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2 EMA/CHMP/264860/2023
3 Committee for Human Medicinal Products (CHMP)

4 **Concept paper on the need for revision of the Paediatric**
5 **addendum to the guideline on clinical investigation of**
6 **medicinal products for the treatment of pulmonary**
7 **arterial hypertension (EMA/CHMP/213972/2010)**
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Agreed by the Cardiovascular Working Party	1 June 2023
Agreed by the PDCO	28 March 2023
Adopted by CHMP for release for consultation	22 June 2023
Start of public consultation	11 July 2023
End of consultation (deadline for comments)	30 September 2023

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

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14 Comments should be provided using this [EUSurvey form](#). For any technical issues, please contact
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Keywords	pulmonary arterial hypertension, modelling and simulation, extrapolation, paediatrics
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17 **1. Introduction**

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

27 Since the *Paediatric Addendum to the Guideline on the Clinical Investigations of Medicinal Products for*
28 *the Treatment of Pulmonary Arterial Hypertension (EMA/CHMP/213972/2010)(2)* came into effect in
29 2012, a variety of alternative approaches for the clinical development have been undertaken and often
30 deviated from the requirements as outlined in the Addendum. These approaches incorporated a) One
31 pivotal outcome study, b) A large pharmacokinetic (PK) study with secondary clinical endpoints, PopPK
32 modelling to extrapolate exposure from adults to paediatric patients and a pharmacodynamic (PD)
33 similarity assessment c) 6-minutes walking test (6-MWT), d) 6-MWT together with a modelling
34 extrapolation approach e) Mainly PK data complemented by exploratory efficacy data, and f) Invasive
35 haemodynamics and PK data complemented by exploratory efficacy data.

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

39 **2. Problem statement**

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

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

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

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

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

83 **3. Discussion (on the problem statement)**

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

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

- 87 1. The role of invasive haemodynamic data for the clinical development should be discussed and
88 it should be clarified how information sufficient for dose selection in the paediatric population
89 can be gathered and how to support extrapolation from adults to the paediatric population
90 without invasive measurement of haemodynamic data.
- 91 2. The application of M&S approaches in the extrapolation framework should be addressed in
92 more detail for dose selection and extrapolation of information from adult to paediatric patients
93 and between different age groups. This includes a discussion about which clinical and PD
94 endpoints are suitable, how the PD parameters will be collected and analysed and how to pre-
95 define criteria for success.
- 96 3. The definition of endpoints reflecting TTCW for confirmatory trials should be re-discussed in
97 order to explore possibilities to include more components into such an endpoint.
- 98 4. Within the revision it should be explored whether the position of some additional endpoints in
99 the clinical development has to be reconsidered. This includes a discussion of what effect sizes
100 could be considered clinically relevant for endpoints gaining importance. Among these are
101 echocardiography-based parameters, PROs, actigraphy, biomarkers and PD parameters
102 currently not considered as pivotal evidence.

103 **4. Recommendation**

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

107 **5. Proposed timetable**

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

112 **6. Resource requirements for preparation**

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

115 **7. Impact assessment (anticipated)**

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

119 **8. Interested parties**

120 The following interested groups may provide additional valuable input:

121 Disease specific patient representatives

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

124 **9. References to literature, guidelines, etc.**

125 (1) 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: ...
126 European Heart Journal, Volume 43, Issue 38, 7 October 2022, Pages 3618–3731,
127 <https://doi.org/10.1093/eurheartj/ehac237>;

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

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

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

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