liver transplantation, cirrhosis related clinical events, and histological diagnosis of cirrhosis

has been accepted.

- Event driven evaluation considered the most feasible approach and acceptable (= no fixed duration of trial).
- Non-invasive regular screening for cirrhosis manifestation is acceptable (despite reduction of clinical events composite); cirrhosis is regarded to be a sufficiently strong surrogate
- The death component should include all-cause mortality but not only liver-related mortality
- The list of „cirrhosis related events“ should be as complete as possible (e.g. HCC etc.)
- The inclusion of prognostic scores into the composite (e.g. MELD-score >14) is acceptable
- The evaluation of the non-cirrhosis (non-histological) components should support the overall conclusions (but statistical significance not expected).

Problems identified Study design

- Study design should clearly define „background treatment“ with regard to
  - Diabetes medication
  - Treatment of obesity – More than „simple counselling“ expected; effect of treatment on weight will be looked at
  - Use of „NASH“-medication (Vitamin E; metformin, pioglitazone etc)
- Central evaluation of histology welcomed
- Problem: Serial liver biopsies
  - The more biopsies are pre-planned, the more missing data can be expected
  - Primary emphasis with regard to completeness of the data should lie on the interim evaluation

Problems identified Interim endpoint

- (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)

Problems identified Safety evaluation

- Is a similar safety documentation as e.g. for diabetes products necessary ?
  - Products treat a similar population with increased baseline risk of CV disease
  - Is the „Reflection paper on assessment of CV risk of medicinal products for the treatment of cardiovascular and metabolic disease“ (EMA/CHMP/50549/2015; draft) applicable?
  - The consideration of the paper is recommended, however, a „flexible“ approach is possible, depending on the mechanism of action of compounds, and the phase 2 trial (safety) results
    - A CV outcome study is usually not expected
    - Inclusion of all-cause mortality into the primary evaluation does partly take account of concerns
    - Evaluation of MACE and MACE-plus recommended as safety outcome, including meta-analytic approach for all data available.
    - Exclusion of „thresholds“ for increase in CV events not regularly considered necessary

Problems identified: Statistics

- The splitting of the type I error is considered acceptable, including the „asymmetric“ split, showing a stronger level of evidence for the interim (i.e. 0.01 and 0.04)
- The split itself does, however, not account for the fact that only one study is presented!
- According to guideline „CPMP/EWP/2330/99“ („one-pivotal study guideline“) the following will be expected:
    - Concordance of results across subgroups
    - External validity of the results (e.g. limitation of missing data)
    - More extreme levels of type I error (e.g. if usually two trials are the minimum, the type I error should be at least half of the „usual“, i.e. 0.005 at interim and 0.02 at final)

Problems identified: Statistics

- Can the interim analysis conducted for conditional approval be used for sample-size re-calculation for the final evaluation?
  - Currently only a proposal to conduct an interim based on a 100% evaluation of the interim histology has been discussed and found to be acceptable
  - Caveats: Statistical implications: Should be blinded, but this might not be possible (evaluation for the „interim endpoint“ already available, which will include the final endpoint „cirrhosis“!). Type I error control might become an issue
  - „Linearity“ of occurrence events (of cirrhosis and its compliactions) might not hold (but an assumption of „linearity“ might be sufficiently conservative).

Problems identified: Trial design

- Problems of further conduct of the study after interim results become available/licensing of the medicinal product has taken place:
  - Enhanced measures to prevent increase in drop-outs might become necessary (this problem might increase when other products apart from the investigational product are already available)
  - Maintenance of blinding might become an issue
  - Potential for changes in recruitment might become an issue (hence plan for analyses of potential differences of the recruitment groups)

Thank you for your attention!

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