30 March 2023
EMADOC-1700519818-1054252
Executive Director

Letter of support for the development of the PAH-SYMPACT Instrument for use in Pulmonary Hypertension clinical trials

On 04 June 2021 the applicant Janssen-Cilag International requested qualification advice for the patient reported outcome (PRO) instrument, Pulmonary Arterial Hypertension – Symptoms and Impact (PAH-SYMPACT®) pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

The PAH-SYMPACT assesses change in symptoms and impacts on physical and emotional/cognitive functioning over time in patients with Pulmonary Hypertension (PH).

A discussion meeting with the Applicant took place on 05 April 2022. During its meeting held on 7 – 10 June 2022, the SAWP agreed on the qualification advice to be given to the applicant. During its meeting held on 20 – 23 June 2022, the CHMP adopted the qualification advice to be given to the applicant.

This letter of support is issued, based on the qualification advice provided for PAH-SYMPACT, to encourage further validation work and use of the PRO instrument in clinical trials with patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).

Background and Context of use

The clinical classification of Pulmonary Hypertension (PH) categorizes multiple conditions into five groups, including PAH and CTEPH, according to their similar underlying pathophysiology, haemodynamic characteristics and clinical presentation. PH patients typically experience symptoms such as shortness of breath, fatigue, weakness, chest pain, and syncope, that impact patients' functioning and well-being.

PAH-SYMPACT is a PRO instrument that measures the presence and severity of symptoms associated with PH and their impact on physical and emotional/cognitive functioning in adult PH patients. The instrument assesses efficacy endpoints in clinical trials evaluating treatments for PH. PAH-SYMPACT was developed in accordance with regulatory and scientific PRO guidance documents for use in clinical research to capture changes in symptoms and impacts experienced and reported by patients with PH. In addition, with the knowledge that patients with CTEPH exhibit symptoms similar to patients with PAH, the Applicant sought to evaluate the appropriateness of PAH-SYMPACT for patients with CTEPH.

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The Applicant sought Qualification Advice on the development and validation of PAH-SYMPACT and its use as an efficacy endpoint in clinical studies to be included in the EU Product Information for medicinal products for the treatment of PAH and CTEPH.

Available data and discussion

Use in PAH

Overall, the construction of PAH-SYMPACT and the validation approach for adult patients with PAH is acceptable.

PAH-SYMPACT was initially developed for use in adult patients with PAH. The items were generated based on a literature review, followed by a 3-stage qualitative development study. Stage I: concept elicitation with patients with PAH and expert input; Stage II: cognitive interviews and expert input; and Stage III: usability study. Following the qualitative development, it was validated in a psychometric validation study. Further validation included an assessment of the applicability in 3 European countries in the respective languages (French, Italian, Spanish).

The domains cover relevant items affecting the well-being of patients. The final conceptual model includes for the symptom part of the instrument 2 domains—Cardiopulmonary (6 items) and Cardiovascular (5 items)—and for the impact part 2 domains—Physical Impacts (7 items) and Cognitive/Emotional Impacts (4 items). Focus on frequently reported items subject to change was considered appropriate in the context of a PRO instrument designed to capture the effect of treatment on symptoms and impacts. In addition, a single item about oxygen use stands on its own and is not included in any of the domains. However, evaluating oxygen use is of key importance due to its effect on physical performance. Recall periods were 24 h (symptoms) and 1 week (impact), which is considered appropriate.

The overall validation strategy is reasonable, the validation exercise is at an advanced stage and the information provided is promising. Additional analyses are welcomed to assess:

- Prospective validation of meaningful change thresholds (MCT)
- Responsiveness over a range of patients at different stages of severity of the disease
- Analyses on correlations with disease progression and deterioration
- The impact of missing data

Provided additional supportive analyses are presented, PRO endpoints reflective of the symptom and impact domains of the PAH-SYMPACT can be considered for regulatory decisions and included in the EU Product Information for medicinal products for the treatment of PAH.

Use in CTEPH

Despite differences in the frequency of symptoms, there is considerable overlap between PAH and CTEPH in how the disease affects adult patients' well-being. For patients with CTEPH, some symptoms may be more likely, and others may either be due to the disease or related to medication (e.g., coughing blood, oedema).

Content validity of the PAH-SYMPACT is sufficiently established for patients with CTEPH. The proposed psychometric evaluation of the PAH-SYMPACT for use in CTEPH patients will follow similar procedures as were conducted in the validation for its use in PAH patients. Overall, the methodology is endorsed. The proposed validation strategy is reasonable. Provided the validation in CTEPH patients is considered sufficient and consistent with data as obtained during the validation for PAH, results regarding symptom- and impact domains related PRO endpoints can be considered for regulatory decisions and

included in the EU Product Information for medicinal products for the treatment of CTEPH. The same considerations as outlined above for PAH apply to CTEPH.

Continuing and future investigations

The overall validation strategy of the PAH-SYMPACT is reasonable. The Agency supports further investigation and development of the PAH-SYMPACT in patients with PH. Continued psychometric analysis planned for clinical trials in PAH and CTEPH is welcomed.

In conclusion, the EMA acknowledged the potential of PAH-SYMPACT as promising to assess change in symptoms and impacts over time in patients with PH. Hence, the EMA has issued this Letter of Support to encourage further development.

Sincerely,

Emer Cooke

Executive Director