21 April 2015
EMA/87232/2015
Human Medicines Research and Development Support Division

Report of the paediatric hepatitis C therapy expert meeting

European Medicines Agency, London, 09 December 2014

Introduction

The European Medicines Agency (EMA) held an expert meeting on 09 December 2014 to review key areas in the development of therapies for the treatment of chronic hepatitis C in children.

Purpose and objectives of the expert meeting

The purpose of the workshop was to advise the EMA and its Paediatric Committee (PDCO) on how

- to approach the large number of direct-acting antiviral (DAA) medicines in development in view of the relatively limited numbers of children with chronic hepatitis C available for clinical studies.
- to best set out detailed requirements for clinical paediatric studies in order to agree with applicants high-quality and feasible Paediatric Investigation Plans (PIPs) for chronic hepatitis C therapy that will ensure rapid access of children to these innovative new therapies.

The objectives were to learn from the invited experts about their experience with clinical trials and clinical practice in children with chronic hepatitis C, and to collect their opinions on how paediatric clinical studies should be conducted in this condition. No confidential information was presented or discussed.

Programme

EMA/PDCO participants briefly introduced the Paediatric Regulation, which came into force in the European Union on 26 January 2007. Its objective is to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0 to 17 years, ensuring that medicines for use in children are of high quality, ethically researched and authorised appropriately and improving the availability of information on the use of medicines for children. It aims to achieve this without subjecting children to unnecessary trials or delaying the authorisation of medicines for use in adults.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5510
Send a question via our website www.ema.europa.eu/contact

As a requirement of the Paediatric Regulation, all new medicines developed for the treatment of chronic hepatitis C in adults, must have an agreed paediatric investigation plan (PIPs) in place, ensuring the necessary data are obtained through studies in children to support the medicine's authorisation for use in children (note, if a product is not of interest in children, the PDCO can alternatively grant a product-specific waiver). The Paediatric Committee (PDCO) of the EMA is responsible for agreeing these PIPs.

An outline was presented of the current regulatory requirements in adult and paediatric chronic hepatitis C medicine development including current, upcoming therapies and agreed PIPs for paediatric chronic hepatitis C. In addition, prior to the meeting, a questionnaire on the topics for discussion was sent to the experts and written responses were summarised and presented to the experts.

Topics for discussion

1. Addressing medical need in different populations in paediatrics

Some of the timelines of currently agreed PIPs for DAAs extend as far as the early 2020's. Although, it was acknowledged that results of the adult development could inform paediatric development justifying such a lag, in principle, it was considered that too much of a delay should be minimised in order to ensure timely access to these new therapies for children. It was noted that in particular regimens spanning across different companies were currently subject to such a delay, to the potential detriment of those children in urgent need of treatment.

Regarding adolescents, the experts shared the view that an inclusion of this age group in adult trial could be considered. This would be further facilitated by the experience that these patients would also generally use the adult formulation and dose.

However, as an organisational challenge to a combined adult-adolescent study and as an argument of separate studies the need for parents' consent was given. It was also noted that adherence may differ between adolescents and adults. This was still a challenge despite the high motivation amongst families participating in clinical trials. Therefore, the needs of adolescents may be best served in a dedicated paediatric study, which should however initiate as early as possible after adult studies.

2. Drug prioritisation for development in children

The number of children and adolescents with chronic hepatitis C qualifying to receive treatment is limited and hence it may be not feasible to conduct all PIPs as currently agreed. The experts acknowledged this and pointed out that this may lead to a situation where data will only be generated for the earliest PIPs (as these studies are the first ones to recruit based on timelines). These earliest PIPs, however, may not necessarily investigate the products most appropriate to address the current medical needs in the paediatric population.

Given the multiplicity of DAA candidate therapies and the expected limited number of children and adolescents with chronic hepatitis C experts discussed whether it could prove useful to prioritise some regimens for paediatric development, and, if so, based on which criteria this prioritisation could take place.

The experts agreed that, in principle, it would be useful that some regimens were prioritised for paediatric development. It was generally agreed that a minimum SVR12 rate of more than 90-95% in adults would be expected to qualify as a promising regimen. Tolerability was considered critical and an acceptable safety profile based on non-clinical and adult clinical data was considered essential. Other

factors were also viewed as important but not necessarily as deciding factors, such as the length of therapy or the complexity of the regimen (e.g. the number of drugs and number of doses).

The availability of suitable age-appropriate formulations was stressed by the experts as highly important with palatability being of particular concern. The development of a palatable, age-appropriate formulation can be requested by the PDCO as a legally-binding measure in a PIP.

Importantly, with regard to the development of first-generation DAAs (still to be used in IFN-containing regimens) the experts shared the view that these products were no longer of primary interest in children. However, at present, the new more appropriate DAAs have still to be authorised in children making it difficult for PDCO to waive any development proposal for a first-generation DAA based on the lack of significant therapeutic benefit. Instead, it was suggested that for these products a longer deferral for the development program may potentially be granted allowing for a potential granting of a waiver at a later stage when the more appropriate therapeutic alternatives would become available.

3. Clinical trial design and feasibility issues

Specific aspects of clinical study design were discussed:

- Treatment-experienced children: There was a general agreement that these children should be included in clinical trials, but that they will become very rare in the future, also considering that physicians may currently prefer to attend until DAAs will become available. It was further noted that peginterferon/ribavirin does not select for viral resistance, and therefore no difference is expected in the virus of a child who previously failed peginterferon/ribavirin treatment and a treatment-naïve child. Thus, it was suggested to not specify minimum numbers of peginterferon/ ribavirin treatment-experienced children that must be enrolled in PIP studies. With regard to children that have failed DAAs, however, those would likely have to be considered in the future, taking into account cross-resistance.
- Comparator: considering the multiple DAAs in development and the limited patient pool, comparative studies appear unrealistic and likely unnecessary given the overall high efficacy of the newly available treatments.
- Facilitation of clinical trials through the use of research platforms: The experts considered that the use of research platforms could aid with the standardisation of protocols and potentially allow optimal use of a limited patient pool. However, the decision whether or not to use a research platform and which one to use will remain at the applicant's discretion and outside the remit of a regulatory body.
- Genotype coverage of clinical trials: It was generally agreed that development in children should focus on those genotypes also studied in adults. The limited data generated in children would not be able to support an indication in a genotype in which no data were available in adults. Because PIPs are agreed early in the development, potentially before a scientific or strategic decision has been taken on which genotypes to pursue in adults, a mismatch between genotypes included in the PIP study and in the adult development may occur. However, the experts did not see this as a critical issue in practice as children would be enrolled based on information available in adults.
- Treatment duration: The experts considered that it should be investigated whether the treatment duration in children could be shortened compared to adults due to the expected better response in children.

- Feasibility of and the need for a response-guided therapy: Given the high efficacy of the new treatments, it has not been possible, so far, to identify positive or negative predictors of response. It was thus questioned, whether response-guided therapy was feasible or necessary.
- Long-term follow-up after sustained viral response (SVR): Some experts had concerns regarding the feasibility of extended follow-up periods. Cured children may not want to attend follow-up visits as they would present reminders of the disease. Nevertheless, the general consensus was that a long-term follow-up between 2-3 years would be appropriate. However, facing the multiplicity of DAA candidates and a limited patient pool, it was highlighted that a drug with a potential paediatric safety concern that would have to be followed long-term should not be prioritised for development.

To accelerate the development and to ensure that a range of products would become available to children and adolescents without undue delay, experts considered whether pre-authorisation studies could be limited in size to 30-40 patients distributed across the age range from 3 to less than 18 years old. These studies could primarily focus on the determination of pharmacokinetics, but would also collect, albeit in a rather limited fashion, data on tolerability and SVR. After authorisation, additional safety data would then have to be collected, possibly in form of a registry.

Further steps

- The Expert's opinion will be taken as stimulus for further discussions at PDCO on the most appropriate approach for the development of hepatitis C therapies.
- The PDCO cannot adopt a modification of previously already PIPs on its own motion. Hence, if a revision of the development approach appears reasonable and in line with the growing knowledge and improved pharmaceutical developments in this field, applicants are advised to get in contact with the PDCO to explore room for modifications of their agreed PIPs. The PDCO from its side may also reach out to applicants.

Acknowledgments

We thank all participants for their many contributions, and in particular Dr Mentzer for his valuable input in the preparation of the meeting and for chairing the meeting.

Annex 1: list of participants

Role	Name (in alphabetical order)
Chair	Dirk Mentzer (PDCO)
External experts	Sanjay Bansal (UK) Suzanne Davison (UK) Carlo Giaquinto (IT) Loreto Hierro (ES) Guiseppe Indolfi (IT) Deirdre Kelly (UK) Florence Lacaille (FR) Valerio Nobili (comments in writing) (IT) Małgorzata Pawłowska (comments in writing) (PO) Stefan Wirth (DE)
Participants from National Competent Authorities	Sybille Fuchs (DE; by TC) Nathalie Morgensztejn (FR) Daniel Vittecoq (FR)
PDCO members	Sylvie Benchetrit (FR) Maria Fernandez-Cortizo (ES) Marianne Orholm (DK) Francesca Rocchi (IT) Paolo Rossi (IT) Peter Szitanyi (CZ) Jan Taminiau (NL; Healthcare professional representative)
CHMP members	Filip Josephson (SE)
EMA scientific staff	Radu Botgros Marco Cavaleri Andrea Ecker Jordi Llinares Sofia Nordenmalm Thorsten Olski Sabrina Spinosa-Guzman