Review of the EMA reflection paper on chronic liver disease and report from the stakeholder meeting at EMA (December 2018)

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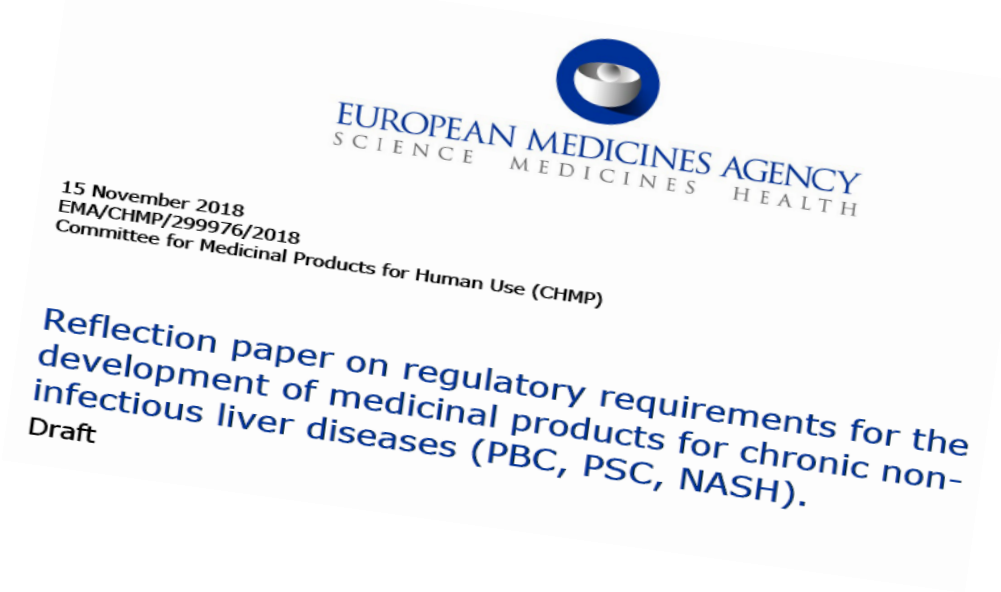
No conflict of interest

Review of the EMA reflection paper and report from the stakeholder meeting

Contents of the reflection paper, overview:

- General considerations (4.1)
- Patient population(s) (4.2.2.)
- Trial design and endpoints (4.2.3.)
  - Stage 2 and 3 fibrosis
  - Stage 4 fibrosis
  - Additional considerations on MoA
  - Target of estimation
  - Combination therapy
- Safety in NASH (4.6.2.)
- NASH in children and adolescents (4.7.1)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15 November 2018
EMA/CHMP/299976/2018
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH).

Draft

FDA Draft Guidance for Industry: Noncirrhotic NASH with liver fibrosis

- Comparison to EMA reflection paper.

Stakeholder meeting December 2018

- Presentations
- Discussions/controversial points

First written comments received.

Contents of the EMA reflection paper

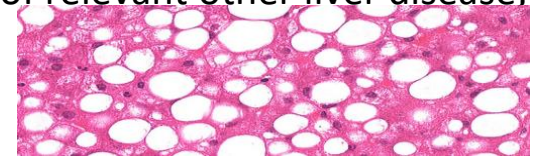
General considerations:

- Slowly developing disease process, long-term, „hard“ outcomes difficult to study
- Development relying on interim evaluations with „intermediate“ endpoints and confirmation at later time point is possible
- Requires the demonstration of the unmet medical need, the conclusion on positive-benefit risk
    - Also, but not included in the guidance: the disadvantages of putting a product on the market outweigh the risks, and a high likelihood that comprehensive data will be provided at a later time
- Evaluations (=endpoints) are currently mainly based on histology, requiring liver biopsy
- This, however, is unwanted in the long-term: Development of non-invasive methods encouraged

Contents of the EMA reflection paper

Patient population:

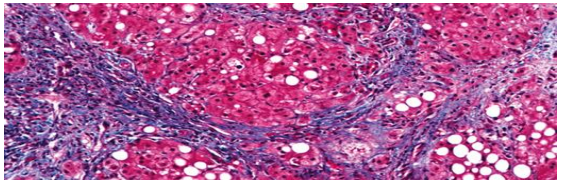
- General: Should be representative of the target population, well balanced (e.g. demographics, concomitant disease)
- Screening: presence of features of metabolic syndrome, exclusion of relevant other liver disease; need for biopsy in all patients



Non-cirrhotic population:

- Stages: Fibrosis stage 1 should be excluded (minimal risk with regard to progression to end-stage disease)
- Include stages 2-4
- Include stages 2 and 3 based on the following features of NASH: either NAS>5 or NAS≥4 with at least NAS≥1 in lobular inflammation and ballooning

Contents of the EMA reflection paper



Patient population:

Cirrhotic population

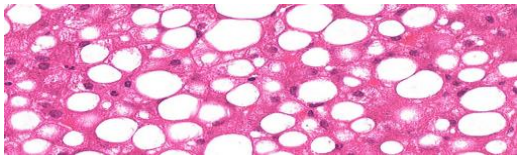
- Include stage 4 based on: Historical biopsies with NASH, or high likelihood of NASH based on biomarker/imaging and co-morbidity (T2DM, obesity)
- Inclusion of late stage cirrhosis (decompensated) patients possible after other populations have been studied.
- Due to additional risks of biopsies in these patients, inclusion based on historical biopsies may be possible

Other

- Non-invasive inclusion criteria could be used in early stage trials (with conditions!)
- Patients to be included should have undergone at least one unsuccessful attempt of weight reduction
- Comorbidities: Should be adequately treated with stable doses at inclusion. May be used as stratification factor.

Contents of the EMA reflection paper

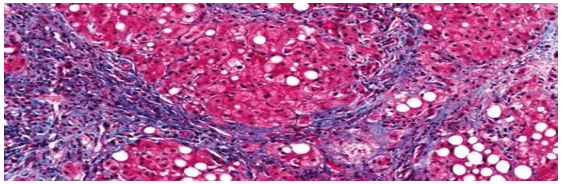
Trial design and endpoints:



Non-cirrhotic population:

- Long-term endpoint:
    - Composite of histological diagnosis of cirrhosis, MELD>14, decompensation events, liver transplantation and death
- Intermediate endpoint with co-primary evaluation of:
    - 1. The resolution of NASH without worsening of fibrosis.
    - 2. The improvement of fibrosis without worsening of NASH
- The co-primary evaluation proposed because stringency is required based on the uncertainties associated with the „interim“ strategy

Contents of the EMA reflection paper

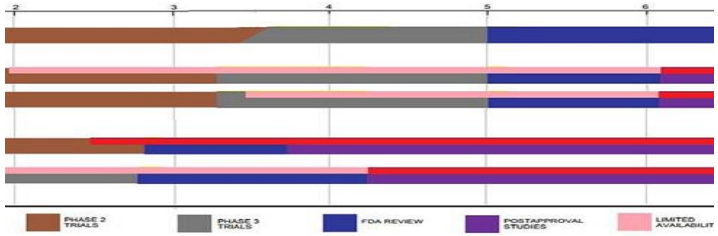


Trial design and endpoints:

Cirrhotic population:

- Use of all-cause death and liver decompensation events acceptable
  - Can be used in an „all-comer“ study (within a strategy without „intermediate endpoints“), as well as with „late-stage“ cirrhosis, and has to be used as „hard outcome“ in case an „intermediate strategy“ is followed.
- If a need for „intermediate endpoints“ ist identified :
  (due to long-term development of the above in „early cirrhosis“ endpoints can be the following):
  - Histological reversal of cirrhosis (to stage 3 fibrosis or less) – possible
  - Problem: Material to support that reversal of cirrhosis associates with a similar reduction of the risk than progression from non-cirrhotic stages to cirrhosis is currently lacking.
- In patients with „late stage cirrhosis“, the following may be possible:
  - Lowering of MELD score (threshold to be defined)
  - Lowering of HVPG (e.g. below 10 mmHg)

Contents of the EMA reflection paper



Trial design and endpoints:

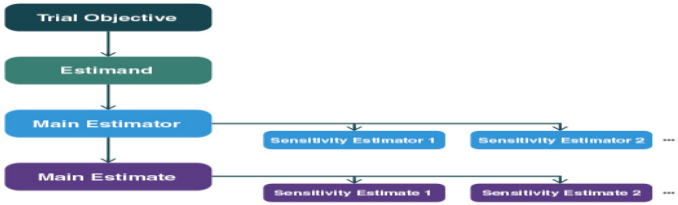
Considerations on mode of action:

- Usual MoA includes reduction of „fat toxicity“ and/or reduction of inflammation
- If the molecular target is fibrosis development, the treatment goal of „resolution of NASH“ could be out of reach
- In such cases, when an „intermediate endpoint strategy“ is followed, the following is possible:
    - Strengthen the endpoint for fibrosis regression:
        - Regression of 2 stages without worsening of NASH

Duration of trials:

- Duration needed for the proposed endpoints currently uncertain
- Generally, a 2-year intermediate evaluation study duration, and an overall 5-year final duration is recommended.
- Modification possible based on factors trial size, magnitude of effect, patient characteristics, statistical rigour needed.

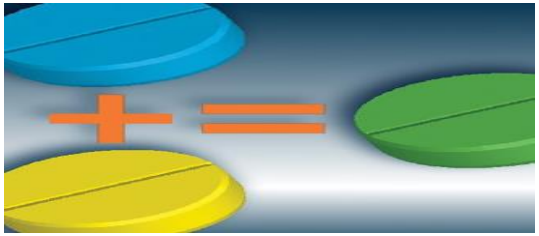
Contents of the EMA reflection paper



Target of estimation (estimand):

- Trial planning, design, conduct, analysis and interpretation must be aligned with the estimand (Reference given to ICH E9(R1) Draft Addendum
- Evaluation of potential „intercurrent“ events necessary:
  - Treatment discontinuation (including study discontinuation)
  - Use of additional medication
- For an intermediate endpoint strategy:
  - Follow the treatment policy strategy (measured outcome regardless of the occurrence of intercurrent events)
  - However, all outcomes of interest should be collected independently from the occurrence of an intercurrent event.
  - Align statistical analysis with regard to imputation of missing data with the target of estimation.
- For the „hard endpoint“ evaluation:
  - Also use „treatment policy strategy“ and aim at complete follow-up
  - Especially important due to the expectation that censoring of patients with incomplete follow-up may have a different prognosis (leading to informed censoring).
  - Refusal of biopsy may need to be counted as event

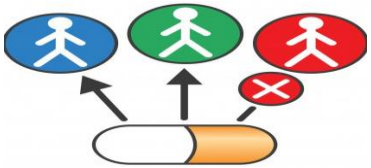
Contents of the EMA reflection paper



Combination treatment:

- Caution needed in a situation when no treatment is available at all
- Reference is made to the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017)
- Combination treatment should be based on
  - valid therapeutic principles and
  - the demonstration of the contribution of each of the combination partners
- Before a combination treatment is explored and investigated, the single substances should have been fully investigated
- Adequate patient population definition proposed:
  - High risk of progression or
  - Insufficient response to mono-therapy

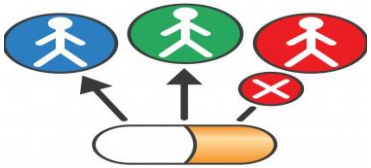
Contents of the EMA reflection paper



Safety:

- Problem: Overlap of symptoms of the disease, as well as fluctuation of biomarkers also used for safety, and the potential toxic effects on the liver
- Identify true cases of drug-induced liver injury (DILI)
  - Use tools available (e.g. RUCAM) as well as expert adjudication, and biopsy
  - Search and identify Hy‘s law cases
- Define rules for safety evaluation (potentially different from „regular approaches“) due to existing baseline abnormalities. This includes:
  - Stopping rules, thresholds for clinically relevant events
  - Recommendation to use „experimental“ safety biomarkers

Contents of the EMA reflection paper



Safety:

- Safety evaluation also hampered by the high-risk of patients for cardiovascular events (and death)
- Consideration should be given to the „Reflection paper on assessment of cardiovascular safety profile of medicinal products“ (EMA/CHMP/505049/2015)
- Further research into the natural history of NASH-patients with regard to CV risk, and occurrence of such events warranted.
- Evaluate also development of parameters related to CV-risk such as:
    - Lipid profile
    - Glucose homeostasis
    - Inflammatory parameters
    - Occurrence of MACE

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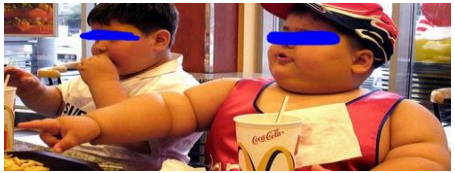
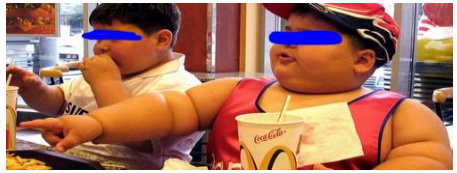


Children

- NASH is a relevant health problem in the paediatric population
- Two specific problems in children:
  - Ethical issues associated with repeated biopsy
  - Unclear meaning of different histological pattern
- Consequently, further data and re-evaluation of existing data on the natural history is warranted
- Adequate age range has to be determined (unclear whether pharmacological treatment is appropriate under the age of 10)
- Unclear how much data in adults are needed to start investigations in children (current recommendation is to wait until long-term outcome data become available)
- Further natural history data as well as outcome data for substances, may allow a more procise estimation of the extent of extrapolation possible

Contents of the EMA reflection paper



Children

- Necessary in any case: PK, and determination of appropriate dose, as well as age-appropriate pharmaceutical formulation
- Conduct of clinical studies with histological endpoints may ultimately be needed but ethical concerns may need to restrict to e.g. older age groups, and more advanced disease
- Further validation of imaging methods, and biomarkers desirable

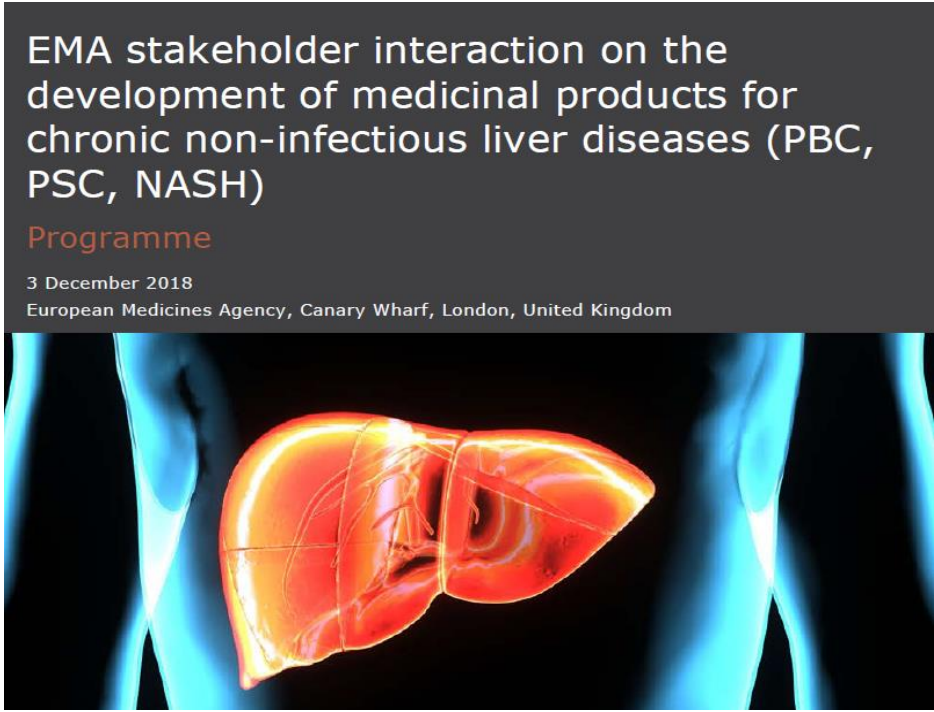
EMA stakeholder meeting

- Questions

- Discuss the difficulties and opportunities for drug development in the field of chronic liver disease which should include:
  - Identification of appropriate endpoints including validation of adequate surrogate endpoints/biomarkers
    - Suitable study populations
    - Potentially adequate trial designs.
- Discuss similarities and differences of the disease entities and their impact on regulatory requirements.
- Specify needs and anticipated problems of Paediatric drug development (especially for NASH)

- Presentations

- Discussion Controversies



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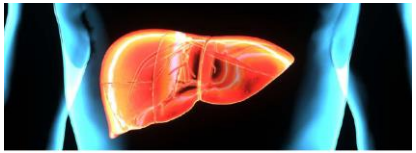

NASH – the patient perspective

Yvonne Gray – Newcastle, UK

Overall Summary:

Report on a personal patient history with some of the “typical” co-morbidities and history being present

Typical “late diagnosis” after years of slightly elevated transaminases attributed to type II diabetes, then diagnosed with grade III fibrosis.

Urgent appeal to the audience to pay attention to “light elevation of liver enzymes”, to hardships of chronic disease, and to abstain from any stigmatisation

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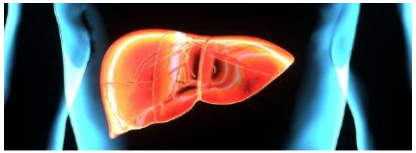
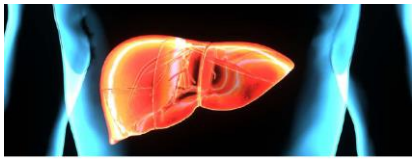


Definition, natural history and current therapy

F. Tacke, Aachen, Germany

Overall Summary:

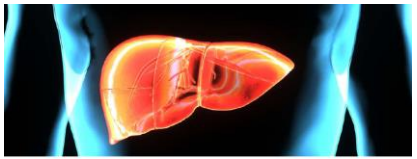
- Metabolic liver diseases increase tremendously and will become the main cause for cirrhosis, liver transplantation and liver cancer
- Fibrosis is considered the key mechanism for prognosis – can be assessed by non-invasive tests, risk scores and (if needed) liver biopsy
- effective lifestyle changes or bariatric surgery can improve liver histology - no general recommendation for vitamin E, pioglitazone, UDCA, silymarin
- surveillance for liver-related complications (cirrhosis, portal hypertension, HCC) and comorbidities (cardiovascular, metabolic, renal, malignancies) is needed in high-risk patients



Outcome in NASH trials: histology, hard outcomes, surrogates

L Castera, Paris, France

- Problem: High rate of screen failures for trials in NASH with histological evaluation
- Evaluation of non-invasive tests:
  - TE and MRE are not reliable in defferentiating NASH from simple steatosis
  - TE and also MRE have high accuracy in diagnosign advance fibrosis (F3-4)
  - Serum biomarkers are acceptable to rule out advanced fibrosis
  - NAFLD fibrosis core and FIB-4 are the most accurate and best validated



Outcome in NASH trials: histology, hard outcomes, surrogates

L Castera, Paris, France

- Surrogate endpoints:
  - Generally accepted endpoint is „regression of fibrosis (of at least 1 stage) without worsening of NASH in phase 3.
- Lessons learned from viral hepatitis:
  - In viral hepatitis, eradication or virus suppression is associated with decrease of liver stiffness over time.
  - In the absence of paired liver biopsies, it is difficult to discriminate whether this is related to improvement in inflammation or fibrosis.
  - Liver stiffness cannot be currently used as a good surrogate of cirrhosis regression.
  - No standardized definition of liver stiffness improvement is available and no correlation with clinically relevant hard endpoints has been shown.

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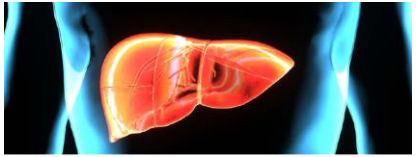
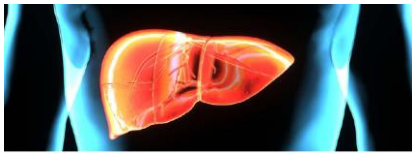
Outcome in NASH trials: histology, hard outcomes, surrogates

L Castera, Paris, France



Take home messages:

- Serum biomarkers have limited value for enriching populations for clinical trials
- No highly sensitive and specific blood tests neither imaging modality can reliably discriminate NASH from simple steatosis
- TE is useful to identify NAFLD patients with advanced fibrosis, who are at the greatest risk of disease progression and appears as the method of choice
- The added value of CAP is currently under investigation
- MRI-PDFF is the most accurate method for detection and grading of steatosis and seems sensitive to changes. Relevant cut-offs for steatosis improvement remain to be defined and validated
- MRE appears as the tool of choice for assessing treatment response but value of liver stiffness as a surrogate of fibrosis regression remains to be demonstrated
- Liver stiffness decrease needs to be correlated with hard clinical outcomes



Trial designs and study populations

Q. Anstee, Newcastle, UK

- Study population:
  - Has to consider placebo response which is 25% for ≥2 point improvement in NAS and 21% for ≥1 stage improvement in fibrosis; response higher in lower baseline severity
  - Non-cirrhotic population:
    - Early trials: Histologically defined study population not mandated
    - Phase 2b/3/4: NAS≥4 (with ≥1 for each component) and F2-F3 (F3 preferred)
  - Cirrhotic population:
    - Early trials: Histologically defined study population not mandated but advisable
    - Phase 2b/3/4: NAS≥3 (with ≥1 for each component) plus F4 fibrosis.

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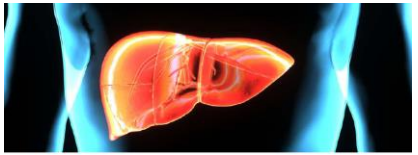
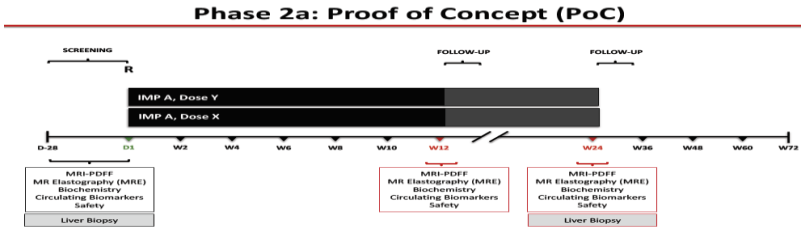
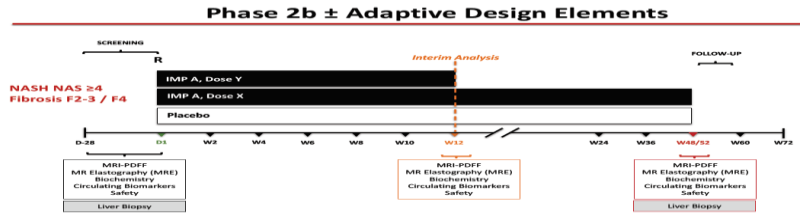
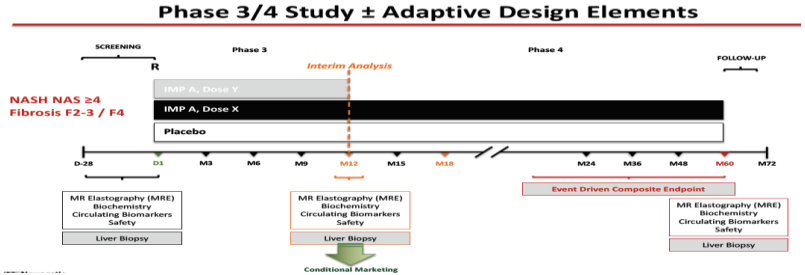
Trial designs and study populations

Q. Anstee, Newcastle, UK









- Trial designs:
- Phase 2a
  - histology not always necessary
  - Placebo not mandated
- Phase 2b
  - Histology necessary
  - Adaptive elements possible
- Phase 3-4
  - Histology primary endpoint for CMA
  - Event driven endpoint for full approval
  - Adaptive design elements possible

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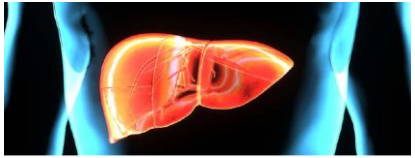

Trial designs and study populations

Q. Anstee, Newcastle, UK

- Endpoints:
  - Pre-cirrhotic population:

Phase 2a: Histologically defined study endpoints not mandated*

Phase 2b/3: Histologically defined study endpoints with NASH + Fibrosis*

Resolution of NASH, without worsening of Fibrosis (NAS component Ballooning = 0 and Inflammation = 0-1)

Improvement of Fibrosis by ≥1 stage(s), without worsening of NASH

Phase 3/4: Event-driven endpoints*

Composite endpoint composed of histopathologic progression to cirrhosis, liver-related clinical outcomes, and all-cause mortality

Event Free Survival (Hepatic Decompensation, HCC, OLT, Liver-Related and/or All-Cause Mortality)

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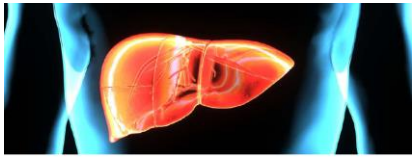


Trial designs and study populations

Q. Anstee, Newcastle, UK

- Endpoints:
  - Cirrhotic population:

Phase 2a: Histologically defined study endpoints not mandated but should be considered*

Improvement Portal Hypertension (HVPG <10 mmHg) and/or MELD

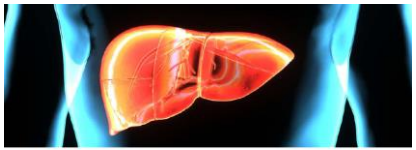
Phase 2b/3: Histologically defined study endpoints with NASH + Fibrosis required*

Improvement of Fibrosis by ≥1 stage(s), without worsening of NASH

Improvement Portal Hypertension (HVPG <10 mmHg) and/or MELD

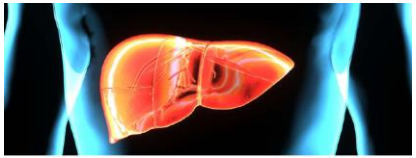
Phase 3/4: Event-driven endpoints*

Event Free Survival
(Hepatic Decompensation, HCC, OLT, Liver-Related and/or All-Cause Mortality)



Children – Piotr Socha, Warsaw, Poland

- How to define the population in need for pharmacotherapy
  - Advanced disease? Significant steatosis?
  - Can diagnosis be made without liver biopsy – Non-invasive methods (imaging + biomarkers)
- Appropriate endpoints: Synopsis of previous trials in children – wide variety
- Appropriate trial duration: Synopsis of previous trials: ranging from 4 months to 96 months
- Proposal:
  - Select population based on liver biopsy, consider risk/surrogate markers/genetic factors
  - Prefer surrogate markers as endpoints
  - Study duration minimum 6 months, but at least 1 year if fibrosis is the outcome parameter



Children – The PDCO apprach:

Chrissi Palidis, EMA, London, UK

Agreed PIPs: Elafibranor, Simtuzumab, Obeticholic acid, GS-0976, Selonsertib, Cenicriviroc plus 3 additional procedure under evaluation/discussion (as of December 2018)

- Waivers: Variable, between „below 2 years“ to „below 8 years“
- Clinical study proposals/requirements:
  - Double-blind, placebo controlled; PK necessary (either separate or as part of main study)
  - Primary endpoint: % of subjects with fibrosis improvement and no worsening of NASH
  - Secondary endpoints: biomarkers, incidence of liver related clinical events, imaging methods
  - Study duration: 1 to 2 years.

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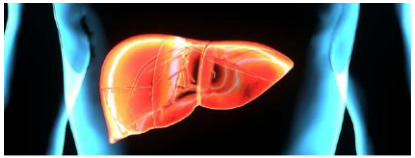
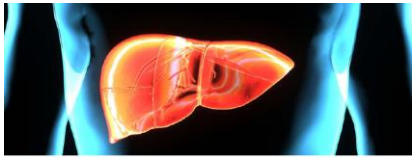


Discussion:

- Proposed primary endpoint for the „intermediate evaluation“ of efficacy:
  - Co-primary as requested by the reflection paper vs. alternative as requested by FDA of:
    - 1. The resolution of NASH without worsening of fibrosis.
    - 2. The improvement of fibrosis without worsening of NASH

- Part of the audience was questioning the EMA-proposed endpoint based on:
  - One of the components may be important enough from the patient‘s perspective (e.g. resolution of NASH and holding fibrosis progression)
  - Not adequate for certain mechanism of action
  - The additional requirements if only one of the co-primary EPs is achieved (e.g. the 2-stage improvement in fibrosis) may be of questionable clinical relevance (i.e. low treatment effect)
  - „too strong“ of a requirement,
  - Different requirements in the two areas/agencies (EMA/FDA)
  - Will valuable treatments with positive benefit-risk be missed wrongly?
  - Fulfilling both end-points may require too long duration of trials (observation time)



Discussion:

- Position defending the rationale of the EMA concept paper:
- The (legal) requirements for conditional approval (CMA) aimed at with the „intermediate“ endpoints requires the following four elements. :
  - A positive benefit-risk balance at the time of first licensing
  - Unmet medical need is present and likely to be fulfilled with the compound
  - The benefit to public health with immediate availability outweighs the risks due to incomplete data
  - It is likely that the applicant will be able to provide comprehensive data
- Unclear whether these can be fulfilled
- Improvement of 1 stage of fibrosis may lie within the variability of histological evaluation (at least for non-cirrhosis, especially stage 2 patients) and its clinical relevance would need definition.
- Improvement/resolution of NASH without improvement of fibrosis may not relevantly improve the prognosis of the patient (or may indicate a too short observation)

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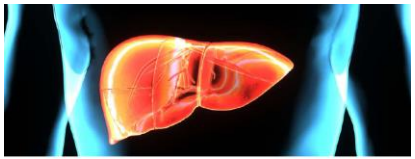
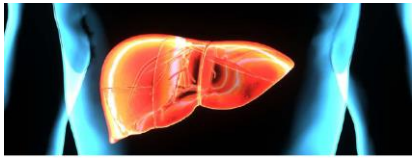


Discussion (continued):

- Problems with pure „anti-fibrotic“ mode of action:
  - Would raise concerns in terms of HCC
  - Would point to the need for combination therapy. Combination therapy currently unresolved
- Problems attached to life-style and medication (exercise and diet, alcohol, and concomitant medication)
  - Needs standardisation, should it be implemented at inclusion and during trials (and to what extent), need for more specific recommendations identified for the reflection paper
- Problems attached to safety evaluations:
  - Extent of cardiovascular safety documentation (No. of patients, time of observation)
  - presence of symptoms (and thus potential for adverse events) has been underestimated previously
  - Need for development of PROs
- Problems of definition of the adequate paediatric population
  - Presence of genetic factors
  - Differences to adult disease,
  - Endpoints: (ethical) problems with biopsy, need for non-invasive markers
  - age limits



Full recording of the meeting available:

https://www.youtube.com/watch?v=TAYO2gOEwBU&list=PL7K5dNgKnawa9_BzHhuWZIxIbejBBnqMT&index=3

EMA reflection paper – Comments received

First comments received:

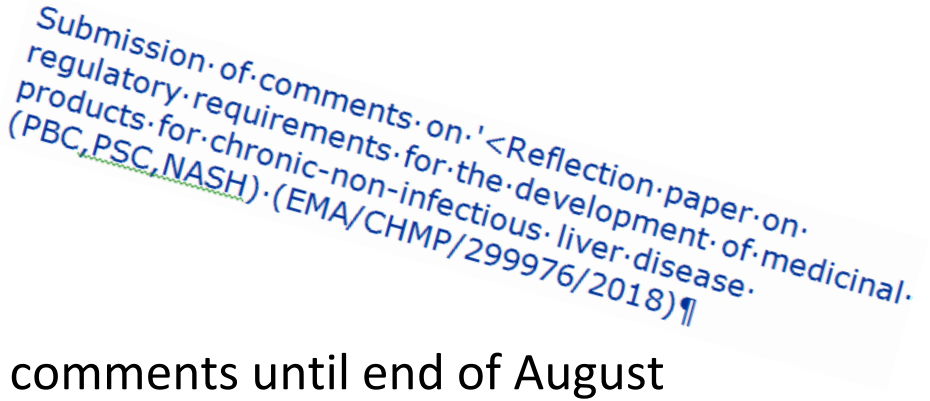
- Number of comments received up to end of June: 2

First comment:

- Short comment only, only one remark on NASH part, suggesting different inclusion criteria for NASH-cirrhosis population (based on Child-Pugh classification

Second comments:

- Main message: Requirement for co-primary endpoints may be too conservative, set up too high hurdles.
- Requirements for additional endpoints in case only one of the two co-primary is fulfilled (e.g. the 2-stage improvement in fibrosis) may also be too strict
- Requirement of a (fixed) 2-year duration too strict/long
- Combination treatment: Should not be limited to second line only
- Safety: It should be clarified that cardiovascular outcome trials are not required
- Limiting the non-cirrhotic population to fibrosis stage 2 and 3 could leave out „fast progressors“; these should be addressed



Further procedure:

- Open for receiving comments until end of August
- All comments will be commented upon, and will then be published with the final reflection paper
- Final Reflection paper to be drafted by GDG until end of 2019
- Further discussion at CHMP level expected.

Thank you for your attention!

In early March, EMA has relocated from London to the Spark building in Amsterdam Sloterdijk. This is a temporary accommodation.