EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CHMP/EMA HCV clinical trials

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Guideline on clinical evaluation of medicinal products for the treatment of chronic hepatitis C.

Draft

Draft Agreed by Infectious Diseases Working Party	January 2011
Adoption by CHMP for release for consultation	20 January 2011
End of consultation (deadline for comments)	31 August 2011

Provides guidance on the clinical development of compounds for the treatment of Chronic Hepatitis C (CHC), including directly acting antivirals (DAAs) as well as host targeting antivirals (HTA).

Drafted in the fall of 2010

- Since then, the first NS3/4A inhibitor dossiers have been assessed, and boceprevir and telaprevir have been approved
- Proof-of-concept of SVR with interferon-free regimens has been obtained
- More data relevant to the issue of drug resistance have emerged

EMA policy has been undergoing progressive change, resulting in subsequent scientific advice to sponsors in some cases deviating from the draft guidance

The definition of SVR

- The draft guidance refers to SVR24 as the primary endpoint in clinical trials
- Based on emerging data, the EMA now accepts SVR12 as the primary endpoint in clinical trials; implying that filing for licensure can be done on the basis of SVR12, provided that SVR24 follows

General statements on confirmatory trials

- Comparative studies are expected to be randomised and, whenever possible, double-blinded.
- Open-label designs can be justified for practical reasons
- In several circumstances (e.g., in the study of certain special populations) single arm studies (= studies without a licensed control or placebo comparator regimen) are considered justified.

Genotype 1 naive, prior relapsers

- For a novel DAA/HTA to be used in combination with peginterferon and ribavirin, pivotal comparative studies with a licensed state-of-the art regimen (=DAA+pegIFN/ribavirin) are anticipated. Such studies are anticipated to have non-inferiority designs.
- As the field is expected to advance rapidly, it is recommended that regulatory advice be sought on appropriate study design and comparative regimen, as well as, when appropriate, on the non-inferiority margin, prior to initiating studies.

Genotype 1, Prior non-responders

- In principle, comparative trials with a DAA+pegIFN/ribavirin are recommended; however, the development of the field is recognised
- If there is a virological rationale and/or early data strongly indicating the possibility of a substantial gain in efficacy over licensed alternatives, single arm studies in null responders may be justified, according to recent scientific advice by national European agencies. This has not yet been officially stated as EMA policy
- Prior partial responders?

Studies in genotype 2/3

- Comparative studies with a licensed treatment option are expected in treatment naïve populations.
- "The relative scarcity of treatment experienced patients with these genotypes is recognised, and if a sponsor considers other approaches (e.g., single arm studies), European regulatory advice should be sought."
- According to national scientific advice, studies without a pegIFN+ribavirin control is acceptable; however, no official EMA position has been expressed

Genotype 4, regulatory requirements

- For an investigational compound used in combination with pegIFN and ribavirin, a specific (=fully powered on SVR endpoint) demonstration of efficacy against GT4 would not be necessary for labelling, given that in vitro activity and available viral response data, including early viral kinetics and SVR rates, show adequate consistency between GT1 and GT4
- No detailed definition of "adequate consistency" has been stated

Confirmatory trials of pegIFN sparing regimens

- For confirmatory trials of pegIFN sparing regimens, a licensed therapeutic option would be the most appropriate reference treatment provided that this is relevant for the target population.
- In case licensed therapeutic options are not appropriate or are contraindicated in the intended target population, no active control is expected
- Emerging data on what SVR rates are reached with interferon sparing combinations may impact the European regulatory position

PegIFN sparing regimens, ”interferon uneligibile” patients

- pegIFN sparing regimens may be studied an without an active comparator in ”interferon uneligible” patients
- According to scientific advice given by the EMA, ”Interferon uneligible” include patients with absolute as well as relative contraindications, and patients with a documented unwillingness to use interferon
- Studies without an active comparator are foreseen in patients with decompensated liver disease

Other special populations where, for the time being, trials without an active reference control regimen are anticipated

- Patients post transplantation
- HCV/HIV co-infected
- Patients with prior DAA experience
- Pediatric patients