EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 March 2026
EMA/CHMP/60723/2026
Committee for Medicinal Products for Human use (CHMP)

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

Draft

Adopted by CHMP	5 December 2011
Date for coming into effect	5 June 2012
Stakeholders meeting on the revision of the paediatric addendum to the PAH guideline	24 September 2024
Draft agreed by the CVS WP	14 November 2025
Draft adopted by CHMP	19 March 2026
Start of public consultation	31 March 2026
End of consultation (deadline for comments)	30 September 2026

This document replaces Guideline EMA/CHMP/213972/2010.

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	**Pulmonary arterial hypertension; paediatric; persistent pulmonary hypertension of the newborn, congenital heart disease**

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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 (EMEA/CHMP/EWP/356954/2008)* intended 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)

1.1. Paediatric pulmonary arterial hypertension

In line with the adult guideline, the term PAH is used for a subgroup of Pulmonary Hypertension (PH) known as group 1. (refer to Table 1 in the *Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension [EMEA/CHMP/EWP/356954/2008]*).

Paediatric PAH is a life- threatening rare disease that affects children's physical, emotional, and social well-being, and impacts the whole family. Pulmonary arterial hypertension is the most frequent type of PH in children, with the vast majority (82%) of cases being infants with transient PAH (i.e. persistent pulmonary hypertension of the newborn [PPHN] or repairable cardiac shunt defects) (4, 22, 10). More than half of children with non-transient pulmonary hypertension (PH) can be classified as having PH in group 1 (PAH), and around one third up to one half of children with non-transient PH is classified as having PH group 3 (PH associated with respiratory disease, especially developmental lung diseases) (10). Pre-term infants with bronchopulmonary dysplasia and genetic developmental lung disorders are also included in this category. Other conditions associated with PAH are rare in infants and children (4, 22, 23, 10).

Transient forms of PAH due to Persistent Pulmonary Hypertension of the Newborn (PPHN) or repairable cardiac shunt defects represent the majority of PAH in infants. PPHN is a clinical syndrome characterised by failure of the elevated foetal pulmonary vascular resistance (PVR) 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 is discussed separately (11).

1.2. Adult versus paediatric PAH

There are similarities and shared features between adult and paediatric patients with PH that support extrapolation of evidence from adults to paediatric patients. Underlying pathophysiological mechanisms are overlapping. Elevations in PVR and pulmonary arterial pressure (PAP) are characteristic of PAH in both children and adults, and the definition of PH is similar in both populations when based on haemodynamic assessment. Life expectancy is similarly poor, and prognostic factors are largely the same.

However, extrapolation of evidence from adults to children is not straightforward. Genetic background, age-dependent diagnostic and treatment approaches, and disease monitoring differ. Injury to developing foetal, neonatal, or paediatric lung circulation is a specific feature in paediatric PH (10). The prevalence of the subtypes of PAH is different among both populations. Paediatric PAH is predominantly idiopathic PAH (IPAH), hereditary PAH (HPAH) with a high proportion of associated PAH (APAH) cases associated with mainly due to congenital heart disease (CHD) (10). PAH associated with connective tissue disease is more prevalent in adults. Childhood PH is more often associated with chromosomal, genetic, and syndromic anomalies compared to PH in adults. Some symptoms like dyspnoea on exertion are shared but heart failure and oedema are more prevalent in adults and syncope is more common in the paediatric population. The anticipated lifespan of children is longer.

Considering the similarities between adult and paediatric patients, extrapolation of evidence on pharmacokinetics (PK), efficacy and safety, generated in adult patients, is an important element of the development programme in paediatric patients with PAH. However, due to differences as outlined above, additional data must be provided to support conclusions on the benefit/risk ratio (B/R).

For specific aspects to be considered in neonates reference is made to *the Guideline on the investigation of medicinal products in the term and preterm neonate (EMEA/536810/2008)*.

2. Scope

This guidance document addresses IPAH, HPAH and APAH as well as PPHN. It explicitly includes APAH due to CHD (Eisenmenger syndrome, PAH associated with systemic to pulmonary shunts, PAH with small defects and PAH after corrective cardiac surgery).

3. Legal basis

This addendum to the *Guideline on Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension [EMEA/CHMP/EWP/356954/2008]* 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)*
- *ICH guideline E11A on pediatric extrapolation - EMA/CHMP/ICH/205218/2022 (ICH E11A)*
- *Reflection paper on the use of extrapolation in the development of medicines for paediatrics - EMA/189724/2018*
- *Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population - EMEA/CHMP/EWP/147013/2004*
- *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*
- *Draft ICH M15 Guideline on general principles of model-informed drug development - EMA/CHMP/ICH/496426/2024*
- *Guideline on the investigation of medicinal products in the term and preterm neonate - First version - EMEA/536810/2008*
- *Concept paper on the need for revision of the Guideline on the investigation of medicinal products in the term and preterm neonate - EMA/PDCO/362462/2016*
- *Reflection paper on patient experience data - EMA/CHMP/PRAC/148869/2025*

4. Idiopathic, hereditary and associated pulmonary arterial hypertension

4.1. Development strategy

Data in adult PAH is usually available by the time of assessment of data of the paediatric development, or development programmes are proceeding in parallel but slightly offset, making extrapolation

possible. Pharmacodynamic (PD) and efficacy endpoints should be included in the adult programme that may become relevant for extrapolation to paediatric patients.

Theoretically, adult and paediatric PAH clinical programmes may proceed independently, or a medicinal product could be developed for the paediatric population only. This is a rare hypothetical case that may apply to subgroups of paediatric patients without equivalent adult counterparts. In such instances data in the paediatric population have to stand on their own. Regulatory requirements differ in these two situations.

Whenever possible, it is recommended to include adolescents already in the adult clinical program. Sufficient representation should be ensured to allow for recommending use in this paediatric age group; their results should be presented separately and based on a study where randomisation was stratified by age.

4.1.1. Extrapolation

Considering similarities between adult and paediatric patients with PAH, for a paediatric clinical development program for medicinal products where the B/R is known in adult PAH, extrapolation from data in the adult population is an acceptable approach. However, considering differences between adults and paediatric patients with PAH, additional data beyond exposure matching have to be provided to support extrapolation.

4.1.1.1. Model informed extrapolation

4.1.1.1.1. General approach

The extrapolation concept and plan should be defined according to ICH E11A. When a model informed drug development (MIDD) approach is planned to be used for either to describe the available data or to analyse the data to be collected as part of the extrapolation plan, this should be done according to ICH M15. The starting point in the extrapolation concept includes assessing the available information on the characterization of the similarity and differences in disease, response to treatment (efficacy, short- and long-term safety) and PK that would eventually impact the selection of age-appropriate therapeutic doses and the benefit-risk assessment in children.

Considering differences between adults and paediatric patients as outlined above, the extrapolation concept and plan can not only be based on exposure. However, matching exposure that falls into the exposure range of adults or combination of exposure matching with PK/PD is an important element contributing to extrapolation based on exposure-response (E-R) related to efficacy or safety in adults and/or children. The appropriateness of the use of parameters like imaging-based variables, NT-proBNP, exploratory results on clinical endpoints as well as PD and efficacy endpoints as response variable should be discussed during the description of the extrapolation concept and plan.

The need for generation of data in children as part of the extrapolation plan will depend on the uncertainty identified at different levels (e.g. PK, PK/PD, E-R).

Whenever data generation is deemed necessary, the study design should be optimized: a sufficient number of paediatric patients should be included in clinical trials to enable a scientifically sound assessment of PK over all age groups, to inform paediatric pop-PK modelling and to allow an assessment of E-R.

4.1.1.1.2. Assessment of similarity of response to treatment

Assessing similarity of response to treatment of various variables obtained in adult and paediatric patients is an option to complement matching exposure. Functional capacity e.g. as assessed by placebo corrected change in the 6-minute walking distance (6MWD) in older children and adolescents can be a relevant component (14). Other parameters like imaging-based variables, NT-proBNP and exploratory results on clinical endpoints should be integrated. The approach to assess similarity of

response should consider all relevant PD and efficacy endpoints and should be predefined including a statistical testing or model assessment strategy.

4.1.1.3. Bridging biomarker approach

A bridging biomarker, as defined in ICH E11A, is a biomarker that is correlated with a clinical response endpoint in the reference population and also correlated with clinical response in the target population. For a bridging biomarker approach a biomarker that correlates with efficacy as established in the adult program is investigated in paediatric patients (6). As a prerequisite, candidate biomarkers should sufficiently capture a pathway or an outcome that is linked to clinical outcome. In the paediatric population with PAH this can be achieved by demonstrating the prognostic value in adult and paediatric patients. Robust validation across different age groups and disease related specific aspects is required, to demonstrate the bridging approach. Candidate biomarkers have to be investigated in the adult and in the paediatric studies in parallel. The choice of the biomarker(s) to be used for extrapolation depends on demonstration of a sufficient correlation with clinical efficacy endpoints in the pivotal studies in adults, as assessed by functional capacity during exercise or by time to clinical worsening (TTCW).

It should be considered that biomarkers (including imaging-based parameters) representing conditions at rest may not correlate well with functional capacity during exercise. A biomarker may differentially correlate with exercise capacity and with clinical outcome.

Among the candidates to be explored are BNP/NT-proBNP and non-invasive methods to measure PVR or other imaging-based parameters. However, challenges of obtaining echocardiography and MRI data are well known. For BNP and NT-proBNP, age and disease related factors must be further characterized. When following this strategy fit for purpose validation of the biomarker(s) used is necessary. In the absence of sufficient validation, a bridging biomarker approach may support extrapolation as exploratory or supportive evidence.

4.1.2. Stand-alone development

In case extrapolation from adults is not pursued or this is not useful for other reasons, a complete paediatric development programme is expected.

This should usually follow the same principles as a programme required for adults. As stated in the PAH guideline which addresses development programmes for adults, efficacy could be investigated in terms of exercise capacity (in developmentally able children, usually above 7 years) or TTCW. As these are difficult to investigate in the younger paediatric groups, it should be evaluated whether extrapolation from older to younger children is an option in such cases to complement conclusions on efficacy over the whole age range.

Once efficacy has been demonstrated in older children based on exercise testing or TTCW, extrapolation to younger age groups based on an extrapolation plan may be an option to consider.

It is, however acknowledged that feasibility of conducting such a stand-alone clinical development program should consider well-known difficulties of recruiting enough paediatric patients to show a significant improvement or even a strong trend on either TTCW or exercise capacity. This is even more the case if such a development aims at subgroups of patients without equivalent in adult patients. Planning for a stand-alone clinical program in paediatric patients with PH should therefore be discussed with EMA.

4.2. Human pharmacology studies

The development of age-appropriate paediatric dosage forms and formulations is usually required.

Adequate definition of the associated condition, in particular the type of CHD is important. PK studies should include a sufficient number of paediatric patients over the whole age range representing the relevant different conditions of patients suitable for treatment to allow an assessment of exposure in

comparison to adults, to inform a population PK (Pop-PK) model-based evaluation. A staggered approach from older to younger patients may be advisable depending on the profile of the medicinal product and the existing knowledge.

PK studies should include an assessment of relevant PD parameters and outcome measures to inform E-R analyses and generate data on efficacy and safety to support the respective extrapolation approaches.

For medicinal products being developed for a stand-alone paediatric indication, additional studies may be necessary to characterise the PK/PD relationship.

4.3. Efficacy

4.3.1. Clinical question of interest

The usual clinical question of interest for confirmatory studies is: "Does the experimental therapy improve clinical outcomes compared to placebo when used on top of standard therapy in paediatric patients (aged …) with PAH (type …), considering fatal adverse events, and irrespective of discontinuation of the treatment?"

This clinical question may be appropriate in the context of a stand-alone development and also for extrapolation-based approaches.

4.3.2. Estimand attributes

4.3.2.1. Intercurrent events and corresponding strategies

Beyond the population attribute which will differ by definition, there will be potential differences between the adult reference and the paediatric target populations in the framework of an extrapolation. Consequently, intercurrent events and certain attributes of the estimand may not align perfectly (e.g., dosing regimen, variable). When they differ, the estimand will always differ, and employing identical strategies for intercurrent events across reference and target populations may not be feasible. However, for attributes consistent across populations, it is recommended to apply the same strategy for intercurrent events.

In order to determine estimands in paediatric PAH trials, all potential intercurrent events with regard to clinical study objectives should first be considered, along with how their occurrence should be addressed with a corresponding strategy.

The discontinuation of the assigned treatment is a relevant intercurrent event in this setting. The primary regulatory interest is in the outcome, regardless of whether patients discontinue the treatment (treatment policy strategy). Correspondingly, the outcome after the discontinuation of treatment is relevant for the regulatory assessment and all efforts should be made to collect them.

For continuous-type endpoints, i.e. 6MWD, occurrence of fatal adverse events and death lead to non-existing measurements. Therefore, use of treatment policy strategy is not possible. A composite endpoint strategy is considered as an acceptable strategy for handling death in the analysis of continuous endpoints like 6MWD. For those who have missing data due to fatal adverse events their 6MWD at the analysis timepoint (i.e. Week 24) should be assigned as 0 meters and change from baseline is calculated accordingly.

Apart from those, it would be expected that all intercurrent events are pre-defined in the study protocol together with the corresponding estimand strategy. It is recommended that within an extrapolation approach intercurrent events are aligned across adult and paediatric trials and preferably handled using the same strategy. In case of deviations (e.g. use of slightly different definition for TTCW in paediatrics), the discrepancies should be clearly described between paediatric and adult trials.

Among potential intercurrent events to be taken into account are lack of adherence to treatment (e.g. treatment interruption, use of rescue medication, dosing deviation and intake of not allowed

concomitant medication), occurrence of malignancy and death, change to background PAH medication (initiation, change in dose, discontinuation), initiation of supplemental oxygen for a 6-minute walking test (6MWT). For use of rescue medication, a treatment policy strategy is generally preferred. If an imbalance in the frequency of rescue medication intake that favours the investigational arm is foreseen or observed, alternative strategies may be considered as supplementary estimands.

Similarly, estimands for secondary endpoints should be defined. Differences about estimand strategies between primary and secondary endpoints should be explained.

It is important to perform sensitivity analysis when imputations are used as indicated in ICH E9(R1); the purpose for each of these analyses should be described in relation to a given assumption.

4.3.2.2. Treatment condition

The treatment condition depends on the overall strategy and the respective study design as outlined in Section 4.3.4, below.

4.3.2.3. Target population

Paediatric age groups should be adequately represented to allow the respective recommendation for the included age. Proper representation of subgroups as recommended in the *EMA guideline on investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013)* is necessary if specific claims are made relating to aetiology and functional class.

As disease type can be an important predictive factor, randomisation of pivotal clinical trials should be stratified into the IPAH and APAH categories.

4.3.2.4. Variable (endpoint)

4.3.2.4.1. Exercise capacity

Exercise capacity can be used as a primary endpoint in developmentally able children (14) or be used to inform ER modelling for extrapolation from adults to paediatric patients. However, feasibility issues are acknowledged due to the high number of patients needed to establish a statistically significant effect even in case of a moderately relaxed alpha. Both the 6MWT, and cardiopulmonary exercise testing (CPET) are acceptable. Selecting the same exercise test that is used in adult patients with PAH and the same time point of assessment is recommended for E-R model-based extrapolation approaches.

4.3.2.4.2. Time to clinical worsening

TTCW captures important information on outcome in paediatric patients with PAH and should always be assessed in the clinical programme. It can be used as a primary/confirmatory endpoint in a paediatric study in a stand-alone development, and exploratory in extrapolation-based programmes. Feasibility issues are acknowledged due to the high number of patients and long observation times needed to establish a statistically significant effect even in case of a moderately relaxed alpha. In a clinical programme based on extrapolation, generating exploratory data on TTCW and its components is sufficient. How to integrate data on TTCW in an assessment of similarity of response to treatment of various variables should be predefined. Criteria used to define TTCW 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. Adapting the definition of TTCW to paediatric patients, e.g. by including symptoms like syncope more likely to occur in paediatric patients, may be considered. In such a case, supplementary analyses based on the definition for adults should also be presented.

TTCW and its components including cardiovascular and all-cause mortality should be analysed in all studies and in a follow-up study to assess both exploratory efficacy and safety.

4.3.2.4.3. Haemodynamic parameters

Obtaining invasive haemodynamic measurements for study purposes beyond assessing data available from routine clinical workup is not considered feasible due to risks associated with these procedures. Such data, if available, may therefore be considered for inclusion of patients in trials and may be reported as exploratory information but should not be requested as clinical endpoints for dose selection or extrapolation purposes.

4.3.2.4.4. Echocardiography

Echocardiography is used in clinical practice to assess patients´ prognosis and for follow up, often being assessed in the context of risk scores. Since similar single or combined echocardiography parameters are correlated with prognosis in paediatric and adult PAH patients' echocardiography has the potential to support extrapolation. However, there are limitations when used in clinical trials. Among these are inter- and intra-observer variability, quality of acquisition (even if core laboratory parameters are involved), cooperation of patients and the impact of the aetiology of PAH on the quality of echocardiography acquisition. Therefore, currently echocardiography parameters are not considered sufficiently reliable to be used as key endpoints for extrapolation in multicentre trials in PAH patients. This does not exclude obtaining echocardiography parameters as supportive evidence, particularly in trials conducted in single highly experienced centres.

4.3.2.4.5. MRI

MRI has advantages over echocardiography as concerns variability. However, due to limited availability across centres for study purposes, the requirement to use MRI may limit the number of paediatric patients included in a trial. Furthermore, sedation mainly in children below about 7 years old has an impact on some parameters and further limits recruitment of patients to a study. For these reasons MRI may not be suitable to characterize cardiac and haemodynamic variables in the broad paediatric population. MRI could be considered in a subset of older children and adolescents to support extrapolation if accessibility is ensured and experienced operators interpreting the results in children with PAH are available.

4.3.2.4.6. Health related quality of life (HrQL)

The effect on HrQL can be measured as an additional endpoint acknowledging that indirect assessment by involving the child's parents/carers is inevitable for the younger patient groups. Reliability of the results is higher in a double-blind controlled study as compared to open-label studies. Considering the lack of a validated disease-specific HrQL instrument for the paediatric population with PH, further research is encouraged in this regard in order to support the use as a confirmatory secondary endpoint. Assessing quality of life by the use of non-disease specific overarching HrQL instruments may provide relevant information on physical, emotional, and social functioning (EMA/CHMP/PRAC/148869/2025).

4.3.2.4.7. Risk scores

Risk scores integrating prognostic factors like clinical signs and symptoms, growth, 6MWD, WHO functional class, biomarkers like BNP/NT-proBNP, imaging-based and haemodynamic variables are commonly used to support clinical decision making in individual patients. Currently they are not sufficiently validated as clinical endpoints and changes in predicted risk do not necessarily translate into outcome in the same direction. Developing and validating specific paediatric risk scores for PAH and aligning adult and paediatric risk assessment is a prerequisite for using such tools either in the context of extrapolation or as endpoints in paediatric clinical trials.

4.3.2.4.8. BNP/NT-proBNP

Due to its prognostic value BNP/NT-proBNP is clinically used to assess disease progression and treatment response in individual patients, e.g. by considering thresholds or rapid increases as prognostic markers (21). It is currently not sufficiently validated to be used as a primary efficacy endpoint. Age-specific ranges, impact of development, disease, renal function, and treatment have to be considered. Shunts, dysfunctional ventricles and diuretic therapy may be associated with lower values. Furthermore, the choice of the assay may have a relevant impact on the results. When considering BNP/NT-proBNP as supportive evidence contributing to a similarity assessment or being further validated as a bridging biomarker such factors have to be taken into account, as well as patient characteristics relevant for BNP/NT-proBNP levels in adults. NT-proBNP is preferred over BNP when to be used as an endpoint.

4.3.2.4.9. Functional class

WHO functional class (FC) has prognostic value but the applicability in younger children is limited. WHO functional class should be assessed in paediatric patients as a secondary or exploratory endpoint. The Panama Functional Classification allows a more comprehensive assessment of paediatric patients with PAH by incorporating symptoms developmental and social functions. However lacking validation, the use of the Panama FC is currently not supported.

4.3.2.4.10. Other variables

During long term follow up 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. Among these, accelerometry provides objective data on physical functioning of patients and further research and validation are encouraged. Extrapolation of artificial intelligence-based approaches is also welcomed.

4.3.2.5. Population-level summary

Statistical analysis strategy should be aligned with the estimands of interest. Analyses estimating supplementary estimands can also assist in the interpretation of trial data and may supplement benefit-risk assessment.

For continuous endpoints, estimated least-squares mean difference (LSMD) between intervention and control is recommended.

For time to event endpoints, hazard ratio is recommended.

4.3.3. Study design

PK studies to characterize exposure in the different age groups should be conducted in accordance with overarching guidelines as outlined in the *Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004)*, and *ICH E11A Guideline on pediatric extrapolation (EMA/CHMP/ICH/205218/2022)*.

Studies in an extrapolation plan should mirror estimands in adults as much as possible, e.g. if a 6MWT is assessed at 3 months in adults, the same exercise test and the same 3-month time point of assessments should also be selected in the paediatric population. This holds also true for an assessment based on similarity of response to treatment. For extrapolation an additional estimand can be pre-specified in the adult population that matches the paediatric estimand even if not the primary estimand for the MAA in adults.

Confirmatory studies and studies supporting extrapolation should be double-blind and controlled, preferably with a placebo control arm on top of standard of care as locally applicable. However, since

placebo-controlled studies may be considered as an obstacle to recruitment, alternative approaches are conceivable. Among these are cross over of patients assigned initially to placebo to active treatment with study drug or of an approved treatment in the control arm or investigating different doses of the study drug covering expected differences in efficacy. Whether studies with an active control arm may be suitable should be evaluated in the context of an extrapolation plan taking information available for the respective control into account.

Background treatment with medicinal products approved for the treatment of paediatric PAH should be allowed provided there are no reasons related to the mechanism of action or safety to preclude coadministration with the study drug. 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. Changes of background treatment should be at the discretion of the treating physician and should be documented.

Patients should be stratified by age groups and by underlying disease (e.g. IPAH vs. APAH).

For a stand-alone development, the design of studies should usually follow the same principles as applicable for adult patients as outlined in the PAH guideline for adults. As a rule, randomized controlled trials are expected. Considering the well-known difficulties in recruitment the proposed development plan should be discussed with EMA.

4.3.4. Statistical methods

Efforts should be made to collect all relevant data for the primary and important other estimands (e.g. follow-up regardless of intercurrent events) to minimise the need to rely on untestable assumptions in the analysis and interpretation of the trial results. Still, in many cases, due to relevant amount of missing data (often differential between treatment arms) carefully handling of missing data is required.

Descriptive statistics should be provided for the number of the different intercurrent events and missing data at all measurement timepoints stratified by treatment group. Additionally, within the same overview, information should be included on whether data became missing after the intercurrent event.

Generally, handling of missing data should be based on clinically plausible assumptions, or when a range or assumptions is plausible, adequately conservative assumptions making it unlikely that the treatment effect is biased in favour of the new treatment or its variance underestimated.

When missing data need to be imputed following treatment discontinuation, the analysis should not (implicitly) assume that all the benefit from treatment is retained, which is not considered clinically plausible. Particularly, methods based on the missing-at-random assumption are not acceptable for estimating the treatment effect regardless of treatment discontinuation if they are (primarily) based on data collected while on treatment and if they are not accounting for the actual treatment status (particularly, the discontinuation of treatment of some subjects). Instead, reference-based multiple imputations (with a justified assumption on the amount of benefit retained after discontinuation of treatment, if any) or return to baseline values could be considered.

Assumptions underlying the primary analysis should be examined through pre-specified and justified sensitivity analysis (e.g. tipping point analyses) addressing the same estimand.

However, when the percentage of subjects experiencing an intercurrent event such as death is high, the use of composite strategy brings additional difficulties for handling remaining missing data in the dataset. For example, when the subjects who die are imputed with a value of 0 for 6MWD in a substantial amount of subjects, the remaining missing data is imputed based on this artificially imputed dataset. When such an approach is used for another intercurrent event, the choice of imputation value should not affect the results of the study. Therefore, the use of imputation methods can be considered first, followed by the analysis model.

4.4. Safety

Short-term safety data should be collected from all studies and compared with the known safety profile in adults. All studies should be followed by long term extension studies to allow investigation of long-term safety in terms of growth, neurological and sexual maturity.

5. Persistent pulmonary hypertension of the newborn

5.1. Human pharmacology studies

The development of age-appropriate paediatric dosage forms and formulations is usually required. Generating data on clinical PK and PD should follow general principles as appropriate for the target group of neonates. Separate studies are needed to establish proof of concept and dose selection for phase 3 studies.

5.2. Efficacy

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.

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 standardised criteria e.g. oxygenation index);
- time on NO;
- time to weaning from mechanical ventilation;
- ventilation index;
- time on supplemental oxygen and
- duration of ultrasound-detectable right-left shunting (hours or days).

5.3. Safety

Neonates with PPHN should be followed up for at least 24 months to document outcomes in terms of mortality and central nervous system development.

Abbreviations

6MWD	6-minute walking distance
6MWT	6-minute walking test
APAH	associated pulmonary arterial hypertension
B/R	benefit/risk ratio
CHD	congenital heart disease
CPET	cardiopulmonary exercise testing
ECMO	extracorporeal membrane oxygenation
E-R	exposure-response
FC	functional class
HPAH	hereditary pulmonary arterial hypertension
HrQL	health-related quality of life
IPAH	idiopathic pulmonary arterial hypertension
MIDD	model informed drug development
NO	nitric oxide
PAH	pulmonary arterial hypertension
PAP	pulmonary arterial pressure
PD	pharmacodynamic
PH	pulmonary hypertension
PK	pharmacokinetics
Pop-PK	population pharmacokinetic
PPHN	persistent pulmonary hypertension of the newborn
PVR	pulmonary vascular resistance
TTCW	time to clinical worsening

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