Provisional Translation (as of January 2025)*

Consideration in the development of drugs for pulmonary arterial hypertension (Early Consideration)

January 7, 2025
Office of New Drug II
Pharmaceuticals and Medical Devices Agency

1. Introduction

Pulmonary arterial hypertension (PAH) is a serious disease resulting in right heart failure and even death due to increased pulmonary arterial pressure and pulmonary vascular resistance caused by constriction and remodeling of pulmonary vessels[1)-3)]. PAH is a designated intractable disease, and it is reported that there were 4,682 patients with PAH in FY 2024 based on the number of recipients of specific medical expenses (designated intractable disease) in Japan[4)]. To date, several drugs with different mechanisms of action and routes of administration have been approved in Japan for the treatment of PAH. However, medical needs remain for patients whose prognosis is not sufficiently improved by these treatments. Therefore, the development of new PAH therapies is ongoing, and the design of studies including efficacy endpoints is also under discussion[5)-8)].

The purpose of this document is to present the current considerations for clinical development strategies of PAH therapeutics in Japan. It should be noted that these considerations are based on currently available knowledge and may change as new findings emerge.

2. Key Considerations for Overall Development Strategy (Clinical Data Package)

The goal of treatment of PAH is to improve prognosis. Since PAH is a rare disease, it would be difficult to conduct a confirmatory trial with morbidity/mortality events ("M/M events") as the primary endpoint in Japan alone. Therefore, active participation in multi-regional clinical trials should be considered from the early stage of development.

If results from overseas confirmatory trials are available, or if such trials are ongoing but difficult for Japan to participate in, a development strategy could involve conducting clinical trials to compare efficacy and safety between the non-Japanese and Japanese populations. This could include domestic trials or multi-regional trials with countries/regions not

* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

participating in the referenced overseas confirmatory trials to evaluate the similarity of the trial results to that of the referenced overseas trials and explain efficacy and safety in Japanese patients with reference to the results of overseas confirmatory trials.

In such a strategy, the design of the clinical trial for evaluating similarity should align as closely as possible with the referenced overseas clinical trials. However, if a different study design is adopted, the reasons should be explained, and it should be demonstrated that the similarity of the trial results can still be evaluated despite the design differences.

If it is difficult to set M/M events as the primary endpoint due to feasibility or other reasons, it may be acceptable to use other primary endpoints allowing comparison with the results of overseas clinical trials (see "3.2 Primary Endpoints"). Consultation with the PMDA regarding specific study designs is strongly recommended.

Since PAH also affects pediatric patients, it is strongly recommended to develop a plan for pediatric patients with PAH in parallel with development for adult patients (e.g., conducting clinical trials to explore pediatric dosage and administration, establishing pediatric formulations, etc.). For specific considerations regarding pediatric development, refer to "4. Considerations for Development in Pediatric Patients with PAH" for more details.

3. Considerations for Confirmatory Trials

3.1 Study Design

In principle, a confirmatory trial should be a randomized, double-blind, comparative study with an appropriate control group. Placebo is used as a control in comparative studies while maintaining appropriate PAH treatment. However, in cases where the aim is to demonstrate superiority or non-inferiority to existing PAH drugs, it is appropriate to use existing PAH drugs as the control.

3.2 Primary Endpoints

The goal of treatment of PAH is to improve prognosis. Therefore, the most recommended primary endpoint of a confirmatory trial is the M/M events, a composite endpoint of death and clinical worsening of PAH.

M/M events other than death should be defined based on their relevance to survival and clinical significance, including hospitalization due to worsening of PAH, lung transplantation, and appropriately defined disease progression. M/M events should be defined as specifically as possible in the study protocol. To reduce the variability in assessments regarding event eligibility among trial sites, participating countries, or regions and to ensure objective assessments, evaluation should be based on central assessment in a blinded manner by an independent endpoint adjudication committee.

If it is difficult to set M/M events as the primary endpoint due to feasibility or other reasons, the following endpoints may be considered.

1) Pulmonary Vascular Resistance (PVR)

PVR is an objective measure and has been reported to correlate with the prognosis of patients with PAH[9]. If physical differences are expected in the study population, pulmonary vascular resistance index (PVRI), adjusted for body surface area, should be considered. Either change from baseline or the rate of change in PVR can be set as the primary endpoint, but it is important to evaluate from both perspectives. Although right heart catheterization is commonly performed in Japan to assess treatment effects, it may be considered ethically challenging to perform such an invasive test in other countries and regions.

2) 6-Minute Walk Distance (6MWD)

Although 6MWD has been used as the primary endpoint in many clinical trials of PAH drugs approved in Japan and overseas, it is significantly influenced by factors other than the drug intervention, such as age, height, learning effects, and the patient motivation, and its relevance to the prognosis of PAH patients is not established. Therefore, it is no longer recommended as a primary endpoint in confirmatory trials in recent years. However, 6MWD may be acceptable in cases where evaluation based on PVR is challenging or when it is considered appropriate to set 6MWD as the primary endpoint for comparability with the results of existing clinical trials, etc.

3.3 Efficacy Endpoints Other Than Primary Endpoints

Secondary or exploratory efficacy endpoints in confirmatory trials may include:
Pulmonary hemodynamic parameters (e.g., PVR, mean pulmonary artery pressure),
Exercise tolerance (e.g., 6MWD,), WHO functional class, Echocardiographic parameters (e.g., estimated right ventricular pressure, tricuspid annular plane systolic excursion (TAPSE)), or Cardiopulmonary exercise test (CPET) parameters (e.g., peak oxygen consumption (peak VO_2)).

3.4 Evaluation Period

When the primary endpoint is M/M events, an event-driven study design may be appropriate. If setting a fixed evaluation period, the study duration should be set considering the time needed to achieve treatment effect in the target population.

When PVR or 6MWD is the primary endpoint, an evaluation period of 24 weeks may be considered. However, since PAH drugs are expected to be used for a long time in clinical settings, safety data for at least 52 weeks of administration is generally required.

3.5 Statistical Analysis Methods

For comparisons of M/M events between groups, survival analysis of the time to event is generally appropriate. For other endpoints, analysis methods suited to the characteristics of individual endpoints should be employed. The handling of patients who had missing values or intermediate events should be predefined in the analysis plan. Depending on the components of M/M events, analytical methods taking into account the clinical importance of each component may be considered.

3.6 Target Patients

It is appropriate to include patients with all severity of pulmonary hypertension symptoms (WHO functional class) for whom the administration of the drug is expected in clinical settings. If concomitant use of existing PAH drugs with different mechanisms of action is permitted during the study period, the following measures should be taken to minimize their impact on the efficacy evaluation of the study drug as much as possible:

to include patients who have been receiving stable doses of existing PAH treatments for a certain period before the study drug administration; or to prohibit dose modification of existing PAH treatments during the study period.

3.7 Dosage and Administration

When setting a dosage and administration that allows dose adjustment (titration, dose reduction, dose increase after reduction, etc.), the timing and criteria for judgment should be specified as specifically as possible in the study protocol.

In pediatric trials, it is appropriate to consider the need for titration from a low dose to ensure the safety of patients.

4. Considerations for Development in Pediatric Patients with PAH

As described in "2. 2. Comprehensive Considerations for Development Strategy (Clinical Data Package)", it is strongly recommended to formulate a development plan for pediatric patients in parallel with the development of adult patients. See also the notification[10] for development plans and the timing of consultations with the PMDA.

The number of pediatric patients with PAH is extremely limited. Therefore, it is expected to be very challenging to conduct a confirmatory trial with M/M events as the primary endpoint exclusively in pediatric patients with PAH. Therefore, given that the pathophysiology, diagnostic criteria, clinical classifications, disease severity classifications, and treatment algorithms for PAH are similar for children and adults[11), 12)], if there are no significant differences in exposure between children and adults when recommended doses are

administered, it may be possible to adopt a development strategy that utilized the results of the confirmatory trials in adult patients with PAH to explain efficacy in pediatric patients with PAH. In such cases, the primary endpoints of clinical trials in pediatric patients with PAH should be set based on comparability with the results from clinical trials in adult patients. The study design should be considered so that a certain level of evaluation is possible for patients in each age or weight category. However, it should be noted that it may be difficult to set the same endpoints as those for adults in some age categories.

It is recommended to consult with PMDA regarding the development plan for pediatric patients with PAH and the study design of specific clinical trials.

5. References

1) Marius M Hoeper, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013; 62: D42-50
2) Ralph T Schermuly, et al. Mechanisms of disease: pulmonary arterial hypertension. Nat Rev Cardiol 2011; 8: 443-55
3) A A Roger Thompson, et al. Targeting Vascular Remodeling to Treat Pulmonary Arterial Hypertension. Trends Mol Med 2017; 23: 31-45
4) https://www.nanbyou.or.jp/wp-content/uploads/2024/11/koufu20241.pdf (Last Accessed January 6, 2025)
5) Vallerie V McLaughlin, et al. End points and clinical trial design in pulmonary arterial hypertension. J Am Coll Cardiol 2009; 54: S97-107
6) Mardi Gomberg-Maitland, et al. New trial designs and potential therapies for pulmonary artery hypertension. J Am Coll Cardiol 2013; 62: D82-91
7) Olivier Sitbon, et al. Clinical trial design and new therapies for pulmonary arterial hypertension. Eur Respir J 2019; 53: 1801908
8) Jason Weatherald, et al. Clinical trial design, end-points, and emerging therapies in pulmonary arterial hypertension. Eur Respir J 2024: 2401205
9) Raymond L Benza, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010; 122: 164-72
10) Partial revision of “Planning of the Pediatric Drug Development Program during Development of Drugs for Adults (PSB/PED Notification No. 0329-1, March 29, 2024)
11) R J Barst, et al. Pulmonary arterial hypertension: a comparison between children and adults. Eur Respir J 2011; 37: 665-77
12) Guidelines for the Treatment of Pulmonary Hypertension (JCS 2017/JPCPHS 2017)