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Executive Director

Letter of support for a Composite endpoint method for acceptability evaluation of oral drug formulations in the paediatric population

On 07/06/2022, on behalf of a public-private partnership comprising the University Hospital Düsseldorf, M.A.R.C.O. GmbH & Co. KG, Novartis Pharma AG and Pharmaplex bvba, the Applicant Novartis Europharm Limited requested a Qualification Opinion for its composite endpoint method for acceptability evaluation of oral drug formulations in the paediatric population pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

The Applicant proposes to use a composite acceptability endpoint method to select the most suitable dosage form during the clinical development of a paediatric medicine.

The procedure started on 08/05/2023, and a discussion meeting with the Applicant took place on 29/08/2023. On 29/09/2023, the SAWP agreed on the advice to be given to the Applicant. On 12/10/2023, the CHMP adopted the advice to be given to the Applicant.

The CHMP considered that the uncertainties associated with the proposed composite endpoint method do not allow, currently, a positive conclusion with respect to a Qualification Opinion for the claimed context of use. For a restricted context of use, the CHMP agreed to provide this letter of support.

The responses given by the CHMP were based on the questions and supporting documentation submitted by the Applicant, also in advance and during the discussion meeting, considered in the light of the current state of the art in the relevant scientific field.

This letter of support is issued, based on the qualification advice provided, to encourage further development and validation work of this method for evaluation of oral drug formulations in the paediatric population. This could, in turn, support a future EMA Qualification Opinion.

Background

Patient's adherence to the prescribed treatment is the prerequisite for achieving efficacy of medicines. Offering therapeutic substances in dosage forms that facilitate patient compliance is therefore key in medicines development process.

Especially for paediatric patient populations, the clinical development of an age-appropriate medicine is not only requiring the demonstration of efficacy and safety, but also of the acceptability of the formulation. With this in mind, there is a need for a broadly accepted, objective and scientifically sound acceptability assessment methodology, including validated evaluation criteria, in the clinical

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development of dosage forms for the paediatric population. The European Medicines Agency (EMA) Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2) emphasizes the importance of considering both factors in the assessment of acceptability.

The Applicant proposes an acceptability determination method purposed for oral formulation(s) to be used for the whole paediatric age range (0-18 years) in the clinical development of a new paediatric medicine. The method attempts to introduce a composite acceptability endpoint by combining palatability and swallowability assessments. In this method, swallowability and palatability are assessed in a standardised way by trained investigators and raters or, for palatability in children >6 years, by self-assessment after physical exposure to the formulations.

Context of use and available data

The proposed context of use (CoU) foresees the application of the proposed method at two occasions within the clinical development process:

- At an early stage, by testing placebo formulations to identify the most suitable formulation principles for children in the respective age ranges
- As a secondary endpoint to confirm the acceptability of the active formulation, e.g., within a safety and efficacy trial for a new medicine in development agreed upon within a paediatric investigation plan.

Between 2010 and 2022, the Applicant performed various clinical studies with individuals aged from newborn to 18 years. They first improved a published scoring scheme for swallowability and identified the complexities in performing such a study under standardised conditions in a paediatric hospital environment in a pilot study before starting the first statistically powered study in paediatric patients comparing swallowability and acceptability of a mini-tablet with syrup assessing under standardised investigator-performed observation and scoring conditions. Since then, the team investigated - with this methodology - in total, six different placebo dosage form presentations: single/multiple uncoated and coated mini-tablets, oblong tablets, round tablets, orodispersible films and syrup.

The studies focused on:

a) assessing swallowability and defining acceptability when the patients swallowed the dosage forms completely or partially. Data obtained this way provided the basis for a new standardised swallowability scoring.

b) investigation of palatability. Experience from these studies resulted in a new standardised palatability scoring.

Based on the data obtained from swallowability and palatability assessments in these studies, the Applicant developed the concept of a new composite acceptability endpoint based on a new scoring scheme integrating swallowability and palatability.

A retrospective analysis using data from previously performed studies applied the new integrating scoring scheme for definition of acceptability in order to establish the validity, expediency, and applicability of the developed composite acceptability endpoint. Recently, this method was used for the first time in a prospective clinical study.

Discussion

The European Medicines Agency (EMA) guideline emphasizes the importance of considering both factors in the assessment of acceptability. However, the guideline also states that acceptability is more than just swallowability and palatability. Even considering that swallowability and palatability are two important qualifiers, it is not justified to apply them as the only indicators of acceptability – i.e.,

patient-centred elicitation of an 'acceptability' construct is not evident, and the acceptability concept and its individual domains/items need underpinning with reference anchoring.

It is also important to acknowledge that the studies conducted thus far have utilized only placebo formulations, which means that the proposed methodology has not been tested using formulations that contain ingredients capable of significantly altering palatability.

The standardized process of observing the swallowing act by trained investigators in a controlled setting is considered essential to obtain unbiased data. This raises the question if the proposed assessment could be robustly used outside this setting.

The methodology aims at addressing the need for a standardised and scientifically sound approach while adhering to the EMA guideline's expectations for considering both swallowability and palatability in the assessment of acceptability. However, there are important aspects that need to be further implemented and taken into account before a qualification can be further considered.

The stated limitations preclude, currently, the qualification of this method for its use as an absolute measure of acceptability. However, the CHMP sees value in the presented method as a relative comparative standardized assessment of swallowability and palatability and their combination to compare different placebo formulations to enable selection of the most promising formulation concept at an early stage of the paediatric formulation development process when only placebo formulations are available. Pending further development work, this could - in turn -be potentially used as a tool that medicines developers could use to de-risk the development of paediatric formulations, in order to facilitate compliance to treatment.

The CHMP encourages the Applicant, jointly with other stakeholders in the field if available, to plan further work to address prospectively the stated limitations robustly and perform validation studies for the proposed endpoint with a view to forming a basis for qualification and further integration in paediatric medicines development.

Sincerely,

Emer Cooke
Executive Director