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Human Medicines Development and Evaluation

Minutes of Expert Meeting on Clinical Investigation of New Drugs for the Treatment of Chronic Hepatitis C in the Paediatric Population

Monday 4 April 2011-chaired by Ian Weller

Role	Name
Chair	Ian Weller (IW)
Present:	Stefan Wirth (SW), Giorgina Mieli-Vergani (GMV), Deirdre Kelly (DK), Florence Lacaille (FL), Lawrence Serfaty (LS), Filip Josephson (FJ), Nathalie Morgensztejn (NM), Luis Mendao (LM) Daniel Brasseur (DB), Johannes Taminiau (JT), Maria Jesus Fernandez Cortizo (MFC) by TC, Marianne Orholm (MO) Sophie Olivier (SO), Nathalie Seigneuret (NS), Cecile Ollivier, Enes Leonor Linda Lewis (LL) by TC
Apologies:	Jose Luis Calleja (JLC), Rachel Turner (RT)

1. Welcome – Introduction and Declaration of conflict of interest

Participants were asked to declare any conflict of interests on the matters for discussion (in particular any changes, omissions or errors to the already declared interests).

Many attendees, primarily members of the ESPGHAN (European Society of Paediatric gastro-enterology, Hepatology, and Nutrition) were graded Level 2 or 3 by DIAG. Their participation was accepted as representative of ESPGHAN on the basis that no particular product will be discussed and that they could not participate to any final discussion and agreement on the revision of the EMA guidelines for the clinical investigation of new drugs for the treatment of chronic hepatitis C.

2. Draft EMA Guidelines – Paediatric Studies

Filip Josephson (FJ) presented the agreed wording for drug development in the paediatric population in the draft EMA/CHMP guidance by the Infectious Disease Working Group (IDWP) after consultation with the HIV / Viral Diseases Scientific Advisory Group (SAG) and PDCO members. Of note, the SAG met on October 6, 2010 to discuss several pending issues, including the wording for the paediatric section of

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the revised guidelines; however, no paediatric hepatologists were invited to the SAG meeting, and the full rationale of the ESPGHAN position was not available to the SAG.

The current wording includes the following aspects:

- Studies in the paediatric population are deferred up to collection of comprehensive efficacy and safety data in the adult population.
- The major medical need pertains to children with genotype 1 where increased efficacy and shorter duration are key objectives.
- Single-arm studies are favoured if efficacy and safety have been demonstrated convincingly in adults; as new drugs are licensed, comparative trials may be required for future drugs.
- Patients should be followed up to 5 years with focus on growth and pubertal development.
- The current wording in the guidelines does not address PK/PD assessment, dose selection in children, and evaluation of other strategies such as response guided therapy (that could justify comparative trial versus fixed duration tri-therapy regimen).

3. ESPGHAN recommendations (November 2009)

Stefan Wirth (SW) presented the position held by ESPGHAN in November 2009 regarding the clinical development of new drugs, in particular direct antiviral agents (DAA) in combination with peginterferon/ribavirin, in the paediatric population. ESPGHAN members were unanimously in favour of a comparative trial to demonstrate superior efficacy or better safety of the tri-therapy regimen over standard of care. The ESPGHAN position is consistent with IDWG with regards to lack of significant benefit of treating children less than 3 years, deferral of paediatric studies up to establishment of efficacy and safety of the tri-therapy regimen in adults, target population (all children with measurable HCV RNA genotype 1, with or without inflammation and/or fibrosis on liver biopsy), primary endpoint sustained viral response 24 weeks after the end of treatment (SVR24), recommendation to avoid therapy during rapid growth spurt or puberty (but does not constitute a contraindication), and duration and focus of the long-term safety follow-up.

4. Recent Decisions on PIP applications

Sophie Olivier (SO) presented a summary of recent opinions granted by the PDCO for new DAA in combination with Standard of Care (SOC), ie, peginterferon α-2a/b and ribavirin, for the treatment of chronic hepatitis C. Over the past 3 years, the PDCO has granted opinions for Standard of Care products and for DAA in combination with SOC:

- Peginterferon α-2b and ribavirin: single-arm study, 48-week therapy, 100 naïve children with genotype 1 and inflammation/fibrosis on liver biopsy. Primary endpoint: SVR24. 5-year follow-up.
- Peginterferon α-2a: comparative trial (pegI + ribavirin vs. pegI alone), 48-week therapy, 100 naïve children genotype 1. Primary endpoint: SVR24, superiority trial. 5-year follow-up.
- -Telaprevir: First DAA assessed by PDCO for PIP application, before adoption of ESPGHAN position in favour of comparative trial vs. SOC. The granted opinion includes a comparative clinical study with safety as primary objective, efficacy (SVR24) being a secondary objective. Number of subjects (100) is too small to demonstrate superior efficacy over SOC, unless drug effect size is much larger than expected.

- TMC 435: PIP assessed after adoption by the PDCO of ESPGHAN position. The granted opinion includes a comparative clinical trial with superior efficacy over SOC as primary objective. The study is powered (n=200, randomization 1:1) to detect a superiority over SOC of at least 20% points. Eligibility criteria: naïve subjects with genotype 1 and at risk of progressive disease.
- Boceprevir: nearly same design and objectives as agreed study for TMC 435. Both PIPs include an additional single arm for experienced subjects (n=50). Unlike PIP for TMC 435, the boceprevir study will enroll genotype 1 children with or without inflam/fibrosis on the liver biopsy.
- Finally, 2 PIP procedures are still ongoing (BI 201335 and alisporivir).

Of note and as mentioned above, all agreed PIPs for the investigation of a DAA in combination with SOC include a comparative trial versus SOC. The differences between PIP agreed before and after the ESPGHAN position statement are the objectives of the trials (safety as primary and efficacy as secondary moving to efficacy primary objective) and eligibility criteria (naïve children at risk of severe or progressive disease moving to all children with genotype 1).

5. Problem Statement and Initial Discussion

As the draft guidelines for the clinical investigation of new drugs for the treatment of chronic hepatitis C is under public consultation (end of consultation 31 August 2011), it was felt important that EMA should achieve a consensus regarding the type of study to be conducted in the paediatric population after establishment of a positive benefit/risk balance in the adult population. For the past year, the PDCO, following the position from ESPGHAN, has recommended a comparative trial designed to demonstrate superiority of the new regimen (tri-therapy) over the standard of care in the paediatric population; however the IDWG is of the opinion that efficacy can be extrapolated from adults to children and there is no need to further include a SOC arm in paediatric trials.

6. List of questions

The objectives of the meeting were to address the following 6 original questions, supplemented with 2 additional questions from the FDA:

- Question 1: Can efficacy data from adult program with tri-therapy be extrapolated to children?
- Question 2: Can the same tri-therapy regimen be proposed to all age groups in the paediatric population, including before or after puberty?
- Question 3: Does the potential risk of growth retardation in children with peginterferon/ribavirin justify the conduct of a comparative trial to assess superiority of the tri-therapy versus standard of care?
- Question 4: Should response-to-treatment guidance established in adults be validated in children before appliance to the paediatric population?
- Question 5: Should other sub-groups of the paediatric population be investigated (eg, genotypes 2-4? HIV co-infection)?
- Question 6: What study design would be the most appropriate to evaluate the efficacy/safety of novel agent for the treatment of chronic hepatitis C in the paediatric population?
- Question 7: Should dose finding study in children be requested or strategy to target adult exposure dose is acceptable?

- Question 8: Does the panel foresee a time when paediatric testing of such drugs may become unfeasible because there are not enough children requiring treatment to study all drugs currently in development?

7. Panel Discussion

- Question 1

Overall, the majority of the panel was of the opinion that efficacy data could be extrapolated to children. However, in particular amongst ESPGHAN members; there was a view that there was still a need for separate studies to confirm the superiority of the tri-therapy over SOC in children. It was acknowledged though that so far children have always performed better than adults, which may result from the lower viral load, as well as from the low incidence of progressive liver disease in children compared to adults. In addition, chronic hepatitis C in children represents probably a more homogenous population (from vertical transmission) with less co-morbidities than adult population. Should the same magnitude of effect be expected in children as in adults (at least 20 to 30% SVR over SOC), investigators (as was the case described by Dr Lewis in the US) and ethical committees may have concerns approving and conducting clinical trials in which half of the paediatric population enrolled is exposed to 48-week SOC (with a known success rate of 50% at best). On the other hand, tri-therapy regimens can be poorly tolerated and may include a large amount of pills (up to 18 tablets per day [tri-therapy with boceprevir in adults] with the last pill intake taking place at 11:00pm and requiring a snack). Therefore the benefit over SOC needs to be substantial to overweigh the potential poor compliance and tolerability profile. In addition, DK and GM mentioned recent observational UK data suggesting a much higher performance of the SOC in children (up to 70% SVR). These data are still under review and analysis, but should such a high performance be confirmed, there may be an even higher necessity for tri-therapy to demonstrate superiority over SOC. It was agreed though that pending publication and an explanation for this higher performance of SOC in children, the assumption should remain that a 50% SVR is the norm, as described in the published randomised studies with peginterferon/ribavirin in the paediatric population.

- Question 2

There was a consensus in favour of the same type of regimen whatever age group. In addition the panel was willing to consider favourably enrollment of post pubertal adolescents in the adult trials.

- Question 3

There was a general agreement that addition of a DAA to the SOC will probably not lead to an additive effect on growth retardation. SW mentioned that in fact the risk of growth retardation is probably minimal and does not constitute a real issue, while DK was of the opinion that without the proper comparative studies, an additive effect could not be ruled out. In addition, DK and GM pointed out that the psychiatric effects reported in the adult population have been poorly documented in the paediatric population and may be a bigger issue than growth retardation risk. Long-term follow-up should include monitoring of psychiatric events (up to at least 6 months after discontinuation of therapy) as well as evaluation of growth, including velocity measurement before treatment for at least 6 months.

- Question 4

FJ strongly stated that data on RGT as a general strategy is robust in naïve adult patients, with a low incidence of relapse. For experienced adults, there are less available data, and the utility of this approach in relevant subgroups has not yet been defined. LW mentioned that for FDA, RGT should work as well in children, but it remains to be confirmed by clinical data. Overall the panel favoured further investigation on RGT in children, possibly in comparison to the 48-week tri-therapy regimen.

- Question 5

It was agreed that non-responders genotypes 2 to 4, as well as co-infected children, represent too small population to make the conduct of clinical studies feasible. NM stated that if a clear benefit of the tri-therapy could be established in the paediatric population genotype 1, it may not be necessary to repeat all adult specific population studies in children, and extrapolation could be accepted.

- Question 6

Consistent with response to question 1, ESPGHAN members (in particular DK and GM) continue to favour comparative trials versus SOC while adult hepatologists favour single arm studies. In addition, another design, ie, comparison of the tri-therapy regimen (as performed in adult population) versus RGT, was extensively discussed and was perceived as one of the best options. Such design would allow validation of RGT in the paediatric population and offer shorter therapy duration. However, it remains to be decided if the study should be set up as a non-inferiority trial (which would be very demanding in terms of sample size) or if demonstration of a trend toward a similar magnitude of response could be accepted.

- Question 7

So far the same strategy as the one used in HIV has been adopted by applicants, ie, selection of the paediatric dose according to the adult exposure dose. The alternative would be to include also a PD target (eg, initial viral response). In both cases it is assumed that the patients included would continue with therapy aiming at SVR. The question was raised whether sponsors should study more than one dose in children. It was acknowledged that PK parameters of DAA are unknown in children and PK studies in infected children are difficult to conduct because of lack of therapeutic benefit. Some data (in HIV) suggest that higher exposure in children could lead to higher response. It was therefore proposed to assess possibly 2 doses (adult exposure dose and a second dose 25% higher) in combination with SOC for 1-2 weeks and look at HCV RNA. Another option would be to test 2 or 3 DAA doses in combination with SOC for 2-4 weeks followed by SOC for a total a 48 weeks. Modelling/simulation exercises should be encouraged to best select the paediatric dose.

- Question 8

It seems inevitable that the first DAAs to reach the market may be required to collect more data and to establish the superiority of the tri-therapy over the standard of care in more depth than follow-on drugs from the same class. It was briefly discussed whether the agencies should select the most promising drug (based on adult data) to be studies more intensively than others, but it was acknowledged that such selection may be unrealistic and inaccurate.

8. Consensus

Overall the panel reached consensus on the theoretical possibility to extrapolate efficacy data in adults to children; however the panel remained divided with regards to the need for comparative trials versus SOC in the paediatric population to confirm the superior efficacy, the acceptable tolerability and the compliance of the tri-therapy over SOC. One study design seemed to please several members of the panel, ie, study comparing the tri-therapy full duration (ie, 48-week total regimen including tri-therapy for approximately 12 to 24 weeks) versus Response Guided Therapy (RGT). However, and depending on the strength of the adult data, a fixed 48-week thearpy may not be the most appropriate control group for all paediatric trials. Additional work is needed to agree on the best strategy for dose selection in the paediatric population. Finally it was agreed that the main medical need lies in genotype 1 and though collection of data in particular subgroups, such as non-responders genotypes 2 to 4 and co-infected patients, the very small populations preclude the feasibility of separate studies.

All participants were reminded that the draft guideline is currently published for public consultation up to 31 August 2011 and comments on this draft were more than welcome. In parallel ESPGHAN members agreed to re-discuss the topic and send consolidated comments to the draft guidelines. Final decision on the paediatric section of the guidelines will be made at the IDWG group after the end of public consultation and analysis/review of all comments received.