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Committee for Medicinal Products for Human Use (CHMP)

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

Agreed by Gastroenterology Drafting Group	February 2017
Adopted by CHMP for release for consultation	18 May 2017
Start of public consultation	1 June 2017
End of consultation (deadline for comments)	31 August 2017

Comments should be provided using this template. The completed comments form should be sent to GastroenterologyDG@ema.europa.eu

Keywords	*Non-alcoholic steatohepatitis (NASH), Primary Biliary Cholangitis (PBC), Primary Sclerosing Cholangitis (PSC), clinical trial design, endpoints, conditional licensing, unmet medical need, liver biopsy.*

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1. Introduction

There is an unmet medical need of pharmaceutical treatment options in the indications Primary Sclerosing Cholangitis (PSC) and Non-alcoholic steatohepatitis (NASH) and also the repertoire of effective and safe drugs for the treatment for Primary Biliary Cholangitis (PBC; previously termed “Primary Biliary Cirrhosis”) remains limited.

Whereas the number of development programs and potential future drug candidates has increased during recent years the current regulatory experience reveals the need for further guidance.

Therefore the drafting of a reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH) is intended in order to address and to avoid potential pitfalls in drug development.

2. Problem statement

The main feature of chronic liver diseases, including PSC, PBC, and NASH is their slow progression across several, if not dozens, of years. The slow progression of these diseases constitutes a major challenge for drug development essentially with regard to a balanced choice of patient populations, clinically relevant endpoints and duration of observation periods.

In all three diseases, symptoms are usually unspecific or at least non-predictive for the long-term outcome of the disease, and the use of hard clinical outcome parameters as endpoint, similar for all three entities, such as liver transplantation and death is struggling with feasibility issues. In addition, the consequent, necessary use of repeated liver biopsies with its inherent risks of complications and deterrence of patients from recruitment points to the need for the validation of surrogate outcome parameters to replace histology..

There is also a need for the identification of the most suitable patient population, balancing unmet medical needs, the mechanism of action of drug candidates, and the disease severity with regard to grade of inflammation and stage of fibrosis development.

The requirement for long-term observation also raises questions on the balance between timely availability of new compounds, the choice of appropriate licensing strategies and the conduct or continuation of clinical studies post-approval with the associated problems of patient adherence and ethics as well as the regulatory need for (repeated) re-assessment.

In addition, whereas NASH is a frequent disease with increasing prevalence and must be regarded to be a consequences of the “obesity epidemic”, two of the three disease entities (PBC and PSC) are rare diseases, and drug candidates in the field usually have orphan drug designation. The most efficient use of a restricted patient population is therefore an additional top level requirement for the conduct of clinical trials.

3. Discussion (on the problem statement)

The proposed Reflection Paper is intended to address the following points:

- Discuss the difficulties and opportunities for drug development in the field of chronic liver disease (PBC, PSC, NASH), 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)

The Reflection Paper is intended to define “landmarks” with regard to the above mentioned topics, with the aim to increase consistency in future regulatory decisions. The Reflection Paper is considered a first step before more detailed regulatory guidance can follow.

4. Recommendation

It is proposed to prepare a Reflection Paper taking into account the background and items displayed above.

5. Proposed timetable

The Concept paper was released for public consultation on 1 June 2017. The deadline for comments is 3 months. The draft Reflection Paper is planned to be published for public consultation 2nd quarter 2018.

6. Resource requirements for preparation

The Drafting of the Reflection Paper will directly involve the members of the Gastroenterology Drafting Group. The Biostatistics Working Party is intended to be consulted for review. A stakeholder meeting may be helpful for additional input.

7. Impact assessment (anticipated)

The Reflection Paper is intended to have an impact on industry’s development plans, clarifying the “high level” requirements for the development of medicinal product under different scenarios. Once established, and at a time when further approvals for new medicinal products in the field have been completed, it may need to be superseded by disease specific guidance.

8. Interested parties

The pharmaceutical industry.

Academia and general or specific Scientific Associations (EASL, AASLD, ESPGHAN, NASPGHAN, PBC Study Group, IPSC Study Group, The Liver Forum).

Other drug regulatory agencies outside the EU (e.g. FDA).

9. References to literature, guidelines, etc.

Ajmera V et al: Novel plasma biomarkers associated with liver disease severity in adults with nonalcoholic fatty liver disease. Hepatology 2016; 65: 65-77.

Assessment report: OCALIVA,EMA/725757/2016, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004093/human_med_002043.jsp&mid=WC0b01ac058001d124 (accessed 28th Dec 2016)

Boonstra K et al: Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. Hepatology 2013; 58: 2045-2055.

Carey EJ et al: Primary biliary cirrhosis. Lancet.2015; 386: 1565.1575.

Dyson JK et al: The inter-relationship of symptoms severity and quality of life in 2055 patients with primary biliary cholangitis. Aliment PharmacolTher 2016; 44: 1039-1050.

Dyson JK et al: Novel therapeutic targets in primary biliary cirrhosis. Nat. Rev. GastroenterolHepatol 2015; 12: 147-158.

European Association for the Study of the Liver (EASL) & European Association for the Study of Diabetes (EASD) & European Association for the Study of Obesity (EASO): EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia (2016) 59:1121–1140

European Medicines Agency post-authorisation procedural advice for users of the centralised procedure (EMEA-H-19984/03 Rev. 67)http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000133.jsp&mid=WC0b01ac058066e978 (accessed 28th Dec 2016)

Goulis J, Leandro G, Burroughs AK. Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: a meta-analysis. Lancet 1999;354:1053–1060.

Hirschfield GM et al: Primary sclerosing cholangitis; Lancet 2013; 382: 1587-1599.

Horley-Silva JL et al: Advances in primary sclerosing cholangitis. Lancet GastroenterolHepatol 2016; 1: 68-77.

Irvine KM et al: Multiplex Serum Protein Analysis Identifies Novel Biomarkers of Advanced Fibrosis in Patients with Chronic Liver Disease with the Potential to Improve Diagnostic Accuracy of Established Biomarkers.PLoS ONE 11(11): e0167001. doi:10.1371/journal.pone.0167001

Lazaridis KN and NF LaRusso: Primary Sclerosing cholangitis. NEJM.2016; 375: 1161-1170.

Ponsioen CY et al: Surrogate endpoints for clinical trials in primary sclerosing cholangitis: Review and results from an International PSC Study Group consensus process. Hepatology 2016, 63; 1357-1367,

Rasi G and S Bonini: Innovative medicines: new regulatory procedures for the third millennium. Expert Opinion on Biological Therapy: 2015: 15: 5-8.

Rotman Y and AJ Sanyal: Current and upcoming pharmacotherapy for non-alcoholic fatty liver disease. Gut 2017; 66: 180-190.

Sanyal AJ et al: Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: Findings and recommendations from an American Association for the Study of Liver Diseases–U.S. Food and Drug Administration Joint Workshop. Hepatology 2015; 61: 1392-1405.

Yonussi ZM et al: Global epidemiology of nonalcoholic fatty liver disease – Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64: 73-84.