26 January 2023
EMA/CHMP/64582/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006, as amended

TAVNEOS

avacopan

Procedure no: EMEA/H/C/005523/P46/003

Note

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

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1. Introduction

On 21 October 2022, the MAH submitted an abbreviated report of the results of Study CL011_168: a randomized, double blind, placebo-controlled Phase 2 Study to evaluate the safety and efficacy of avacopan (CCX168) in patients with C3 Glomerulopathy (ACCOLADE, EudraCT#: 2017-001821-42, NCT03301467), which includes a results summary and associated safety and efficacy data tables for the double-blind period, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The final Clinical Study Report for this study which will be submitted to EMA upon finalisation.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH is providing an abbreviated report of the results of Study CL011_168 which includes a results summary and associated safety and efficacy data tables for the double-blind period. This report is being submitted to the European Medicines Agency (EMA) as well as the relevant competent authorities of the Member States in which the clinical trial was conducted. These results have been submitted to the US ClinicalTrials.gov site (NCT03301467) and will be submitted to the EU Clinical Trials Register. In addition, the final Clinical Study Report for this study which will be submitted to EMA and relevant Member States upon finalization.

The MAH does not plan to submit the results of Study CL011_168 as a subject of a Variation to the Summary of Product Characteristics for TAVNEOS at this time.

As per the cover letter, the study enrolled 2 paediatric subjects, both of whom were randomized to receive placebo in the initial double-blind period followed by avacopan in the open-label treatment period.

2.2. Information on the pharmaceutical formulation used in the study

Not applicable; avacopan 30 mg BID was administered in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH is providing an abbreviated report of the results of Study CL011_168: A randomized, double blind, placebo-controlled Phase 2 Study to evaluate the safety and efficacy of avacopan (CCX168) in patients with C3 Glomerulopathy (ACCOLADE, EudraCT#: 2017-001821-42, NCT03301467), which includes a results summary and associated safety and efficacy data tables for the double-blind period.

2.3.2. Clinical study

A randomized, double blind, placebo-controlled Phase 2 Study to evaluate the safety and efficacy of avacopan (CCX168) in patients with C3 Glomerulopathy (ACCOLADE)

Description

The Phase 2 Study CL011_168 was conducted to evaluate the safety and efficacy of avacopan 30 mg BID as compared to placebo on renal disease activity in patients with C3 glomerulopathy (C3G).

Methods

Study participants

Patients with biopsy-proven C3 glomerulopathy.

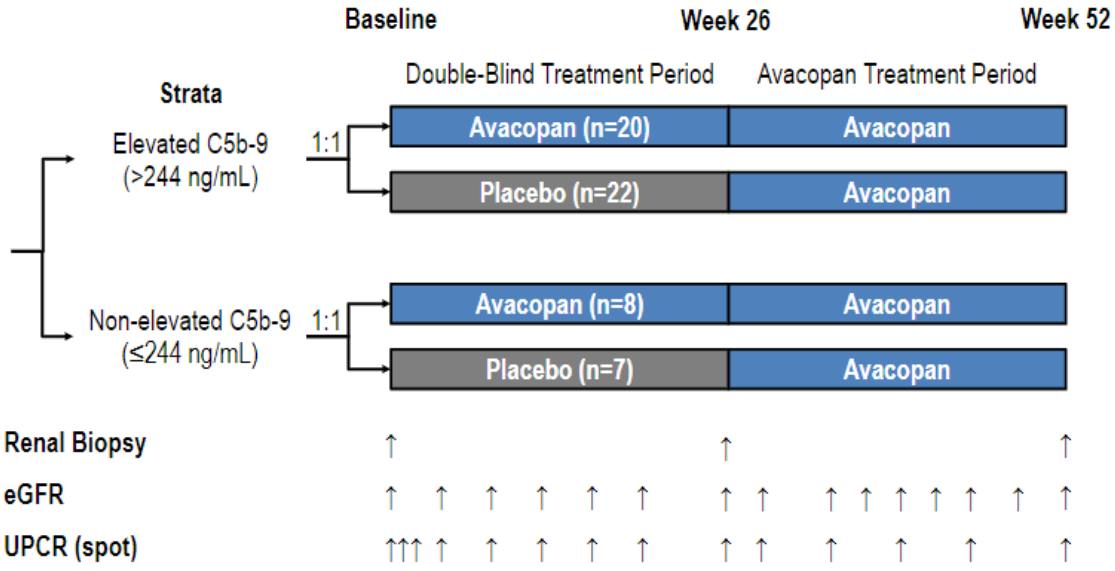
Treatments

The 52-week, randomied, double-blind, placebo-controlled, 2-period, Phase 2 study, included a 26-week, double-blind treatment period (Period 1), followed by a 26-week, open-label, active-treatment period (Period 2), and an 8-week off-treatment Period.

Study participants were stratified by baseline C5b-9 level (>244 ng/mL, ≤244 ng/mL) and randomized 1:1 to avacopan 30 mg BID or placebo for an initial 26-week double-blind treatment period (Period 1). At Week 26, study participants initially randomized to avacopan 30 mg BID remained on this regimen and participants initially randomized placebo were switched to avacopan 30 mg BID for a 26-week active treatment period through Week 52 (Period 2) (Figure 1).

Immunosuppressants, including mycophenolate mofetil (MMF) and calcineurin inhibitors, and renin-angiotensin-aldosterone inhibitors were allowed but not required as concomitant therapy. Eculizumab (and other anti-C5 antibodies) and plasma exchange/infusion were prohibited.

Figure 1: Study Schematic



Objective(s)

Please refer to above heading "Description".

Outcomes/endpoints

The primary efficacy endpoint was change in C3G histologic index of disease activity. Secondary endpoints included change in C3G histologic index of disease chronicity, change in spot UPCR, and change in eGFR.

Sample size

A total of 57 subjects were randomized of which only two were children.

Randomisation and blinding (masking)

The study was randomized and double-blind (see above). No details on the randomization or blinding procedures were provided in this submission.

Statistical Methods

No details on the statistical methods were provided in this submission.

Results

Participant flow

Please see below table on subject disposition.

Table 1: Subject Disposition Double Blind Treatment Period

	Placebo (N=29) n (%)	Avacopan 30 mg (N=28) n (%)
Completed Blinded Treatment Period on Study Drug	25 (86.2)	25 (89.3)
Withdrew from Study During Blinded	1 (3.4)	2 (7.1)
Primary Reason for Study Drug Withdrawal		
Adverse Event	1 (3.4)	0 (0.0)
Lost to Follow-up	0 (0.0)	0 (0.0)
Investigator Decision	0 (0.0)	1 (3. 6)
Sponsor Decision	0 (0.0)	0 (0.0)
Withdrawal by Parent/Guardian	0 (0.0)	0 (0.0)
Withdrawal by Subject	0 (0.0)	0 (0.0)
Related to COVID-19	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (3. 6)

Source: Table 14.1.1

Recruitment

First Subject Randomized: 07 December 2017. Last Subject Last Visit: 27 October 2021.

Baseline data

Please see below table on baseline data. **Two children aged 12-17 years were included; both of whom were randomized to receive placebo in the initial double-blind period.**

	Placebo n (%)	Avacopan 30 mg n (%)
Age (n)	29	28
12-17 years	2 (6.90)	0 (0.0)
18-50 years	20 (68.97)	23 (82.14)
51-65 years	4 (13.79)	4 (14.29)
>65 years	3 (10.34)	1 (3.57)
Gender (n)	29	28
Female	13 (44.83)	9 (32.14)
Male	16 (55.17)	19 (67.86)
C5b-9 Stratum (n)	29	28
>244 ng/mL	22 (75.86)	21 (75.00)
≤ 244 ng/mL	7 (24.14)	7 (25.00)

Source: Clinical trials.gov results posting

According to the Applicant, baseline demographics and disease characteristics were generally comparable between the placebo and avacopan 30 mg BID groups. In the avacopan 30 mg BID and placebo groups, baseline mean eGFR was 79 and 72 ml/min/1.73m2, geometric mean UPCR was 4.11 and 2.80 g/g, and percentage of study participants with UPCR > 1 g/g was 79% and 72%, respectively.

Number analysed

Please refer to table under heading "Participant flow".

Efficacy results

The primary efficacy endpoint (Histologic Activity Score) was not met, see below table.

The outcome of the key secondary objectives was also presented in tabulated form.

Table 2: Change from Baseline to Week 26 in the C3G Histologic Index for Disease Activity - Subjects With Elevated C5b-9

	Placebo n=21	**Avacopan 30 mg n=19**
Least Means Square (95% Confidence Interval)	-0.9 (-2.2 to 0.4)	-1.0 (-2.3 to 0.4)
p-value	0.9670	

Source: Clinical trials.gov results posting

As stated above only two children were included in the study; both of whom were randomized to receive placebo in the initial double-blind period.

Safety results

Please see below tables for overview of Treatment-Emergent Adverse Events (TEAE) and Serious TEAE.

Table 3: Overview of Treatment-Emergent Adverse Events (TEAE) in the Double-Blind Treatment Period

Category[a]	Placebo (N=29) n (%)	Avacopan 30 mg (N=28) n (%)
TEAEs	25 (86.2)	26 (92.9)
Subjects with at least one TEAE	24 (82.7)	25 (89.3)
TEAEs by maximum severity		
Mild	15 (51.7)	14 (50.0)
Moderate	10 (34.5)	8 (28.6)
Severe	0 (0.0)	3 (10.7)
Life-threatening	0 (0.0)	1 (3.6)
Death	0 (0.0)	0 (0.0)
TEAEs possibly related to study medication[b]	10 (41.4)	11 (35.7)
TEAEs possibly related to study medication by maximum severity		
Mild	5 (17.2)	6 (21.4)
Moderate	7 (24.1)	3 (10.7)
Severe	0 (0.0)	1 (3.6)
Life-threatening	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)
Treatment-emergent SAEs	3 (10.3)	3 (10.7)
TEAEs leading to discontinuation of study drug	1 (3.4)	1 (3.6)
TEAEs leading to death	0 (0.0)	0 (0.0)

Source: Table 14.3.1.1.1

[a] Participants may fall into more than 1 category

[b] 'Possibly related' refers to the Investigators' causality assessment

N=number of participants randomized to treatment group in the Safety Population in the specified group; n=number of participants in specified category; SAE=serious adverse event; TEAE=treatment emergent adverse event.

Note: An adverse event was considered treatment-emergent if the start date/time of the event was on or after the date/time of first dose of study medication

Table 4: Summary of Serious Treatment-Emergent Adverse Events for the Safety Population in the Double-Blind Treatment Period

Category	Placebo (N=29) n (%)	Avacopan 30 mg (N=28) n (%)
Any Serious TEAE	3 (10.3)	3 (10.7)
Gastroenteritis salmonella	0 (0.0)	1 (3.6)
Neutropenic sepsis	0 (0.0)	1 (3.6)
Pneumonia	1 (3.4)	1 (3.6)
Bacterial parotitis	1 (3.4)	0 (0.0)
Bronchitis	1 (3.4)	0 (0.0)
Neutrophil count decreased	0 (0.0)	1 (3.6)
Sjogren's syndrome	0 (0.0)	1 (3.6)
Acute kidney injury	0 (0.0)	1 (3.6)
Alcohol withdrawal syndrome	1 (3.4)	0 (0.0)

Source: Table 14.3.1.2.4

As stated above only two children were included in the study; both of whom were randomized to receive placebo in the initial double-blind period.

2.3.3. Discussion on clinical aspects

The MAH has submitted an abbreviated report of the results of Study CL011_168: a randomized, double blind, placebo-controlled Phase 2 Study to evaluate the safety and efficacy of avacopan (CCX168) in patients with C3 Glomerulopathy, which includes a results summary and associated safety and efficacy data tables for the **double-blind period**, in accordance with Article 46 of Regulation (EC) No1901/2006. The final Clinical Study Report for this study which will be submitted to EMA upon finalization.

The primary efficacy endpoint of the study was not met, and the MAH does not plan to submit the results of Study CL011_168 as a subject of a Variation to the Summary of Product Characteristics for TAVNEOS.

The study enrolled 2 paediatric subjects (aged 12-17 years). However, both these subjects were randomized to receive placebo in the initial double-blind period (followed by avacopan in the open-label treatment period). **Thus, the current submission (that only includes data from the double-blind period) does not include any data on paediatric subjects exposed to avacopa**n i.e., information that would be of relevance for the focus of the present procedure.

For the future submission that will include the Clinical Study Report (expected to provide data also from the open label treatment period), the Applicant is encouraged to provide a separate presentation of the data retrieved from paediatric subjects exposed to avacopan.

3. CHMP's overall conclusion and recommendation

The MAH has submitted an abbreviated report of the results of Study CL011_168 which only includes data tables for the double-blind period, in which no paediatric subjects were exposed to avacopan. Thus, **no new information of relevance for the focus of the present procedure has been provided**.

The final Clinical Study Report will be submitted to EMA upon finalization. In this submission, the Applicant is encouraged to provide a separate presentation of the data retrieved from the 2 paediatric subjects exposed to avacopan in the second part of the study.

☒ **Fulfilled:**

No regulatory action required