Amsterdam, 22 June 2023
EMA/CHMP/319165/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Rezolsta

International non-proprietary name: Darunavir/Cobicistat

Procedure no.: EMEA/H/C/002819/P46/007

Marketing authorisation holder (MAH): Janssen-Cilag International N.V.

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	24 Apr 2023	24 Apr 2023
☐	CHMP Rapporteur Assessment Report	30 May 2023	30 May 2023
☐	CHMP members comments	12 June 2023	n/a
☐	Updated CHMP Rapporteur Assessment Report	15 June 2023	n/a
☒	CHMP adoption of conclusions:	22 June 2023	22 June 2023

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1. Introduction

On 21-March-2023, the MAH submitted a completed paediatric study for Rezolsta in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that "A Study to Assess the Acceptability of the Darunavir/Cobicistat (DRV/COBI) Fixed-dose Combination (FDC) Tablet in Human Immunodeficiency Virus (HIV)-1 Infected Children Aged ≥3 Years and Weighing ≥15 kg to <25 kg" (TMC114FD1HTX1001) is part of a Paediatric Investigation Plan EMEA-001280-PIP01-12-M05. The line extension and type II variation application consisting of the full relevant data package (i.e., containing several studies) is expected to be submitted by 2025.

2.2. Information on the pharmaceutical formulation used in the study

The investigational product supplied for this study was formulated as a tablet for oral use containing 650 mg of DRV ethanolate (JNJ-25875382) equivalent to 600 mg of DRV base and 173 mg of COBI on silicon dioxide (JNJ-48763364), equivalent to 90 mg of COBI. Tablets had to be dispersed in water prior to use and contained croscarmellose sodium as disintegrant, mannitol and prosolv as fillers, sucralose as sweetener, and strawberry flavour. The FDC tablet is henceforth referred to as DRV/COBI 600/90.

2.3. Clinical aspects

2.3.1. Introduction

DRV (commercial name: PREZISTA) is an HIV-1 protease inhibitor and COBI (commercial name: Tybost) is a mechanism-based cytochrome P450 3A inhibitor, which is approved to enhance the exposure of co-administered drugs metabolized by CYP3A enzymes, such as DRV. The FDC of DRV 800 mg and COBI 150 mg is indicated, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older, weighing at least 40 kg) in several countries, including the EU/European Economic Area (commercial name: REZOLSTA) and the US (commercial name: PREZCOBIX).

The MAH submitted a final report for:

• Study TMC114FD1HTX1001: 'A Study to Assess the Acceptability of the Darunavir/Cobicistat (DRV/COBI) Fixed-dose Combination (FDC) Tablet in Human Immunodeficiency Virus (HIV)-1 Infected Children Aged ≥3 Years and Weighing ≥15 kg to <25 kg'.

The aim of the study was to assess the acceptability of a 600/90 mg DRV/COBI FDC oral tablet, taken after dispersion in water, in HIV-1 infected children aged ≥3 years and weighing ≥15 kg to <25 kg.

Other studies in the PIP EMEA-001280-PIP01-12-M05 (but not assessed here) include:

- Study GS-US-216-0128 *(evaluating the PK, safety, and efficacy of COBI-boosted atazanavir or COBI-boosted DRV administered with a background regimen in HIV-1 infected, virologically suppressed paediatric participants);*

- Study TMC114FD1HTX1004 *(bioequivalence study in healthy adults conducted to assess the bioequivalence of DRV 600 mg in the presence of COBI 90 mg when administered as an FDC compared to the coadministration of the separate available formulations (as administered in Study GS-US-216-0128).*

2.3.2. Clinical study TMC114FD1HTX1001

Description

This was a Phase 1, open-label, single-dose, multicentre study conducted at sites in the Republic of South Africa, Spain, and the USA that evaluated the acceptability of the 600/90 mg DRV/COBI FDC oral tablet (dispersed in water) in HIV-1 infected children, aged ≥3 years and weighing ≥15 kg to <25 kg.

The study was conducted from 3 August 2022 to 3 September 2022.

Methods

Study participants

The participants enrolled in the study were HIV-1 infected children aged ≥3 years and weighing ≥15 kg to <25 kg. Participants were required to be adherent on an allowed stable unchanged antiretroviral (ARV) medication for at least 3 months prior to screening, HIV-1 RNA <400copies/ml. Dosage changes due to growth in the previous 3 months were allowed. Exclusion criteria included any active condition that could prevent swallowing of dispersions in water (e.g., active oral candidiasis infection).

Assessor's comments:

The study participants are described on a high level. No upper age limit is listed in the inclusion/exclusion criteria (only the upper weight limit). Moreover, an in-depth description of the recruitment population (i.e., the pool of children who were screened) was lacking. Further elaboration on the in- and exclusion criteria would be necessary to appreciate the study's results fully. Such detailed information is considered necessary when the final data package is submitted as part of the line-extension / type II variation.

Treatments

All participants received DRV/COVI 600/90 mg dispersed in water prior to use. Instructions on how to disperse the tablet and about rinsing were detailed in the study site investigational product and procedures manual.

Assessors comment:

A copy of the instructions provided to the caregiver on how to disperse the tablet is relevant to determine how uniformly the procedure of dissolving was followed prior to any potential changes to the SmPC regarding using a tablet dispersed in water. This will be assessed as part of the upcoming line-extension / type II variation.

Objectives

The primary objective was to assess, as part of the acceptability, the ability to swallow the 600/90 mg DRV/COBI FDC tablet dispersed in water.

Secondary objectives were:

1. To assess, as part of acceptability, ease of swallowing, the palatability, and the ease of dispersion of the tablet 600/90 dispersed in water.
2. Acceptability of the intake of the DRV/COBI 600/90 mg FDC tablet dispersed in water, if to be taken daily.
3. Short-term safety and tolerability of the DRV/COBI 600/90 mg FDC tablet dispersed in water.

Outcomes/endpoints

The primary endpoint was ability to take the DRV/COBI 600/90 mg FDC tablet dispersed in water, derived from a questionnaire to be completed by the observing site personnel. The questionnaire consisted of 2 questions (one close-ended and one open-ended) taken no more than 15 minutes after study intervention.

Secondary endpoints were (respectively, see numbering in section objectives):

1. ease of swallowing and palatability using a questionnaire to be completed by the participant and a questionnaire to be completed by the caregiver; ease of dispersion assessed using a questionnaire to be completed by the caregiver.
2. Acceptability, if to be taken daily, using a questionnaire to be completed by the participant and a questionnaire to be completed by the caregiver.

Assessment of adverse events was performed with open-ended and non-leading questioning of the participant and/or caregiver, with the last contact moment a telephone call 8-11 days after intervention intake. Questionnaires were taken by the participant/caregiver no more than 15 minutes after study intervention. A 5-point hedonic scale with facial expressions to depict likeability or difficulty level was used to sort experience into 5 categories "dislike very much", "dislike a little", "not sure", "like a little", "like a lot."

Assessor's comment:

Participants themselves were asked to fill in the questionnaire, and if necessary, the caregivers and/or study-site personnel may have assisted in filling in the questionnaire. As this was an open label study, this is a potential source of response bias.

Sample size

This study had a precision-based (i.e., not power-based) sample size calculation as there was no specific null hypothesis. Assuming that at least 10 of 12 participants would ingest the tablet dispersed in water "fully", it was concluded with 80% confidence that the lower bound of the 1-sided CI for ability to swallow (i.e., the proportion of participants who would be able to fully swallow the tablet dispersed in water), was at least 72% (using the method of Wilson).

Randomisation and blinding

The study was an open-label, single-dose study. There was no randomisation and blinding.

Statistical Methods

All analyses were performed as intention to treat analyses. Primary and secondary endpoints were analysed descriptively using frequency tabulations and percentages. The proportion of participants able to swallow the medication fully versus partially or not at all, based on the questionnaire for the observer, was presented with a corresponding 95% Wilson CI.

Assessor's comment

As this is a single-arm, open-label study with minimal sample size, its results are only considered descriptive, and no formal conclusions can be drawn.

Results

Participant flow

Of the 12 participants screened for the study, all 12 (100%) were enrolled and all 12 (100%) completed the study. Screening took place within 21 days prior to study intervention intake, or on the day of intake (Day 1). The total study duration was a maximum of 11 days (not including screening), with a safety follow-up check occurring between Day 8 and Day 11.

Recruitment

Assessors comment:

It is not clear what the recruitment population was. In the final report expected in 2025 as part of the line-extension / type II variation, this should be outlined to assess the study's generalizability to the paediatric HIV-1 population.

Baseline data

A higher proportion of participants were female (75.0%), and half were Black or African American (50.0%). The median age was 5 years (range 4 to 8 years) and the median weight was 22.65 kg (range 15.1 to 23.9 kg). Three participants (25.0%) were ≥3 to <5 years of age and 9 participants (75.0%) were ≥5 years of age. See table 1.

	DRV/COBI FDC (600/90mg) Tablet Dispersed in Water (N=12)
Age (years)	
n	12
Mean (std)	5.6 (1.38)
Median (Min - Max)	5.0 (4; 8)
Age groups [n(%)]	
≥3 - <5 years	3 (25.0%)
≥5 years	9 (75.0%)
Sex [n(%)]	
Female	9 (75.0%)
Male	3 (25.0%)
Race [n(%)]	
Black or African American	6 (50.0%)
Asian	2 (16.7%)
White	2 (16.7%)
American Indian or Alaska Native	1 (8.3%)
Not Reported	1 (8.3%)
Black or African American + White	0
Native Hawaiian or other Pacific Islander	0
Other	0
Ethnicity [n(%)]	
Not Hispanic or Latino	8 (66.7%)
Hispanic or Latino	4 (33.3%)
Weight (kg)	
n	12
Mean (std)	20.69 (3.379)
Median (Min - Max)	22.65 (15.1; 23.9)
Weight groups [n(%)]	
≥15 - <20 kg	4 (33.3%)
≥20 - <25 kg	8 (66.7%)

Table 1: Demographic Data; Intent-to-Treat (Study TMC114FD1HTX1001)

Number analysed

The 12 screened participants were analysed in an intention to treat analysis.

Efficacy results

According to the results for the swallowability questionnaire for the site observer, most (10/12; 83.3%) of the participants swallowed the tablet dispersed in water fully (table 2). For the 2 (16.7%) participants who swallowed the tablet dispersed in water partially, the following issues were indicated: 1 (8.3%) participant refused to take the tablet dispersed in water fully and 1 (8.3%) participant experienced gagging and bad taste. The participants who did not swallow the tablet fully had listed their history of tablet-taking as "very easy" in the screening questionnaire.

Assessor's comment:

The trial protocol states that a history of swallowing drinks, food or medication in liquid form, and the medical and surgical history would be obtained from the participant or the caregiver. However, it is noted that data from the screening questionnaire is not provided for every participant.

	DRV/COBI FDC (600/90mg) Tablet Dispersed in Water (N=12) n (% - cumulative %)
Questionnaire Response	
Questionnaire contents	
Did the participant take the tablet dispersed in water?	
Fully	10 (83.3% - 83.3%)
Partially	2 (16.7% - 100%)
If the participant did not take the tablet dispersed in water fully, indicate which problems occurred[a]	
Gagging And Bad Taste	1 (8.3% - 8.3%)
Refusing	1 (8.3% - 16.7%)

[a] One participant did not take the tablet dispersed in water fully due to gagging and bad taste. For the second participant who took the tablet partially, no additional information was reported apart from the refusal to take the tablet dispersed in water fully.

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Table 2: Primary endpoint: Site observer questionnaire assessing ability to take the 600/90 mg DRV/COBI FDC tablet dispersed in water.

	DRV/COBI FDC (600/90mg) Tablet Dispersed in Water (N=12) n (% - cumulative %)
Questionnaire Response	
Questionnaire contents	
How much do you like the taste of this tablet dispersed in water?	
Dislike Very Much	4(33.3% - 33.3%)
Like A Little	4(33.3% - 66.7%)
Like A Lot	4(33.3% - 100%)
How easily can you swallow this tablet dispersed in water?	
Difficult	2(16.7% - 16.7%)
Ok	1(8.3% - 25%)
Easy	2(16.7% - 41.7%)
Very Easy	7(58.3% - 100%)
How easy do you think it is to take this tablet dispersed in water every day?[a]	
Dislike Very Much	1(8.3% - 8.3%)
Dislike A Little	2(16.7% - 25%)
Not Sure	1(8.3% - 33.3%)
Like A Little	2(16.7% - 50%)
Like A Lot	5(41.7% - 91.7%)

[a] This response was not recorded for one participant.

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Table 3: Secondary endpoint, ease of palatability, swallowing, dispersion, as rated by the participant/caregiver.

Safety results

There were no adverse events (AEs) or serious adverse events (SAEs) reported in the study.

Assessor's comment

No AEs have been reported during this study (follow up until day 8 to 11), which is not surprising considering the limited sample size. Based upon the current data no conclusions on the safety of the FDC in this population can be drawn.

2.3.3. Discussion on clinical aspects

It is agreed that a considerable part of the paediatric population is expected to have difficulties swallowing a whole or 2 halves of an oral non-disintegrating tablet. It is, therefore, clinically advantageous to have multiple dosage forms of the same medication for this population so that caregivers can select the method best tolerated by the specific child.

This study aimed to assess the acceptability of the FDC darunavir/cobicistat 600/90mg tablets in paediatric patients. The study is part of a PIP, which included studies on the bioavailability and dissolvability of the FDC. A line-extension and type II variation application consisting of the full relevant data package is expected to be submitted by 2025. No quality or pharmacokinetic data were provided within the current procedure.

There were no (severe) adverse events reported in this study. However, 2 of the 12 participants reported not taking the medication fully. The two participants who reported taking the dissolved tablet partially had given their history of taking medication orally as "very easy." Although protease inhibitors have a high barrier to resistance, habitual partial ingestion of any component of HIV therapy with subtherapeutic exposure levels is a concern that needs to be addressed with the type II variation application.

The MAH considers no update of the SmPC is warranted in relation to the outcomes of this study. The Rapporteur can agree with this statement as the current product information does not state that the tablet may be taken after being dispersed. Further, no new safety concerns have been identified based on the currently provided data of 12 study participants. Information regarding the recruitment methods and population, in- and exclusion criteria (i.e., upper age limit), sample size, patient instructions regarding the dissolution of the tablet, the influence of the on-site personnel on the response of the questionnaire, and possible consequences of partial ingestion of the dissolved FDC on disease management should be addressed when the full relevant data package is submitted as part of the line-extension / type II variation (expected in 2025).

3. Rapporteur's overall conclusion and recommendation

The data submitted do not influence the benefit-risk balance for Rezolsta. There is no update of the product information necessary based in the information contained within this study.

☒ Fulfilled:

No regulatory action required.