22 April 2010
EMA/CHMP/EWP/825749/2009
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of the guideline on the clinical development of medicinal products for the treatment of Hepatitis C

Draft Agreed by Efficacy Working Party	April 2010
Adoption by CHMP for release for consultation	22 April 2010
End of consultation (deadline for comments)	31 July 2010

The proposed guideline will replace guideline on the Clinical Evaluation of Direct Acting Antiviral Agents Intended for Treatment of Chronic Hepatitis C (EMEA/CHMP/EWP/30039/2008).

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

Keywords	*Hepatitis C, Directly Acting Antiviral, DAA, Guidance*

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. Introduction

Hepatitis C virus (HCV) is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma, as well as the most common indication for liver transplantation in many European countries. Worldwide, the number of chronically infected persons is estimated at 170 million, or 3% of the global population. About 20-30% of chronically infected persons will advance to cirrhosis within 20 years.

In Europe around 1/3 of HIV-infected patients are co-infected with HCV, with a prevalence of 50% in some regions in southern Europe. Compared to HCV mono-infected patients, these patients have faster progression of liver fibrosis; the risk for manifest cirrhosis is doubled for a middle-aged man carrying both infections.

The present standard of care (SOC) treatment for hepatitis C is a combination of ribavirin and pegylated interferon (PEG-IFN) alpha 2a or 2b. Whereas PEG-IFN is an immunomodulator, the mechanism of action of ribavirin is not precisely understood. The field of hepatitis C therapy, however, is presently one of intense investigational activity, with numerous directly acting antiviral (DAA) compounds with different mechanisms of action presently undergoing phase I-III trials. The first marketing applications for such agents are foreseen in 2010.

2. Problem statement

The first CHMP guidelines on the “Clinical Evaluation of Direct Acting Antiviral Agents Intended for Treatment of Chronic Hepatitis C” (CHMP/EWP/30039/08) were published in May 2009. Due to the limited experience with other approaches to the clinical development of DAAs, this guideline primarily addresses studies in which new DAAs are added to SOC treatment for chronic hepatitis C (CHC). The discussion of other therapeutic approaches, such as the combination of DAAs with or without SOC components, is rather rudimentary, as is the issue of labelling requirements in special populations. Indeed, in the extant guideline it is recognised that “due to the dynamics of the field and the restricted scope of this guideline, revisions and amendments are foreseen to be necessary within a short frame of time”.

Particular issues for new or updated guidance would include:

- Study design, dose selection and populations when evaluating DAA combinations without SOC or PEG-IFN.
- Study design and endpoints in patients with decompensated liver disease.
- Studies pre- and post transplant.
- Requirements for licensure in genotypes with a low prevalence in the developed world.
- Updated guidance on DAA resistance.
- Study design and populations for confirmatory trials in HCV/HIV co-infected patients.
- Benchmark pharmacodynamics, viral load and resistance assays.
- The use of non-invasive methods for liver assessment.
- The study of DAAs in DAA-experienced patients.
- The use of genetic predictors of SOC activity for DAA study design.
- Studies in children.

3. Discussion (on the problem statement)

Since the publication of the first guidelines, the field has greatly evolved. Phase III trials now ongoing in both treatment-naive and -experienced patients. Extensive phase II programmes for the first NS3/4A inhibitors have given more precise indications of the magnitude of increased efficacy in these populations, to be expected from the first generation DAAs, as well as of the requirements in terms of treatment duration for maximal efficacy. More data on drug resistance – a major concern informing the

first CHMP guidelines – have accumulated, though the ultimate consequences of this in terms of retreatment efficacy still remains unclear. Initial data on this highly important issue, however, are expected to emerge within the foreseeable future. Data on the predictivity of response to SOC, as well as of early viral kinetics during DAA treatment, of crucial importance for the rational design of clinical trials, are emerging. The design of confirmatory trials in special populations, including children, as well as the requirements for labelling, is now as an issue where regulatory guidance is needed. Other genotypes than 1 are increasingly the focus of drug development. New genetic markers of SOC response, of great putative importance for risk minimisation in drug development are being described. Finally, and most importantly, many DAA development programmes no longer mainly have the combination of one DAA with SOC in focus as the primary treatment strategy of investigation. On this point, as well as those previously mentioned, there is a need for updated regulatory guidance.

4. Recommendation

The working party recommends a revision of the extant guideline on the Clinical evaluation of direct acting antiviral agents intended for treatment of CHC.

5. Proposed timetable

A first draft guideline is to be released for consultation not later than Q4 2010.

6. Resource requirements for preparation

Preparation of this Guideline will involve the EWP, the ad hoc infectious diseases drafting group, and possibly the anti-viral SAG.

7. Impact assessment (anticipated)

It is anticipated that updated guidelines will facilitate the interaction between regulatory agencies within Europe and Sponsors developing products for the treatment of CHC.

8. Interested parties

- European Association for the study of the Liver.
- European Society of Clinical Microbiology and Infectious Diseases.
- European AIDS Treatment Group.