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The EMA reflection paper on chronic liver disease and its implications for drug development in NASH

Content of the reflection paper and report from stakeholder meeting

Elmer Schabel MD

No conflict of interest.

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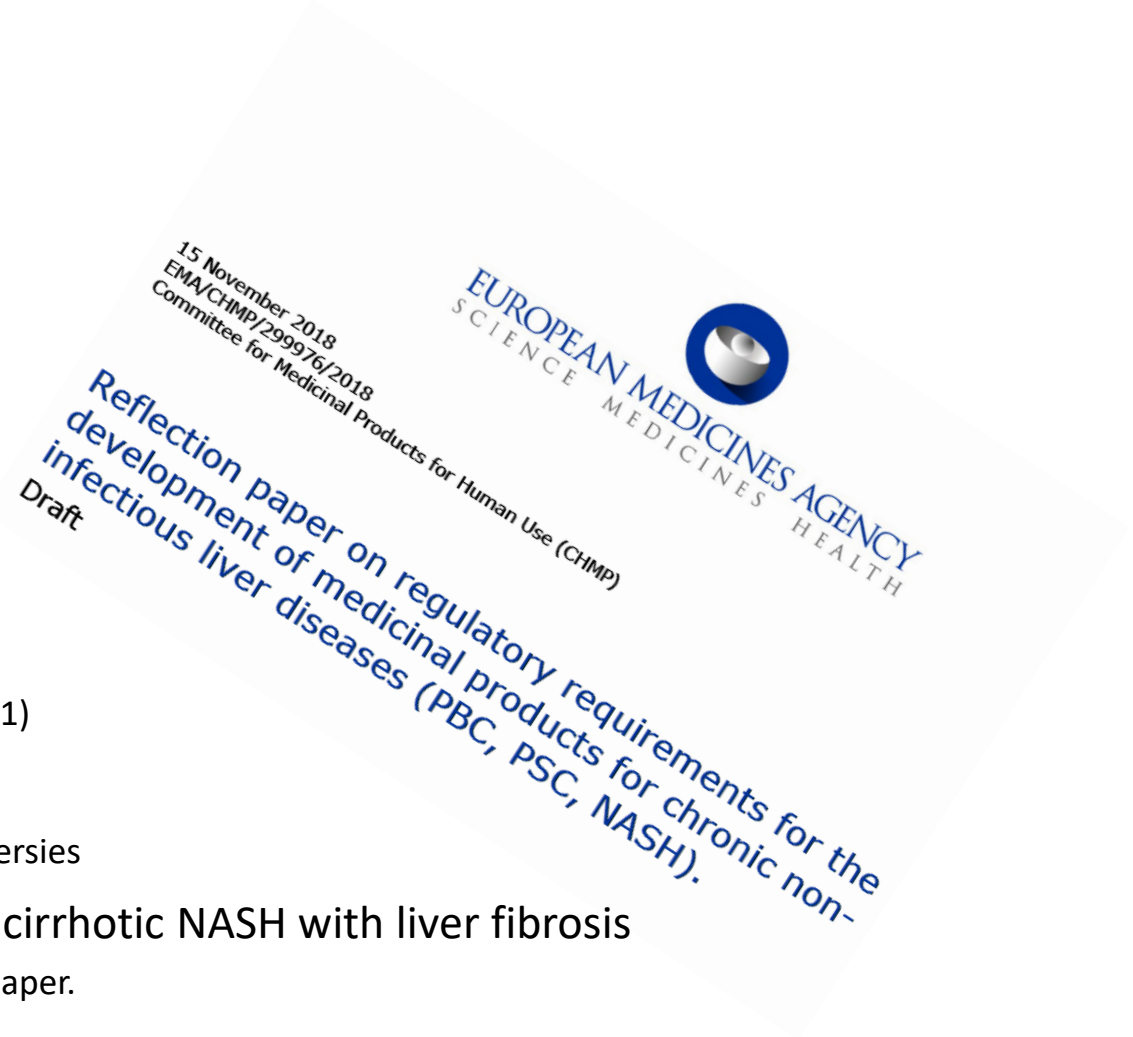
EMA reflection paper

Content 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)



Stakeholder meeting December 2018

- Presentations and main controversies

FDA Draft Guidance for Industry: Noncirrhotic NASH with liver fibrosis

- Comparison to EMA reflection paper.

EMA reflection paper

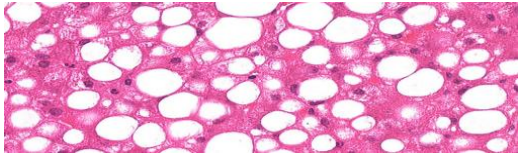
General considerations:

- 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 likelyhood 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

EMA reflection paper

Patient population:

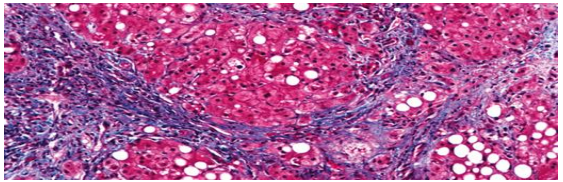
- General: Should be representative of the target population, well balanced (e.g. demographics, concomittant disease)
- Screening: presence of features of metabolic syndrome, exclusion of relevant other liver disease; need for biopsy in all patients



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

EMA reflection paper



Patient population:

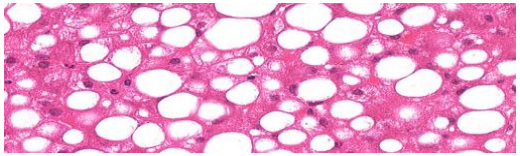
Cirrhotic population

- 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.

EMA reflection paper

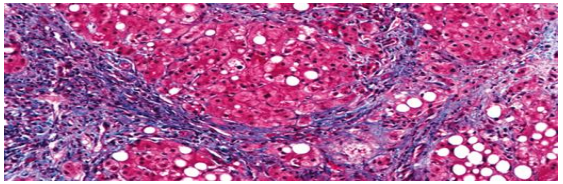


Trial design and endpoints:

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 evlauation 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

EMA reflection paper

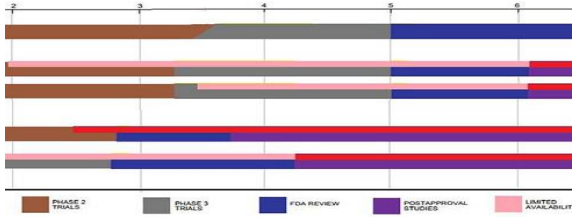


Trial design and endpoints:

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)

EMA reflection paper



Trial design and endpoints:

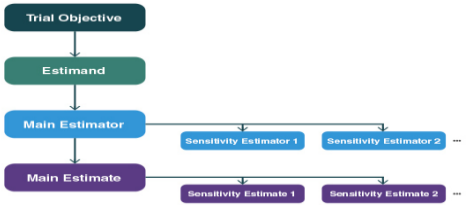
Considerations on mode of action:

- Usual MoA includes reduction of „fat toxicity“ and/or reduction of inflammation
- If the molecular target is fibrosis development, the tretment 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.

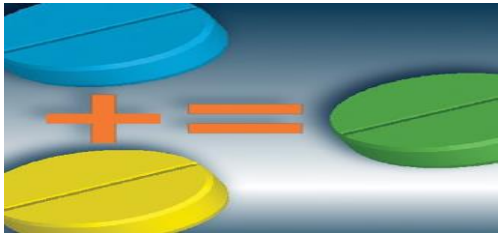
EMA reflection paper



Target of estimation (estimand):

- Trial planning, design, conduct, analysis and interpretation mjus 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 expactation 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

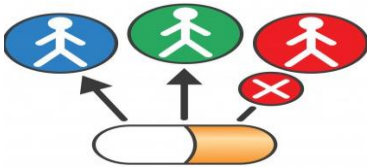
EMA reflection paper



Combination treatment:

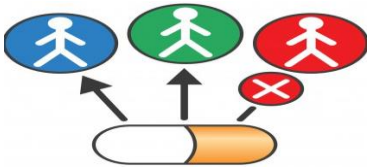
- Caution needed in a situation when no treatment is available at all
- Reference is made to the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017)
- Combination treatment should be based on
  - valid therapeutic principles and
  - the demonstration of the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

EMA reflection paper



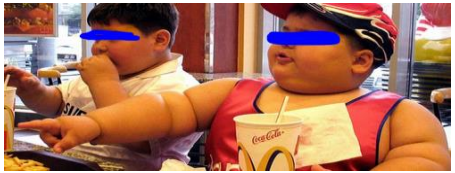
- Safety:
- Problem: Overlap of symptoms of the disease, as well as fluctuation of biomarkers also used for safety, and the potantial toxic effects on the liver
- Identify true cases of drug-induced liver injury (DILI)
    - Use tools available (e.g. RUCAM) as well as expert adjudication, and biopsy
    - 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, threholds for clinically relevant events
    - Recommendation to use „experimental“ safety biomarkers

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 „Refelction 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

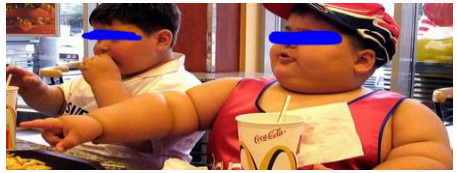
EMA reflection paper



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

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

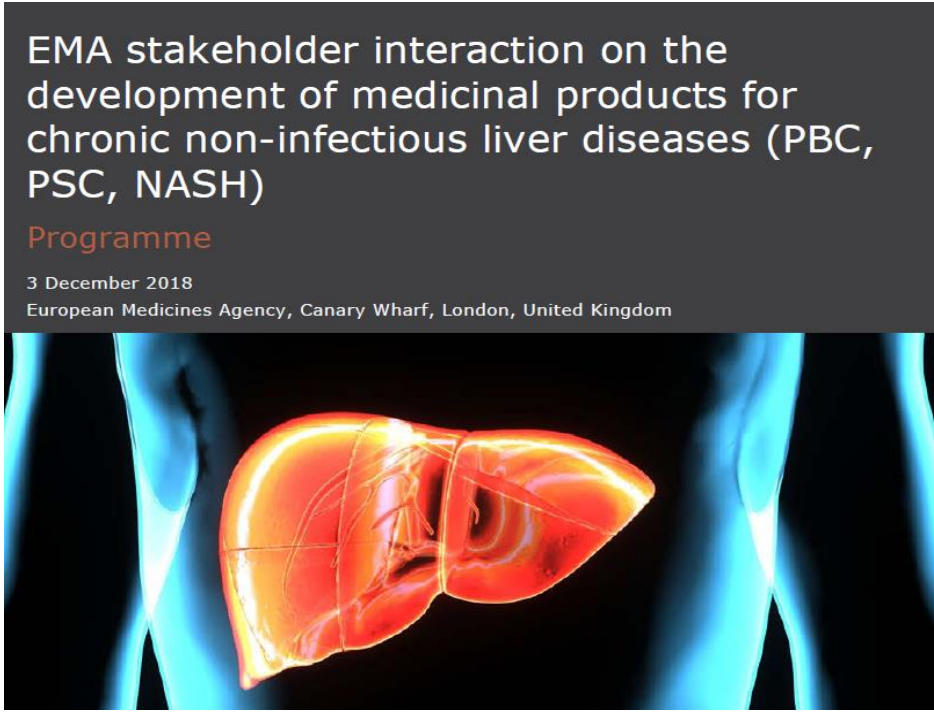
EMA stakeholder meeting

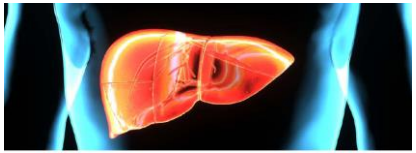
- Questions

- 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

- Controversies



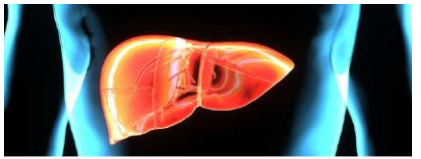


Definition, natural history and current therapy

F. Tacke, Aachen, Germany

Overall Summary:

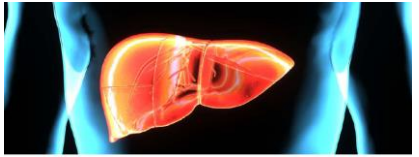
- Metabolic liver diseases increase tremendously and will become the main cause for cirrhosis, liver transplantation and liver cancer
- Fibrosis is considered the key mechanism for prognosis – can be assessed by non-invasive tests, risk scores and (if needed) liver biopsy
- effective lifestyle changes 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

- 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



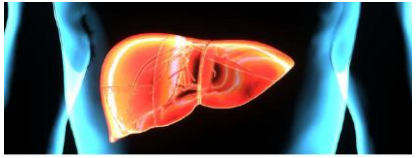
Outcome in NASH trials: histology, hard outcomes, surrogates

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 supression 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.

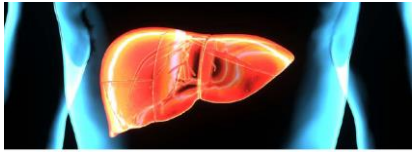
Outcome in NASH trials: histology, hard outcomes, surrogates

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



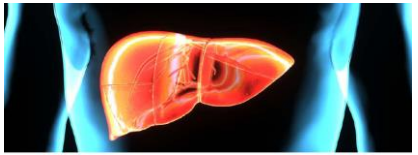
Trial designs and study populations

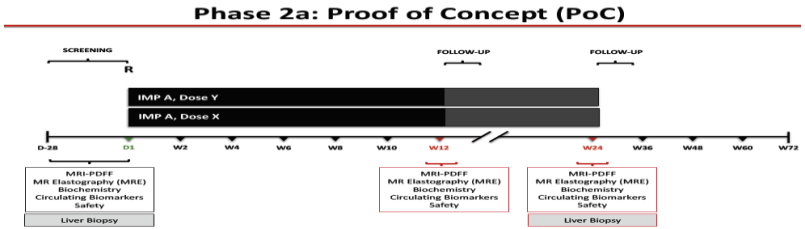
Q. Anstee, Newcastle, UK

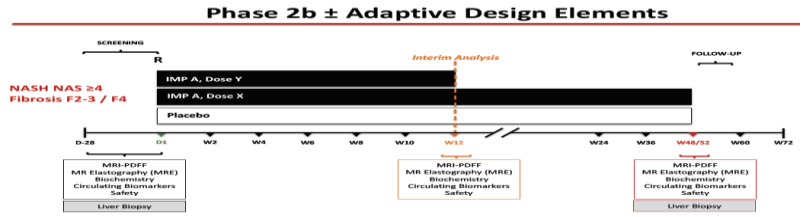
- Study population:
  - Has to consider placebo response which is 25% for ≥2 point improvement in NAS and 21% for ≥1 stage improvement in fibrosis; response higher in lower baseline severity
  - Non-cirrhotic population:
    - Early trials: Histologically defined study population not mandated
    - Phase 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.

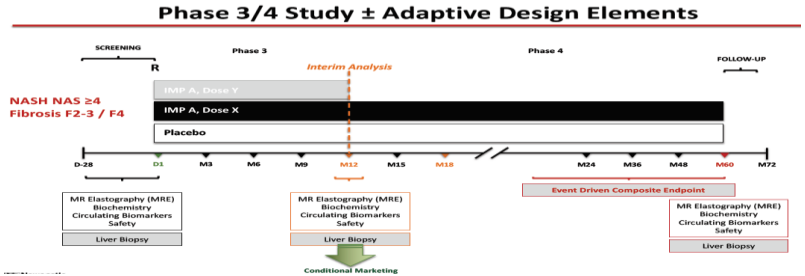
Trial designs and study populations

Q. Anstee, Newcastle, UK

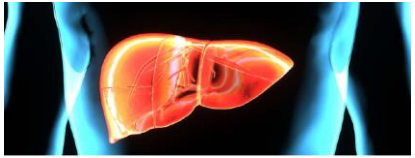








- Trial designs:
- Phase 2a
  - histology not always necessary
  - Placebo not mandated
- Phase 2b
  - Histology necessary
  - Adaptive elements possible
- Phase 3-4
  - Histology primary endpoint for CMA
  - Event driven endpoint for full approval
  - Adaptive design elements possible



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*

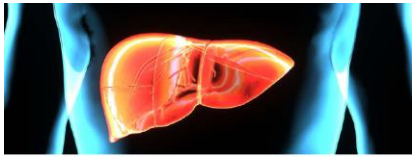
Resolution of NASH, without worsening of Fibrosis
(NAS component Ballooning = 0 and Inflammation = 0-1)

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)



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

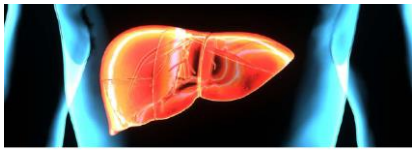
Phase 2b/3: Histologically defined study endpoints with NASH + Fibrosis required*

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

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

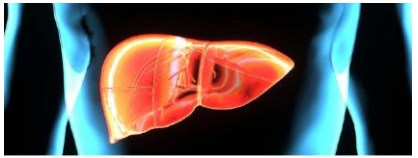
Phase 3/4: Event-driven endpoints*

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

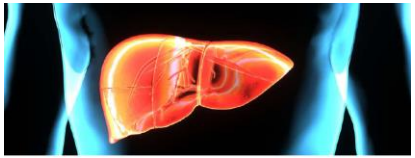


Children – The PDCO apprach:

Chrissi Palidis, EMA, London, UK

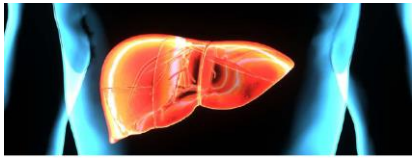
Agreed PIPs: Elafibranor, Simtuzumab, Obsticfholic acid, GS-0976, Selonsertib, Cenicriviroc plus 3 additional procedure under evaluation/discussion

- Waivers: Variable, between „below 2 years“ to „below 8 years“
- Clinical study proposals/requirements:
  - Double-blind, placebo controlled; PK necesssry (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 clincal events, imaging methods
  - Study duration: 1 to 2 years.



Discussion/controversies:

- Proposed primary endpoint for the „intermediate evaluation“ of efficacy:
  - Co-primary as requested by the reflection paper vs. alternative as requested by FDA (and later published in the Draft guidance) 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:
  - Not adequate for certain mechanism of action
  - „too strong“ of a requirement
  - Different requirements in the two areas/agencies (EMA/FDA)



Discussion/controversies:

- EMA position:
- The 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 yavailable outweighs the risks due to incomplete data
  - It is likely that the applicant will be able to provide comprehensive data
- Therefore, „strong“ endpoints are required even at the time of CMA

Federal Institute for Drugs and Medical Devices

Comparison EMA reflection paper – FDA Draft Guideline

	FDA Draft Guideline	EMA reflection paper
Patient population overall:	Non-cirrhotic Cirrhotic not addressed	Cirrhotic and non-cirrhotic In the following specific recomendations for patient population and end-points included.
General considerations, animal models, early phase I	Addressed	Not addressed
Phase 2 studies:	Proof of concept possible without histology	Similar
Patient population:	Co-morbidities should appropriately be represented Stratify be T2DM status	Only briefly described.
Concomitant medication and co-morbidities	Stable doses of concomitant medication allowed. Consider stratification	No specifics mentioned. Co-morbidities should be “adequately and stably” treated.
Patient population: Weight control	Not addressed	Only patients with at least one unsuccessful attempt of weight losing diet.
Specific Recommendations for late phase 2 trials:	Histology recommended Determination of effect size and time-course of response. Trial duration recommended (12-18 years)	Not addressed.
Biomarker development/biomarker strategy:	Detailed recommendations given	Only general recommendations included
Inclusion criteria (non-cirrhotic)	NAS≥4 (with ≥1 for necroinflammation and ballooning); F2 and F3 Other MELD: less than 12	Similar No mentioning of MELD

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Comparison EMA reflection paper – FDA Draft Guideline

	FDA Draft Guideline	EMA reflection paper
Exclusion criteria:	Other relevant liver disease Highly elevated markers of liver injury (Bili, ALT) Portal hypertension	Included in the “characterization of disease”. Restricted to exclusion of “other liver disease”.
Intermediate Endpoints:	Improvement of fibrosis by 1 stage without worsening of NASH Resolution of NASH without worsening of fibrosis - Either of the two or both composites	Similar Evaluate in as co-primary
Final Endpoints:	Composite of: - Progression to cirrhosis - Decompensation events - MELD increase from <12 to >15 - liver transplantation - all cause mortality	Similar, except for: - MELD >14
Endpoint according to mechanism of action:	Not specifically addressed. “Covered” by the general criteria	Specifically addressed. Need to strengthen the endpoint in case e.g. no relevant change is expected in one component (e.g. use 2-stage improvement in fibrosis).

Comparison EMA reflection paper – FDA Draft Guideline

	FDA Draft Guideline	EMA reflection paper
Safety considerations:	Specific approaches to liver monitoring needed Adjudicate cases of liver toxicity CV safety to be adequately monitored	Similar. In addition specifically: MACE events, Metabolic parameters. Ref to: Reflection paper on CV safety
Children:	Different histology mentioned Extrapolation alone not possible Natural history data needed Overall risk-benefit in adults will determine extent of paediatric investigations	Similar. In addition: Ethical problems with repeated biopsy Studies in adults determine the extent of extrapolation Age range
Combination treatment:	Not addressed.	Full evaluation of single substances needed. FDC guideline applicable. Need for the demonstration of the contribution of each combination partner to the overall effect. Definition of suitable patient population needed.

Thank you for your attention!

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