22 June 2023
EMA/CHMP/286099/2023
Human Medicines Division

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

TAVNEOS

avacopan

Procedure no: EMEA/H/C/005523/P46/006

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On 23 March 2023, the MAH submitted a completed study for Tavneos, 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 Randomized, Double-blind, Placebo-controlled Phase 2 Study to Evaluate the Safety and Efficacy of Avacopan (CCX168) in Patients with C3 Glomerulopathy (ACCOLADE)" is a stand alone study. The study enrolled 2 pediatric subjects, both of whom were randomized to receive placebo in the initial double-blind period followed by avacopan in the open-label treatment period. On 21 October 2022, the MAH submitted an abbreviated report of the results of Study CL011_168 which was reviewed under Art. 46 (procedure EMA/CHMP/930450/2022).

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.

2.2. Information on the pharmaceutical formulation used in the study

Avacopan is an orally administered, selective inhibitor of the complement 5a receptor (C5aR). Avacopan 10 mg capsules were administered in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- 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).

2.3.2. Clinical study

Clinical study number and title

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)

Description

A clinical trial to test the efficacy, safety, and tolerability of avacopan in subjects with C3 Glomerulopathy (C3G). Subjects with biopsy-proven C3G with or without a renal transplant, were stratified by elevated or normal levels of C5b-9 and then were randomized 1:1 to receive avacopan or placebo twice daily (BID) for 26 weeks in a double-blind manner followed by open-label avacopan for an additional 26 weeks.

Methods

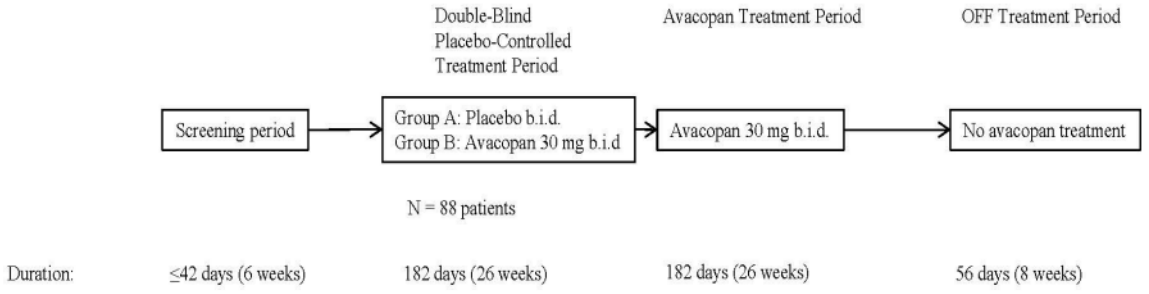
Study participants

Eligible subjects were men and women ≥ 18 years of age with biopsy-proven C3G, either Dense Deposit Disease (DDD) or C3 glomerulonephritis (C3GN), with or without a renal transplant. Adolescent subjects (12 to 17 years of age) were enrolled only in countries and at study centers for which respective approval by Regulatory Authorities and Institutional Review Board (IRB) or Independent Ethics Committee (IEC) was granted. Key exclusion criteria included, but were not limited to, women who were pregnant or nursing, tubulointerstitial fibrosis that appears to be more than 50%, use of eculizumab or another anti-C5 antibody within 26 weeks before dosing, and secondary C3 disease.

Treatments

The 52-week, randomized, 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 to placebo were switched to avacopan 30 mg BID for a 26-week active treatment period through Week 52 (Period 2). After the open-label treatment period, all subjects were followed for an additional 8 weeks (56 days) without study drug treatment. For adolescent subjects, the dose of avacopan or placebo on day 1 of the 26-week, double-blind, placebo-controlled treatment period was calculated based on body weight at screening. Dose could be adjusted based on avacopan plasma exposures (AUC0-6hr) on day 1. Starting on day 183 (open-label avacopan treatment period), adolescent subjects dose was reset based on their body weight determined on that day.

Figure 1: Study Schema



Objectives, Endpoints and Statistical methods

Table 1: Objectives, endpoints and statistical methods

Objectives	Endpoints	Statistical Methods
Primary		
• to evaluate the efficacy of avacopan compared to placebo based on histologic changes in kidney biopsies taken before and during treatment.	• percent change from baseline to week 26 in the C3G Histologic Index for disease activity.	• analysis of covariance (ANCOVA) with treatment group as factor and baseline C3G histologic Index for disease activity as a covariate were used to estimate least-squares (LS) mean and 95% CI. Missing data handled using Missing at Random (MAR) multiple imputation method.
Secondary		
• to evaluate the safety of avacopan compared to placebo based on the incidence of adverse events, changes in clinical laboratory measurements and changes in vital signs	• subject incidence of treatment-emergent serious adverse events, adverse events, and withdrawals due to adverse events.	• number of events and percentages of subjects (subject incidence) of adverse events by treatment group during each of the 3 study periods.
	• change from baseline and shifts from baseline in all safety laboratory parameters.	• subject incidence of abnormal laboratory values as assessed by the central lab were summarized by treatment group and grade (common terminology criteria for adverse events [CTCAE], Version 5). Shifts from baseline to highest CTCAE grade during each study period also provided.
	• change from baseline in vital signs.	• changes from baseline were summarized by a study visit and treatment group during each study period.
• to evaluate changes in laboratory parameters of renal disease including estimated glomerular filtration rate (eGFR), and proteinuria with avacopan compared to placebo	• percent change from baseline in urinary protein:creatinine ratio (UPCR) over the placebo-controlled 26-week treatment period	• using the elevated C5b-9 stratum of the ITT population, subjects whose UPCR was abnormal at baseline were analyzed using a mixed effects model for repeated measures (MMRM) analysis with treatment group, visit, treatment-by-visit interaction and baseline as a covariate. Point estimates and corresponding 95% CI were estimated for the difference between the avacopan and placebo groups across 26 weeks using a simple contrast from the model. Values were log transformed prior to entering MMRM analysis.

Objectives	Endpoints	Statistical Methods
	• change and percent change from baseline in eGFR over the placebo-controlled 26-week treatment period.	• same primary and secondary analyses as for UPCR, except values were not log transformed before entering MMRM analysis.
	• the change from baseline in the C3G Histologic Index for disease chronicity over the placebo-controlled 26-week treatment period	• analysis was carried out as described or C3G Histologic Index for disease activity.
	• the proportion of subjects who had a histologic response, defined as a decrease (improvement) in the C3G Histologic Index for diseased activity of at least 35% from baseline to week 26.	• descriptive statistics for the proportion of responders. Differences between the avacopan and placebo groups were analyzed using the Cochran Mantel Haenszel (CMH) chi-square test.
• to evaluate the pharmacokinetic profile of avacopan in patients with C3 glomerulopathy (C3G).	• serum concentrations of avacopan (and its metabolite CCX168-M1) at each scheduled assessment.	• avacopan (and its metabolite CCX168-M1) plasma concentration results for both C5b-9 level strata combined were used to calculate trough plasma concentrations (C_{min}) over the course of the clinical trial. When possible, the terminal elimination half-life was also calculated. C_{max}, time of maximal concentration (T_{max}), and $AUC_{0\text{-}6hr}$ were determined for subjects 12 to 17 years of age based on avacopan and metabolite plasma concentration data on day 1 and on day 183 (week 26).
Other Efficacy Endpoints		
• to evaluate changes in laboratory parameters of urinary excretion of monocyte chemoattractant protein-1 (MCP-1) with avacopan compared to placebo	• percent change from baseline in urinary MCP-1:creatinine ratio over the placebo-controlled 26-week treatment period	• same primary and secondary analyses as for UPCR.
• to evaluate health-related quality of life changes based on Short Form-36 version 2 (SF 36 v2) and EuroQOL 5D 5L (EQ 5D 5L) with avacopan compared to placebo	• change from baseline in EQ-5D-5L (visual analog scale and index) and Short Form-36 (SF-36) Version 2 (domains and component scores) over the placebo-controlled,	• Same primary and secondary analyses as described for eGFR; includes physical component score, mental component score, and 8 domains of the SF-36 v2, and the visual analog scale and index of the EQ-5D-5L.

Objectives	Endpoints	Statistical Methods
	26-week treatment period	
Exploratory		
• changes from baseline in markers of the alternative complement pathway involvement and other markers of inflammation assessed in plasma/serum or urine over the course of the treatment period	• change and percent change from baseline in plasma biomarkers such as inflammatory cytokine and chemokine levels	• plasma pharmacodynamic markers were analyzed using methods analogous to the efficacy parameters.
	• change and percent change from baseline in urine biomarkers such as urinary sCD163: creatinine ratio, inflammatory cytokine and chemokine levels	• urinary pharmacodynamic markers were analyzed using methods analogous to the efficacy parameters.
	• change from baseline in CBC count (especially WBCs, neutrophils, and lymphocytes) and lymphocyte subset counts including B cells, T cells, and natural killer cells	•
	• the relationship between PK parameters and renal function based on eGFR	•
	• the PK/PD relationship of avacopan treatment for both C5b-9 level strata separately as well as combined (change and/or percent change from baseline in the C3G Histologic Index, UPCR, eGFR, urinary MCP-1:creatinine ratio, and other biomarkers were to be used as PD markers).	• .

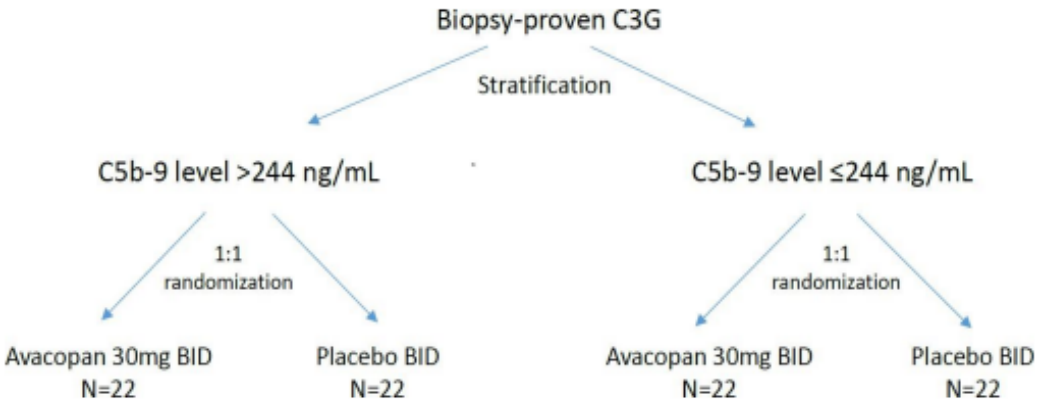
Sample size

Planned enrollment in the study was approximately 88 subjects total with 44 subjects in each arm of the study (ie, avacopan, placebo) and 22 subjects within each C5b-9 strata (ie, elevated and normal) of each arm. Two adolescent subjects (12-17 years of age) were randomized to placebo during the double-blind treatment period.

Randomisation and blinding (masking)

Randomization was performed centrally via an interactive response technology (IRT) system and minimization algorithm, using the stratification factors. In order to protect blinding, the randomization schedule was not accessible to study personnel who had contact with study centers or who were involved in data management and analysis.

Figure 2: Randomization



Avacopan and placebo capsules were identical in appearance as were the bottles containing investigational product. Blinding of the study was also achieved by limited access to the randomization code, unblinded avacopan plasma concentration results were not shared with the study site personnel or study staff who have direct contact with study sites during the study. Data that could potentially be unblinding were not made available unless required for safety monitoring. Investigators, however, were provided with safety laboratory data reports, flagging abnormally high and low values in order to make informed decisions regarding patient care. An individual subject's treatment assignment was only unblinded in order to provide appropriate treatment or management of the subject in the case of an adverse event. The study monitor and sponsor were to be notified as soon as possible in all events of unblinding before study completion.

Statistical Methods

Please refer to table under heading "Objectives, Endpoints and Statistical methods".

Results

Participant flow

A total of 57 subjects (28 avacopan, 29 placebo) were enrolled and randomized into the study. Twenty-six (92.9%) and 28 (96.6%) subjects, respectively, completed investigational product in the double-blind treatment period. At the time of the primary analysis, 4 subjects were still ongoing in the double-blind treatment period. These 4 subjects were excluded from the primary analyses of efficacy but were included in the final analysis tables. Three subjects (2 avacopan, 1 placebo) discontinued investigational product and the study during the double-blind period; reasons for investigational product withdrawal were sponsor decision and 'other' (1 avacopan subject each) and adverse event (1 placebo subject). The remaining 54 (94.7%) subjects (26 avacopan, 28 placebo) entered the avacopan treatment period. Forty-nine (86.0%) subjects completed the avacopan and follow-up treatment period; 47 (82.5%) subjects completed investigational product.

Table 2: Subject disposition (all randomized subjects)

	Placebo n (%)	Avacopan 30 mg n (%)
Randomized	29	28
Completed investigational product during double-blind period	28 (96.6)	26 (92.9)
Withdrew from study during double-blind period	1 (3.4)	2 (7.1)
Primary reason for investigational product withdrawal during double-blind period		
Adverse Event	1 (3.4)	0 (0.0)
Lost to Follow-up	0 (0.0)	0 (0.0)
Investigator Decision	0 (0.0)	0 (0.0)
Sponsor Decision	0 (0.0)	1 (3. 6)
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)
Withdrew from investigational product during avacopan period	3 (10.3)	4 (14.3)
Withdrew from study during avacopan period	1 (3.4)	4 (14.3)
Completed investigational product	25 (86.2)	22 (78.6)
Completed the study follow-up (week 60)	27 (93.1)	22 (78.6)

Both adolescent subjects completed investigational product in the double-blind and open-label avacopan treatment periods and completed the study.

Recruitment

07 December 2017 (first subject enrolled) – 27 October 2021 (last subject completed follow-up).

Baseline data

Table 3: Demographic Characteristics of the Intent-to-Treat Population

Demographic Variable/ Statistical Category	Placebo n (%) N = 29	Avacopan 30 mg n (%) N = 27	Total N = 56
Age at Screening (years)			
Mean	37.2	31.5	34.4
SD	17.5	14.8	16.4
Minimum	13	18	13
Median	31.0	25.0	28.0
Maximum	75	72	75
Age			
12 to 17 years	2 (6.9)	0 (0.0)	2 (3.6)
18 to 50 years	20 (69.0)	23 (85.2)	43 (76.8)
51 to 65 years	4 (13.8)	3 (11.1)	7 (12.5)
> 65 years	3 (10.3)	1 (3.7)	4 (7.1)
Sex			
Female	13 (44.8)	9 (33.3)	22 (39.3)
Male	16 (55.2)	18 (66.7)	34 (60.7)
Race			
White	25 (86.2)	23 (85.2)	48 (85.7)
Asian	3 (10.3)	2 (7.4)	5 (8.9)
Other	1 (3.4)	1 (3.7)	2 (3.6)
Black/African-American	0 (0.0)	1 (3.7)	1 (1.8)
Ethnicity			
Hispanic/Latino	4 (13.8)	2 (7.4)	6 (10.7)
Not Hispanic/ Latino	25 (86.2)	25 (92.6)	50 (89.3)

Table 4: Summary of Baseline and Subgroup Characteristics of the Baseline Elevated, Normal, and Combined C5b-9 Strata in the Intent-to-Treat Population

Baseline and Subgroup Characteristics/ Statistical Category	Elevated (> 244 ng/mL) C5b-9 at Baseline		Normal (≤ 244 ng/mL) C5b-9 at Baseline		Combined Strata (ITT Population)	
	Placebo n (%) N = 22	Avacopan 30 mg n (%) N = 20	Placebo n (%) N = 7	Avacopan 30 mg n (%) N = 7	Placebo n (%) N = 29	Avacopan 30 mg n (%) N = 27
C3GN or DDD, n (%)						
C3GN	20 (90.9)	19 (95.0)	5 (71.4)	4 (57.1)	25 (86.2)	23 (85.2)
DDD	2 (9.1)	0 (0.0)	2 (28.6)	3 (42.9)	4 (13.8)	3 (11.1)
Missing	0 (0.0)	1 (5.0)	N/A	N/A	0 (0.0)	1 (3.7)
History of Kidney Transplant, n (%)						
Yes	1 (4.5)	1 (5.0)	1 (14.3)	0 (0.0)	2 (6.9)	1 (3.7)
No	21 (95.5)	18 (90.0)	6 (85.7)	7 (100.0)	27 (93.1)	25 (92.6)
Missing	0 (0.0)	1 (5.0)	N/A	N/A	0 (0.0)	1 (3.7)
Duration of C3G (months)						
Mean	50.1	49.6	36.0	50.9	46.7	49.9
SD	44.3	50.0	43.6	37.1	43.8	46.3
Stratification Category – EDC, n (%)						
C3GN and Hx of Kidney Transplant	1 (4.5)	1 (5.0)	1 (14.3)	0 (0.0)	2 (6.8)	1 (3.7)
C3GN and No Hx of Kidney Transplant	19 (86.4)	18 (90.0)	4 (57.1)	4 (57.1)	23 (79.3)	22 (81.5)
DDD and Hx of Kidney Transplant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DDD and No Hx of Kidney Transplant	2 (9.1)	0 (0.0)	2 (28.6)	3 (42.9)	4 (13.8)	3 (11.1)
eGFR (ml/min/1.73 m^2)						
Mean	84.5	76.6	34.1	83.6	72.3	78.4
SD	42.5	42.8	15.9	34.0	43.5	40.2

Baseline and Subgroup Characteristics/ Statistical Category	Elevated (> 244 ng/mL) C5b-9 at Baseline		Normal (≤ 244 ng/mL) C5b-9 at Baseline		Combined Strata (ITT Population)	
	Placebo N = 22	Avacopan 30 mg N = 20	Placebo N = 7	Avacopan 30 mg N = 7	Placebo N = 29	Avacopan 30 mg N = 27
UPCR (g/g)						
Mean	3.2	4.7	1.5	2.3	2.8	4.0
SD	2.6	3.6	0.9	1.9	2.4	3.4
> 1 g/g, n %	16 (72.7)	17 (85.0)	5 (71.4)	4 (57.1)	21 (72.4)	21 (77.8)
≤ 1 g/g, n %	6 (27.3)	3 (15.0)	2 (28.6)	3 (42.9)	8 (27.6)	6 (22.2)
Urinary MCP-1: Creatinine Ratio (pg/mg creat)						
Mean	751.0	1429.6	748.2	727.4	750.3	1240.6
SD	519.4	1470.2	438.7	620.4	492.5	1322.7
BMI						
Mean	24.1	24.9	26.4	29.7	24.7	26.2
SD	3.6	5.4	2.3	8.2	3.4	6.4
EQ-5D-5L Index Score						
Mean	0.88	0.90	0.89	0.80	0.88	0.87
SD	0.15	0.10	0.13	0.16	0.15	0.12
EQ-5D-5L VAS Score						
Mean	82.1	76.6	80.0	66.4	81.6	73.9
SD	15.9	18.6	16.1	21.0	15.7	19.4

Number analysed

Please refer to table under heading "Participant flow".

Efficacy results

In the AR for the interim data (EMEA/H/C/005523/P46/003), the applicant was encouraged to provide a separate presentation of the data retrieved from paediatric subjects exposed to avacopan. Both adolescent subjects completed study treatment (placebo) in the double-blind and open-label avacopan treatment periods and completed the study. Demographic and baseline characteristics,

pharmacokinetics, efficacy, and safety data for adolescent subjects enrolled in the study, where available, are described within each section.

Primary efficacy endpoint

The primary efficacy endpoint of change from baseline to week 26 in the C3G histologic index for disease activity was not met.

Table 5: Change from Baseline to Week 26 in the C3G Histologic Index for Disease Activity – Subjects with Elevated C5b-9 in the Intent-to-Treat Population (Primary Analysis)

	Placebo N = 21	Avacopan 30 mg N = 19
Change from Baseline		
LS Mean (95% CI)	-0.9 (-2.2, 0.4)	-1.0 (-2.3, 0.4)
LS Mean Trt Difference (95% CI)	-0.0 (-1.9, 1.8)	
p-value	0.9670	

One adolescent subject showed improvement (ie, decrease of 3.0) in the C3G Histological Index of disease activity from baseline to week 26; there was no change from baseline to week 26 for the second adolescent subject.

Secondary efficacy endpoints

Because the primary study endpoint was not met, the results from analyses of the secondary efficacy endpoints should be considered exploratory according to the MAH.

Table 6: Percent Change from Baseline to Week 26 in UPCR In Subjects with Abnormal UPCR at Baseline - Subjects with Elevated C5b-9 in the ITT Population (Primary Analysis)

	Placebo N = 20	Avacopan 30 mg N = 18
LS Mean (95% CI)	-14 (-34 to 12)	-16 (-36 to 12)
p-value	0.9284	

Among the 2 adolescent subjects, 1 had large decreases (ie, improvement) in percent change in UPCR from both baseline to week 26 (-78.3%) and baseline to week 52 (-86.0%) while the second adolescent subject had large increases at both time points (66% and 90%, respectively).

Table 7: Percent Change and Change from Baseline to Week 26 in eGFR - Subjects with Elevated C5b-9 in the Intent-to-Treat Population (Primary Analysis)

	Placebo N = 21	Avacopan 30 mg N = 19
Percent Change from Baseline		
LS Mean (95% CI)	-4.7 (-12.3, 2.8)	6.1 (-1.9, 14.1)
LS Mean Trt Difference (95% CI)	10.8 (-0.2, 21.9)	
p-value	0.0534	
Change from Baseline		
LS Mean (95% CI)	-3.6 (- 8.4, 1.3)	0.4 (-4.7, 5.6)
LS Mean Trt Difference (95% CI)	4.0 (-3.1, 11.1)	
p-value	0.2638	

Both adolescent subjects entered the study with normal eGFR values (142 and 105 mL/min/1.73m^2, respectively) and values remained in the normal range for both subjects at week 26 (152 and 118 mL/min/1.73m^2, respectively) following 26 weeks of placebo and at week 52 (167 and 89 mL/min/1.73m^2 , respectively) following 26 weeks of avacopan.

Table 8: Change from Baseline to Week 26 in the C3G Histologic Index for Disease Chronicity - Subjects with Elevated C5b-9 in the Intent-to-Treat Population (Primary Analysis)

	Placebo N = 21	Avacopan 30 mg N = 19
Change from Baseline		
LS Mean (95% CI)	1.5 (0.9, 2.2)	1.1 (0.3, 1.8)
LS Mean Trt Difference (95% CI)	-0.5 (-1.5, 0.5)	
p-value	0.3368	

Change from baseline to week 26 in the C3G Histological Index of Disease Chronicity was 4.0 and 3.0, respectively for the 2 adolescent subjects.

Table 9: Proportion of Subjects Who Have a Histologic Response in the Biopsy-based C3G Histologic Index of Activity of at Least 35% from Baseline to 26 Weeks – Elevated C5b-9 and combined C5b-9 Strata of the Intent-to-Treat Population

	Placebo	Avacopan 30 mg
Elevated C5b-9 Stratum (Primary Analysis)		
N	20	18
Responder n (%)	4 (20.0)	2 (11.1)
Non-Responder (n (%)	16 (80.0)	16 (88.9)
p-value	0.4591	
Combined C5b-9 Stratum (Final Analysis)		
N	27	26
Responder n (%)	7 (25.9)	4 (15.4)
Non-Responder (n (%)	20 (74.1)	22 (84.6)
p-value	0.3488	

A histological response was not observed in the 2 adolescent subjects enrolled in study.

Safety results

Table 10: Overview of Subject Incidence of Treatment-emergent Adverse Events in the Double-Blind Period (Safety Population)

Category	Placebo (N = 29) n (%)	Avacopan 30 mg (N = 28) n (%)
At least 1 treatment-emergent adverse event	25 (86.2)	26 (92.9)
Treatment-emergent adverse events 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)
Treatment-emergent adverse events possibly related to investigational product	12 (41.4)	10 (35.7)
Treatment-emergent adverse events possibly related to investigational product 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 serious adverse events	3 (10.3)	3 (10.7)
Treatment-emergent adverse events leading to discontinuation of investigational product	1 (3.4)	1 (3.6)
Treatment-emergent adverse events leading to death	0 (0.0)	0 (0.0)

Table 11: Overview of Subject Incidence of Treatment-emergent Adverse Events in the Avacopan Treatment Period by Randomized Treatment Group (Safety Population)

Category	Prior Placebo (N = 28) n (%)	Avacopan 30 mg (N = 25) n (%)
Treatment-emergent adverse events	23 (82.1)	21 (84.0)
Treatment-emergent adverse events by maximum severity		
Mild	10 (35.7)	9 (36.0)
Moderate	10 (35.7)	9 (36.0)
Severe	3 (10.7)	2 (8.0)
Life-threatening	0 (0.0)	1 (4.0)
Death	0 (0.0)	0 (0.0)
Treatment-emergent adverse events possibly related to investigational product	10 (35.7)	8 (32.0)
Treatment-emergent adverse events possibly related to investigational product by maximum severity		
Mild	8 (28.6)	3 (12.0)
Moderate	1 (3.6)	3 (12.0)
Severe	1 (3.6)	1 (4.0)
Life-threatening	0 (0.0)	1 (4.0)
Death	0 (0.0)	0 (0.0)
Treatment-emergent Serious adverse events	3 (10.7)	5 (20.0)
Treatment-emergent adverse events leading to discontinuation of investigational product	1 (3.6)	1 (4.0)
Treatment-emergent adverse events leading to death	0 (0.0)	0 (0.0)

Table 12: Summary of subject incidence of treatment-emergent adverse events occuring in > 10% subjects in the avacopan or placebo groups during the double blind treatment period

Preferred Term	Placebo (N = 29) n (%)	Avacopan 30 mg (N = 28) n (%)
Any treatment-emergent adverse event	25 (86.2)	26 (92.9)
Oedema peripheral	1 (3.4)	5 (17.9)
Headache	2 (6.9)	5 (17.9)
Vomiting	2 (6.9)	4 (14.3)
Diarrhoea	4 (13.8)	3 (10.7)
Fatigue	0 (0.0)	3 (10.7)
Blood creatine phosphokinase increased	1 (3.4)	3 (10.7)
Blood creatinine increased	0 (0.0)	3 (10.7)
Weight decreased	0 (0.0)	3 (10.7)
Anaemia	3 (10.3)	3 (10.7)
Lymphopenia	0 (0.0)	3 (10.7)
Decreased appetite	0 (0.0)	3 (10.7)
Hypertension	3 (10.3)	3 (10.7)
Upper respiratory tract infection	3 (10.3)	2 (7.1)
Abdominal pain	3 (10.3)	2 (7.1)
Nasopharyngitis	3 (10.3)	1 (3.6)
Nausea	3 (10.3)	1 (3.6)
Back pain	3 (10.3)	1 (3.6)
Muscle spasms	3 (10.3)	0 (0.0)

Table 13: Summary of subject incidence of treatment-emergent adverse events occuring in > 10% subjects in the avacopan or prior placebo groups during the avacopan treatment period (safety population)

Preferred Term	Prior Placebo (N = 29) n (%)	Avacopan 30 mg (N = 28) n (%)
Any treatment-emergent adverse event	23 (82.1)	21 (84.0)
Nasopharyngitis	3 (10.7)	4 (16.0)
Acute kidney injury	2 (7.1)	3 (12.0)
Proteinuria	0 (0.0)	3 (12.0)
Arthralgia	0 (0.0)	3 (12.0)
Diarrhoea	4 (14.3)	1 (4.0)
Nausea	4 (14.3)	1 (4.0)

Summary of Treatment-Emergent Adverse Events in Adolescent Subjects

The types and severity of adverse events reported by the 2 adolescent subjects were similar to those observed in the entire safety population.

One adolescent subject experienced nonserious, grade 1 adverse events of nausea, nasopharyngitis, and increased weight; none of these events were considered related to investigational product by the investigator. The second adolescent subject experienced nonserious, grade 1 adverse events of pyrexia (3 events), hyperkalaemia, cough, abdominal pain, mouth ulceration, and asthenia. This subject also experienced serious adverse events of bronchitis (grade 1) from day 141 to day 145 and pneumonia (grade 2) from day 175 to day 184. The nonserious events of pyrexia and cough, and the serious adverse events of pneumonia and bronchitis in this subject were considered possibly related to investigational product by the investigator. All adverse events in both adolescent subjects, except for the nonserious event of increased weight which was reported as ongoing, resolved; both subjects completed investigational product and the study.

For chemistry parameters, 1 adolescent subject had transient grade 1 elevations in ALT (week 48) and creatine kinase (week 57) that returned to normal by the next visit; AST and ALP values in the subject remained normal throughout the study. The second adolescent subject had grade 1 increases in ALP and bilirubin at baseline; ALP values remained elevated throughout the study while bilirubin values were normal at all postbaseline time points. AST and ALT in the subject were normal throughout the study. This subject also reported grade 1, grade 2, and grade 3 elevations in potassium at several time points throughout the study; 1 of the grade 3 elevations corresponded temporally with an adverse event of hyperkalaemia in the subject. Transient grade 1 elevations in creatine kinase at weeks 32, 54 and 57 were also noted in this subject.

For haematology parameters, 1 adolescent subject had transient grade 1 decreases in haemoglobin reported intermittently at 7 study visits; in each case, values returned to normal within 1 to 3 study visits. The second adolescent subject had grade 1 and grade 2 decreases in haemoglobin at every study time point (including baseline) and a transient grade 1 decreases in leukocytes at a single time point (week 28).

For urinalysis, 1 adolescent subject had grade 3 positive protein results at screening that remained elevated and fluctuated between grades 1 and 4 at every study visit. The 2nd adolescent subject had grade 2 positive protein urine results at baseline that remained elevated and fluctuated between grade 2 and grade 3 at every study visit. Urine chemistry results for both adolescent subjects also returned grade 1 to grade 3 elevations in protein at each study visit, including baseline. No notable changes from baseline in vital signs, weight, and Body Mass Index (BMI) were observed during the study in the overall safety population. One adolescent subject had gradual increases in weight and BMI of 12.5 kg (77.5 kg at baseline to 90.0 kg at week 60) and 3.530 kg/m2 (26.2 kg/m2 at baseline to 29.7 kg/m2 at week 60), respectively, over the course of the study (week 60) accompanied by a 2 cm increase in height over the same time period. The weight gain for this subject was reported as an adverse event. The other adolescent subject also had gradual increases in height (8 cm) and weight (4.3 kg) over the same time period, but a slight decrease in BMI (-0.183 kg/m2). ECG results for both adolescent subjects enrolled in the study were normal or considered nonsignificant by the investigator.

2.3.3. Discussion on clinical aspects

In accordance with article 46 of regulation (EC) No 1901/2006 for paediatric studies, the MAH submitted the final study report of "A Randomized, Double-blind, Placebo-controlled Phase 2 Study to Evaluate the Safety and Efficacy of Avacopan (CCX168) in Patients with C3 Glomerulopathy (ACCOLADE)" which is not part of any Paediatric Investigation Plan. The primary efficacy endpoint of the study was not met and the MAH does not plan to submit the results as a subject of a Variation to the Summary of Product Characteristics for Tavneos. This is agreed.

Only two adolescent subjects (12-17 years of age) participated in the study, both of whom were randomized to receive placebo in the initial double-blind period. The types and severity of adverse

events reported by the 2 adolescent subjects were similar to those observed in the entire safety population. The study does not significantly contribute to the safety and efficacy data of Tavneos considering only two adolescent patients participated in the study.

3. Rapporteur's overall conclusion and recommendation

Subjects with biopsy- proven C3G with or without a renal transplant, were stratified by elevated or normal levels of C5b-9 and then randomized 1:1 to receive avacopan or placebo twice daily (BID) for 26 weeks in a double-blind manner followed by open-label avacopan for an additional 26 weeks. Only two adolescent subjects (12-17 years of age) participated in the study, both of whom were randomized to receive placebo in the initial double-blind period. The types and severity of adverse events reported by the 2 adolescent subjects were similar to those observed in the entire safety population.

The study does not significantly contribute to the safety and efficacy data of Tavneos considering only two adolescent patients participated in the study.

The CHMP consider the application approvable. No regulatory actions are warranted.

The benefit risk ratio for the approved indication remains unchanged.

☒ **Fulfilled:**

No regulatory action required