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Paediatric addendum to CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension

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Executive summary

This is a paediatric addendum to the guideline on the “Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension” for adults. It should be read in conjunction with that guideline. This addendum includes guidance on paediatric clinical medicine development, with highlights on differences from adult pulmonary arterial hypertension PAH and points out paediatric specific issues.

1. Introduction (background)

The most common forms of paediatric PAH are idiopathic Pulmonary Arterial Hypertension (IPAH) and associated Pulmonary Arterial Hypertension (APAH) (refer to table 1 the adult guideline).
Although the definition of PAH is basically the same in both populations, extrapolation from adults to children is not straightforward for several reasons: 1) The prevalence of the subtypes of PAH is different among both populations e.g. the idiopathic form IPAH is more prevalent in adults, whilst PAH associated with congenital heart disease is more frequent in children; 2) the anticipated lifespan of children is longer and 3) before the advent of long-term vasodilator/anti-proliferative therapy, the natural history remained significantly worse for children compared to adult patients.
The choice of endpoints that are relevant and feasible to demonstrate efficacy in the paediatric population is also problematic.
Persistent pulmonary hypertension of the newborn PPHN is a clinical syndrome characterised by failure of the elevated fetal pulmonary vascular resistance to regress after birth. PPHN can be caused by a variety of factors. It is commonly associated with congenital and acquired hypoxic lung disease. Idiopathic forms are rare. Severe forms are associated with significant morbidity and mortality. PPHN is clinically classified with PAH, but due to its specific characteristics, clinical development of medicinal products for PPHN are discussed separately.

2. Scope

This guidance document addresses IPAH and APAH as well as persistent pulmonary hypertension of the new born (PPHN). It explicitly includes APAH due to congenital heart disease [Eisenmenger syndrome, PAH associated with systemic to pulmonary shunts, PAH with small defects and PAH after corrective cardiac surgery]. Distinction is made between medicinal products for which adult PAH data is available and those who are simultaneously developed for adult and paediatric PAH; the former situation is expected to be the more common situation.

3. Legal basis

This addendum to the CHMP guideline on Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension has to be read in conjunction with the introduction and general principles of the Annex I to Directive 2001/83/EC as amended.
All pertinent elements outlined in current and future EU and ICH guidelines and regulations should also be taken into account especially those on:

- Guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension - EMEA/CHMP/EWP/356954/2008
- Clinical Investigation of Medicinal Products in the paediatric population - CHMP/ICH/2711/99 (ICH 11)
- Guideline on clinical trials in small populations - CHMP/EWP/83561/2005.

- Reflection paper on the regulatory guidance for the use of health related quality of life (HrQL) measures in the evaluation of medicinal products - EMEA/CHMP/EWP/139391/2004.

4. Criteria of efficacy

4.1. Idiopathic pulmonary arterial hypertension and associated pulmonary arterial hypertension

Data in adult PAH is usually available by the time of paediatric development, making some extrapolation possible. In rare situations, adult and paediatric PAH clinical programs may procede simultaneously. Regulatory requirements differ in these two situations. Choice of the endpoints is also dependent on the age of the recruited children.

Medicinal Products where the benefit-risk profile is known in adult PAH

This group includes the vasodilators, in particular the prostanoids, endothelin receptor blockers and phosphodiesterdase-5-inhibitors.

For these products, an extensive paediatric development is not foreseen as their efficacy and safety are already established in adult PAH, in addition to current recommendations in treatment guidelines to use these products in children. The main remaining issue in paediatric clinical development is defining the therapeutic dose, short and long term safety. Considering their mechanism of action, the primary endpoint for the dose-finding study should be haemodynamic parameters measured at 12 weeks. One study with adequate representation from all age groups could be acceptable, although a step-wise approach (starting with the older children) is preferred.

Medicinal Products with no adult PAH data

In such situations, a complete paediatric development program is expected. This should usually follow the same program required for adults, dependent on the proposed indication, but should be further discussed on a case by case basis. As stated in the PAH guideline for adults, efficacy should be investigated in terms of exercise capacity (in developmentally able children, usually above 7 years) or time to clinical worsening (TTCW). As these two endpoints are difficult to investigate in the younger paediatric groups, a flexible approach may be considered. When efficacy has been demonstrated in older children based on exercise testing or TTCW, extrapolation to younger age groups may be acceptable provided that the results of other feasible endpoints show comparable results in both age groups. This applies in particular to invasive haemodynamic measurements.

If older paediatric patients are already included in the adult clinical program, adequate representation should be ensured to allow for recommending paediatric use in this paediatric age group; their results should be presented separately.

Relevant endpoints

- Exercise capacity. This can be used as a primary endpoint in developmentally able children. Due to the extensive experience with the 6 minute walking test 6MWT, it is the preferred exercise capacity testing. However, applicants are encouraged to develop and validate further exercise tests for paediatric development.

- Time to clinical worsening. This is the preferred primary endpoint in a PAH clinical program, as it investigates clinical endpoints. Criteria used to define time to clinical worsening in the adult guideline are generally applicable in paediatric development as well, except for deterioration in exercise capacity, which is not applicable for the developmentally unable children. Any further deviations should be justified in the protocol.

- ***Haemodynamic parameters***. This is an important endpoint in the paediatric studies. It can be used as the primary endpoint to establish the effective dose in children for those medicinal products already used in adult PAH. It can also be used to extrapolate efficacy from the older to the younger age groups. Invasive measurements are currently the only acceptable haemodynamic endpoints. Care should be taken to ensure standardization as much as possible throughout all trial sites, including the sedation/anaesthesia protocol for cardiac catheterisation. The role of non-invasive techniques such as echocardiography is less clear at present, nevertheless such measurements are encouraged to complement the understanding of the disease course and any treatment activity.

The effect on **health-related *quality of life*** (HRQL) could be measured as a secondary endpoint acknowledging that indirect assessment by involving the child's parents/carers is inevitable for the younger patient groups. Weight and length gain are also considered relevant indicators of development, response and well being.

Other outcome measures are also encouraged to contribute to validating new endpoints in paediatric PAH studies, in particular serum markers (BNP, cytokines), Doppler echocardiography (as adjunctive tool to cardiac catheterisation) MRI imaging and accelerometry.

4.2. Persistent pulmonary hypertension of the new born (PPHN)

Limited data are available regarding relevant endpoints in the field of PPHN.

The following endpoints are suggested; the first two endpoints are considered of higher clinical relevance and less disputable value:

- all-cause mortality;
- need for extracorporeal membrane oxygenation ECMO (based on standardized criteria e.g. oxygenation index);
- need for additional drug treatment targeting PAH;
- time on nitric oxide (NO);
- time to weaning from mechanical ventilation;
- ventilation index;
- time on supplemental oxygen and
- duration of ultrasound-detectable right-left shunting (hours or days).

5. Patients

5.1. Selection

Paediatric age groups should be adequately represented to allow the respective recommendation for the included age. Proper representation of subgroups is necessary if specific claims are made relating to aetiology and functional class.

5.2. Background treatment

Stabilisation on background medications before recruitment in a study may not always be practicable in paediatric trials as children often present to the hospital with acute deterioration. The rate of deterioration can be fast. The criteria for when to choose which rescue medications should be set out in the protocol. Such reasons and decisions should be centrally adjudicated.

6. Strategy – Design

6.1. Human pharmacology studies

The development of age-appropriate paediatric dosage forms and formulations is encouraged. Specific dosage forms are needed for PPHN.

6.1.1. IPAH and APAH

Adequate definition of the associated condition, in particular the type of congenital heart disease is important. Comparative PK studies versus adults should be performed. For medicinal products not yet approved for adult PAH, separate phase II studies may be necessary to determine the PK/PD relation.

6.1.2. PPHN

Separate studies are needed to study the mechanism of action of the medicinal product for this specific indication.

6.2. Confirmatory Therapeutic Studies

6.2.1. IPAH and APAH

Protocols should clearly state whether paediatric patients are included in the adult program. For products not yet authorised for adult PAH, a timely application for a paediatric investigation plan (PIP) is essential (no later than at the completion of the basic pharmacokinetics studies in adults) to discuss the study design. Placebo-controlled studies as suggested in the adult guideline are not always acceptable in children; different dose levels can be used instead. Patients should be stratified into IPAH and APAH. If the primary endpoint does not include mortality, this has to be additionally investigated in a follow-up study to exclude any negative safety signal. These extension studies should include all randomized patients regardless of their reason for discontinuation. Close monitoring and the possibility of modification of treatment should be clearly set out in the protocol.

6.2.1.1. Medicinal Products with a known benefit risk profile in adult PAH

The aim of these studies is to establish the paediatric dose, based on haemodynamic endpoints measured at 12 weeks. Randomized, blinded studies using different dose levels are requested.

6.2.1.2. Medicinal Products with no adult PAH data

Due to lack of adult data, phase III confirmatory studies in paediatrics are requested. The chosen endpoints should follow those proposed in adult PAH guideline, as mentioned above. A step-wise approach first investigating older paediatric patients is recommended. When consistent efficacy in terms of invasive haemodynamic parameters is shown in both age groups, this could also allow extrapolation of efficacy data to younger patients when exercise testing is not possible. Long-term studies of at least 6 month duration are recommended especially if the chosen endpoints measure clinical endpoints (TTCW).

6.2.2. PPHN

PPHN has to be studied separately from IPAH and APAH. As nitric oxide (NO) is an authorized therapy mainly add-on trials or trials in patients failing treatment with NO should be considered. In case efficacy is shown, this can be followed by direct head-to-head comparative studies to investigate

efficacy and safety as a first line medicinal product.

7. Safety aspects

Short-term safety data should be collected from the controlled studies and compared with the known safety profile in adults. These studies should be followed by long term extension studies to allow investigation of long-term safety in terms of growth, neurological and sexual maturity. Neonates with PPHN should be followed up for at least 24 months to document outcomes in terms of central nervous system development.

Definitions

Refer to section 1.

References

Barst RJ et al.: Vasodilator therapy for primary pulmonary hypertension in children. Circulation 1999 Mar 9; 99(9): 1197-208)

Galie et al.: Guidelines for the diagnosis and treatment of pulmonary hypertension Eur Heart J (2009) 30 (20): 2493-2537

Haworth SG: The management of pulmonary arterial hypertension in children. Arch Dis Child 2008; 93: 620-625

Haworth SG et al.: Survival and quality of life in children with severe pulmonary hypertension. Heart 2006; 92 (Supple II): A14

Haworth SG: Pulmonary hypertension of the young. Heart 2002; 88; 658-664

Ivy DD et al.: Weaning and discontinuation of epoprostenol in children with idiopathic pulmonary arterial hypertension receiving concomitant bosentan. Am J Cardiol 2004; 93: 943-6

Lammers AE et al.: Epoprostenol treatment in children with severe pulmonary hypertension. Heart 2007; 93: 739-743

Li AM et al.: The six-minute walk test in healthy children: reliability and validity. Eur Respir J 2005; 25: 1057-60.

Maiya S et al.: Response to bosentan in children with pulmonary hypertension. Heart 2006; 92: 664-670

Peterson AL et al.: Correlation of echocardiographic markers and therapy in persistent pulmonary hypertension of the newborn. Pediatr Surg Int 2008; 24: 1101-1104

Rosenzweig and Barst: Pulmonary arterial hypertension in children: a medical update. Current opinions in pediatrics 2008; 20: 288-293

Selimovic N et al.: Assessment of pulmonary vascular resistance by Doppler echocardiography in patients with pulmonary arterial hypertension. J Heart Lung Transplant. 2007 Sep;26(9):927-34

Simonneau, G., Clinical classification of pulmonary hypertension. JACC, 2009; 54(1): S43-S54.