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Committee for Human Medicinal Products (CHMP)

# Concept paper on the need for revision of the Paediatric addendum to the guideline on clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension (EMA/CHMP/213972/2010)

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| Agreed by the PDCO | 28 March 2023 |
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| Start of public consultation | 11 July 2023 |
| End of consultation (deadline for comments) | 30 September 2023 |

The proposed guideline will replace *'Paediatric addendum to CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (EMA/CHMP/213972/2010)'*

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| Keywords | pulmonary arterial hypertension, modelling and simulation, extrapolation, paediatrics |



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# 1. Introduction

Pulmonary hypertension in childhood and adulthood share some common features but there are also important differences. When excluding infants with transient forms of pulmonary arterial hypertension (PAH) (i.e. Persistent Pulmonary Hypertension of the Newborn (PPHN) or repairable cardiac shunt defects) most of the children with PAH have either idiopathic pulmonary arterial hypertension (IPAH), heritable pulmonary arterial hypertension (HPAH), or irreversible congenital heart disease (CHD)-associated PAH (1). With respect to pharmaceutical therapeutic options, PDE V inhibitors and endothelin receptor antagonists have been approved for the paediatric population with PAH; information on dosing is included in the SmPC for prostacyclin analogues. Further development programs for medicinal products of these and of other classes are ongoing or at an advanced stage.

Since the *Paediatric Addendum to the Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension (EMA/CHMP/213972/2010)(2)* came into effect in 2012, a variety of alternative approaches for the clinical development have been undertaken and often deviated from the requirements as outlined in the Addendum. These approaches incorporated a) One pivotal outcome study, b) A large pharmacokinetic (PK) study with secondary clinical endpoints, PopPK modelling to extrapolate exposure from adults to paediatric patients and a pharmacodnamic (PD) similarity assessment c) 6-minutes walking test (6-MWT), d) 6-MWT together with a modelling extrapolation approach e) Mainly PK data complemented by exploratory efficacy data, and f) Invasive haemodynamics and PK data complemented by exploratory efficacy data.

It turned out that on the one hand some of the requirements of the addendum can barely be fulfilled. On the other hand, Modelling and Simulation (M&S) is increasingly applied to support dose finding and extrapolation concepts.

# 2. Problem statement

Based on experience that has been gained in clinical development programs in PAH in the paediatric population, some key aspects of the addendum have to be adapted. Carrying out paediatric PAH trials is impeded by  a limited number of patients available, unwillingness to participate in clinical trials if use of the test product is reflected in clinical guidelines, and competition between ongoing trials.

In the current version of the addendum, invasive haemodynamic parameters as obtained by right heart catheterisation (RHC) are expected for dose finding studies and may serve to extrapolate results from adult to paediatric and from older to younger paediatric patients. According to the current version of the addendum, invasive hemodynamic parameters are the only acceptable endpoints. However, due to the inherent procedural related risks, RHC cannot be requested for study purposes only. On the other hand, collecting haemodynamic parameters solely based on clinically indicated procedures is usually not informative. Therefore, different approaches have been applied in clinical development programs for dose finding and extrapolation between age groups as well as from adults to the paediatric population.

Due to progress made within the area of Modelling and Simulation, such approaches have become more and more important (see *Reflexion Paper on the use of extrapolation in the development of medicines for paediatrics* (3)) and have increasingly been applied in paediatric PAH programs. Currently, the addendum does not sufficiently reflect the regulatory requirements and adequate context-related application of M&S in the extrapolation framework for dose selection. In this regard, M&S could inform on the efficiency/feasibility of the proposed trial design prior to patient inclusion and justify critical design features of paediatric studies. Age dependent differences in aetiology, disease characteristics and shortcomings of data available from adult programmes have to be accounted for.

There is also a need to further discuss some endpoints which are not currently used as pivotal evidence for decision making. Due to technical limitations, echocardiography has not replaced invasive haemodynamic measurements in clinical trials. Facing the fact that RHC cannot be used, current state of the art and the place of echocardiographic assessment as well as the importance of other imaging modalities (CT-scan, cardiac MRI) may have to be re-evaluated and discussed. The 6-MWT has limitations as it is not considered reliable, especially not in the younger children. Methods with the potential to replace it like actigraphy may currently not be sufficiently validated. Also, no PAH specific patient reported outcome measures (PROs) are available for the paediatric population. The relevance of additional nonspecific parameters like weight and height gain and daily activity may further be explored. Although validity of such endpoints and clinically relevant effect sizes may be discussed in more detail during the process of the revision, it is unclear whether the revision may result in major changes in this regard.

For medicinal products with no adult PAH data, phase III confirmatory studies in paediatrics are required. As in the current addendum, the chosen endpoints should follow those proposed in the adult PAH guideline with some amendments. However, to facilitate such studies adjusting the definition of "Time to clinical worsening" (TTCW) may be an option to be discussed, e.g., by including specific surgical procedures like lung transplantation or registration for this procedure. Change in therapy when associated with clearly defined worsening criteria that are currently not included in the accepted TTCW definition as per guideline may also be considered. In addition, the WHO functional classification (FC) may not always be suitable for children and an age-adjusted modified classification has been created (PANAMA-FC) (4). The suitability of this classification for describing patient populations or for incorporation in a clinical endpoint will further be discussed.

# 3. Discussion (on the problem statement)

An update of the Paediatric addendum to CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (EMA/CHMP/213972/2010) is foreseen.

The following points are proposed to be addressed in the update:

1. The role of invasive haemodynamic data for the clinical development should be discussed and it should be clarified how information sufficient for dose selection in the paediatric population can be gathered and how to support extrapolation from adults to the paediatric population without invasive measurement of haemodynamic data.

2. The application of M&S approaches in the extrapolation framework should be addressed in more detail for dose selection and extrapolation of information from adult to paediatric patients and between different age groups. This includes a discussion about which clinical and PD endpoints are suitable, how the PD parameters will be collected and analysed and how to pre-define criteria for success.

3. The definition of endpoints reflecting TTCW for confirmatory trials should be re-discussed in order to explore possibilities to include more components into such an endpoint.

4. Within the revision it should be explored whether the position of some additional endpoints in the clinical development has to be reconsidered. This includes a discussion of what effect sizes could be considered clinically relevant for endpoints gaining importance. Among these are echocardiography-based parameters, PROs, actigraphy, biomarkers and PD parameters currently not considered as pivotal evidence.

# 4. Recommendation

The Cardiovascular Working Party (CVSWP) at the EMA recommends revising the Paediatric addendum to the guideline on clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension (EMA/CHMP/213972/2010) taking into account the issues identified above.

# 5. Proposed timetable

This Concept Paper is released for 3 months public consultation. It is anticipated that the draft Guideline may be released within 18 months after adoption of the Concept Paper by the CHMP. The draft document will then be released for 6 months of external consultation and following the receipt of comments it will be finalised within approximately 12 months.

# 6. Resource requirements for preparation

The drafting process will involve the co-operation between the CVSWP, the PDCO, the Methodology Working Party and the Scientific Advise Working Party at the EMA.

# 7. Impact assessment (anticipated)

It is anticipated that the proposed changes and clarifications may streamline planning of clinical programs in the therapeutic field and may better serve as a reference when assessing such programs and the final data.

# 8. Interested parties

The following interested groups may provide additional valuable input:

Disease specific patient representatives

Learned societies: European Society of Cardiology (ESC), the European Respiratory Society (ERS), and the European Society for Neonatology (ESN)

# 9. References to literature, guidelines, etc.


(1) 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: … European Heart Journal, Volume 43, Issue 38, 7 October 2022, Pages 3618–3731, https://doi.org/10.1093/eurheartj/ehac237;

(2) Paediatric addendum to CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (EMA/CHMP/213972/2010) https://www.ema.europa.eu/en/paediatric-addendum-guideline-clinical-investigation-medicinal-products-treatment-pulmonary-arterial;

(3) Reflection paper on the use of extrapolation in the development of medicines for paediatrics. (EMA/189724/2018).

(4) Lammers AE et al., Functional Classification of Pulmonary Hypertension in Children: Report from the PVRI Pediatric Taskforce, Panama 2011. Pulmonary Circulation 2011; 1: 133-299