EMA/CHMP draft guidance on pediatric HCV drug development; what, when, who, how?

Filip Josephson M.D., Ph.D
Swedish Medical Products Agency

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Background

- **The text on pediatric HCV drug development in the draft EMA/CHMP guidance has been agreed on by the IDWP and CHMP following input from the SAG Virology and members of the PDCO.**

What?

- **“It is anticipated that the first studies of new agents in the pediatric population will be the combination of a DAA with pegIFN+ribavirin”**

When?

- **“It is currently not generally anticipated that clinical efficacy and safety studies in children will be performed until comprehensive safety and efficacy data have been accumulated in adults”**
- **“if data from adult trials are encouraging, consideration should be given to initiating studies to explore the appropriate dosage, virological response and safety of the new agent in pediatric populations after completion of phase III studies in adults”**

Who?

- **“The major medical need in the pediatric population pertains to GT1 patients, where increased efficacy above that of pegIFN+ribavirin, as well as a shortened treatment duration with these agents, are considered valuable goals”**
- **“Depending on adult data, treatment experienced patients might be included in pivotal pediatric trials, if they are likely to benefit based on prior response to pegIFN+ribavirin”**
- **“Treatment of different genotypes might be studied in the same trial if virologically rational, but stratification should be used; the same holds for patient IL28B genotype”**

How?

- **“Generally, if efficacy and acceptable safety have been convincingly demonstrated in adults, *single-arm* pediatric trials are anticipated, prior to the licensure of a DAA/HTA option for pediatric patients”**
- **“The relative increment in treatment effect compared to historical data should be consistent with what is seen in adults”**
- **“As new treatment options for children are licensed, comparative designs may be appropriate for confirmatory trials”**
- **“As liver biopsies are still part of the routine management of pediatric HCV infection, such data should be collected at baseline”**

Safety issues

- **Treatment during the pubertal growth spurt should generally not be expected, as well as in patients below the age of three years (due to their known potential for spontaneous viral clearance).**
- **As regards safety issues particular to the pediatric population, on treatment growth should be evaluated, and patients followed up for at least 5 years after therapy. Pubertal development and parental heights should be documented, to allow for a full assessment of any impact of therapy on adult stature.**

Not adressed

- Relevant designs and populations for dose-ranging trials
- Relevant PK or PK/PD targets in dose-ranging trials
- The term ”Single arm” studies as used in the guidance is perhaps a misnomer, primarily meaning to indicate studies without bitherapy control. Design of studies without bitherapy control but investigating different treatment strategies or durations (e.g., randomised comparison to RGT versus fixed duration therapy)
- Other issues?

Philosophy

- **Increased virological efficacy (higher SVR rates) and an important proportion of patients eligible for shortened therapy can be imputed from adults based on virological principles, though the absolute magnitudes of these effects in the pediatric patients are unknown**
- **The treatment duration algorithms from adults (e.g. RGT with 24 or 48 weeks of therapy is the best assumptions to start from, in the absence of a particular rationale for deviation**