Summary Report of Benefit-Risk Assessment

TAVNEOS HARD CAPSULE 10MG

NEW DRUG APPLICATION

Active Ingredient(s)	Avacopan
Product Registrant	Amgen Biotechnology Singapore Pte Ltd
Product Registration Number	SIN17150P
Application Route	Abridged evaluation
Date of Approval	24 December 2024

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A INTRODUCTION

Tavneos is indicated as an adjunctive treatment of adult patients with severe, active anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] or microscopic polyangiitis [MPA]) in combination with standard therapy, including glucocorticoids.

The active substance, avacopan, is a selective antagonist of the complement 5a receptor (C5aR1) that selectively inhibits the binding of complement 5a (C5a) to the C5aR. The specific and selective blockade of C5aR1 by avacopan reduces the pro-inflammatory effects of C5a, which include neutrophil activation, migration and adherence to sites of small blood vessel inflammation, vascular endothelial cell retraction, and increased permeability.

Tavneos is available as hard capsules containing 10 mg of avacopan. Other ingredients in the capsule are macrogolglycerol hydroxystearate and macrogol 4000. Ingredients in the hard capsule shell and sealing band are gelatin, red iron oxide, yellow iron oxide, titanium dioxide and polysorbate 80. Ingredients in the imprinting ink are black iron oxide, shellac and potassium hydroxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, avacopan, is manufactured at Hovione LLC, East Windsor, USA. The drug product, Tavneos Hard Capsule, is manufactured at Patheon Pharmaceuticals Inc., Cincinnati, USA.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at 15ºC – 30ºC with a re-test period of 36 months. The packaging is double low-density polyethylene (LDPE) bags, sealed with a cable tie closure and stored in high-density polyethylene (HDPE) drums.

Drug product:

The manufacturing process involves melting of the excipients and subsequent mixing with the drug substance, which is fully dissolved before filling into hard gelatin capsules. The drug

product solution will solidify upon cooling and the filled capsules are sealed with a gelatin band, followed by drying and packaging.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A guideline and impurity limits were adequately qualified. The analytical methods used were described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30ºC. The container closure system is a high-density polyethylene (HDPE) bottle containing 30 or 180 capsules.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of avacopan as an adjunctive treatment of adult patients with severe, active ANCA-associated vasculitis (GPA or MPA) in combination with standard therapy was based on data from one pivotal Phase III study CL010_168.

Study CL010_168 was a Phase III, randomised, double-blind, double-dummy, active-controlled, multicentre study to assess the efficacy, safety, and tolerability of avacopan in patients with ANCA-associated vasculitis (AAV) when administered in combination with rituximab or with cyclophosphamide followed by azathioprine/mycophenolate. The main inclusion criteria were newly-diagnosed or relapsed AAV where treatment with cyclophosphamide or rituximab was needed, clinical diagnosis of GPA or MPA according to the Chapel-Hill Consensus Conference definitions, positive antibodies to either proteinase 3 (PR3) or myeloperoxidase (MPO), and at least one major item or three minor items or at least the two renal items of proteinuria and haematuria in the Birmingham Vasculitis Activity Score (BVAS).

Patients were randomised in a 1:1 ratio to receive avacopan 30 mg twice daily orally for 52 weeks plus prednisone-matching placebo or a tapering regimen of oral prednisone over 20 weeks according to the protocol-specified schedule plus avacopan-matching placebo. Randomisation was stratified based on concomitant therapy (intravenous [IV] cyclophosphamide, oral cyclophosphamide, or IV rituximab), ANCA status (anti-PR3 or anti-MPO positive), and disease status (newly diagnosed or relapsed disease).

Patients in both groups received one of the following three immunosuppressive regimens, based on the investigator's discretion:

- IV rituximab 375 mg/m^2 per week for 4 weeks.
- IV cyclophosphamide for 13 weeks (15 mg/kg up to 1.2 g on Day 1 and at Weeks 2, 4, 7, 10, and 13), and from Week 15 onwards, oral azathioprine at 1 mg/kg/day, with titration up to a target dose of 2 mg/kg/day at 2 weeks. If azathioprine was not tolerated, mycophenolate mofetil at a target dose of 2 g/day could be given. If mycophenolate mofetil was not tolerated or not available, enteric coated mycophenolate sodium could be given at a target dose of 1440 mg/day.

- Oral cyclophosphamide for 14 weeks (2 mg/kg/day up to 200 mg/day) followed by oral azathioprine or mycophenolate mofetil/sodium starting at Week 15 (same dosing regimen as above).

The study allowed non-study supplied glucocorticoid use, i.e., glucocorticoids not supplied as study drug but allowed for AAV, for patients who experienced a relapse or worsening of disease, pre-treatment for medications (e.g., rituximab), adrenal insufficiency, and other conditions at the discretion of the investigator.

The two primary efficacy endpoints were the proportion of patients achieving disease remission at Week 26 and the proportion of patients achieving sustained disease remission at Week 52. Disease remission was defined as a BVAS of 0 as determined by the Adjudication Committee (AC), no administration of glucocorticoids for AAV within 4 weeks prior to Week 26, and no BVAS >0 during the 4 weeks prior to Week 26 (if collected for an unscheduled assessment). Sustained disease remission was defined as disease remission at Week 26 and at Week 52 (defined as a BVAS of 0 and no administration of glucocorticoids for AAV within 4 weeks prior to Week 52), as well as no disease relapse between Week 26 and Week 52 as determined by the AC.

The secondary efficacy endpoints were glucocorticoid-induced toxicity as measured by change from baseline over the first 26 weeks in the Glucocorticoid Toxicity Index (GTI), BVAS of 0 at Week 4, change from baseline over 52 weeks in health-related quality of life as measured by the domains and component scores of the Short Form-36 version 2 (SF-36v2) and EuroQuality of Life-5 Domains-5 Levels (EQ-5D-5L) Visual Analogue Scale (VAS) and Index, proportion of patients and time to experiencing a relapse, as well as change from baseline over 52 weeks in estimated glomerular filtration rate (eGFR), urinary albumin:creatinine ratio (UACR), urinary monocyte chemoattractant protein-1 (MCP-1):creatinine ratio, and Vasculitis Damage Index (VDI).

The avacopan group was evaluated for non-inferiority and superiority compared with the prednisone group, for both primary endpoints. Statistical significance was claimed based on the one-sided Type 1 error of 0.025. The two primary endpoints were tested sequentially using a gatekeeping procedure to preserve the overall Type 1 error rate at the 5% level, according to the following sequence: non-inferiority at Week 26, non-inferiority at Week 52, superiority at Week 52, and superiority at Week 26. The secondary endpoints were not controlled for multiplicity. Non-inferiority of avacopan to the prednisone group was tested using a margin of -0.20. This margin was derived from a meta-analysis of 20 published studies and the RAVE study, which investigated rituximab versus cyclophosphamide for AAV. The lower bound of the 95% CI for remission rates across these studies was approximately 0.60. With glucocorticoids estimated to contribute 50% of the effect, and after applying a one-third discount, the non-inferiority margin was set at -0.20. While the non-inferiority margin was considered wide, the overall assessment of efficacy was based on the totality of data and not solely on the non-inferiority test.

A total of 331 patients were randomised – 166 in the avacopan group and 165 in the prednisone group. One patient in the prednisone arm did not receive any study medication, therefore the intent-to-treat (ITT) population comprised 166 patients in the avacopan group and 164 patients in the prednisone group.

The patient demographics and baseline disease characteristics were generally balanced between the treatment groups. The mean age was 60.9 years, and most patients (67.6%) were

between 51 and 75 years. Most patients (84.2%) were White and 9.7% were Asian. There were slightly more males in the avacopan (59.0%) compared to the prednisone group (53.7%). More patients had newly diagnosed disease (69.4%) (compared to 30.6% with relapsed disease), a diagnosis of GPA (54.8%) (compared to 45.2% with MPA), and MPO positivity (57.0%) (compared to 43.0% with PR3 positivity). Most patients received concomitant treatment with rituximab (64.8%), with the balance predominantly receiving concomitant treatment with IV cyclophosphamide (30.9%) and only a small number receiving oral cyclophosphamide (4.2%). The proportion of patients with prior glucocorticoid use was higher in the prednisone group compared with avacopan (82.3% vs 75.3%). Nonetheless, baseline disease severity measures including BVAS, VDI, and eGFR were comparable between treatment groups, which did not suggest imbalances in disease severity.

The mean total cumulative prednisone-equivalent dose (i.e., the protocol-specified, 20-week prednisone taper in the prednisone group, as well as the non-study supplied glucocorticoids in both groups) over 52 weeks was 1348.9 mg per patient or 3.9 mg/patient-day in the avacopan group compared to 3654.5 mg per patient or 10.5 mg/patient-day in the prednisone group. The difference between the groups was more apparent in the first half of the study (6.1 mg/patient-day in the avacopan group vs 17.9 mg/patient-day in the prednisone group) compared to the second half of the study (1.6 mg/patient-day in the avacopan group vs 2.7 mg/patient-day in the prednisone group) due to the protocol-specified prednisone tapering regimen in the prednisone group. In view that the glucocorticoid use in the prednisone group was specified in the study design between Week 0 and 20, it was difficult to attribute the differences in glucocorticoid use to avacopan's control of disease activity. Nevertheless, the analyses of the reasons for use of non-study supplied glucocorticoids showed a numerical difference between the groups in the treatment of relapse, with more patients in the prednisone group than in the avacopan group requiring non-study supplied glucocorticoids for relapse, both in the first half (17.7% vs 6.6%, respectively) and second half of the study (15.2% vs 4.8%, respectively). Similar trends were observed in both rituximab and cyclophosphamide strata.

Summary of efficacy results

	Avacopan (N=166)	**Prednisone (N=164)**
Primary endpoints		
Remission at Week 26, n (%)	120 (72.3)	115 (70.1)
Estimate of treatment difference in % (95% CI)	3.4 (-6.0, 12.8)	
p-value[a]	<0.0001 (non-inferiority) 0.2387 (superiority)	
Sustained remission at Week 52, n (%)	109 (65.7)	90 (54.9%)
Estimate of treatment difference in % (95% CI)	12.5 (2.6, 22.3)	
p-value[a]	<0.0001 (non-inferiority) 0.0066 (superiority)	
Secondary endpoints[c]		
GTI Cumulative Worsening Score		
Week 13 (LSM ± standard error of the mean [SEM])	25.7 ± 3.40 (n=160)	36.6 ± 3.41 (n=161)
p-value[b]	0.014	
Week 26 (LSM ± SEM)	39.7 ± 3.43 (n=154)	56.6 ± 3.45 (n=153)
p-value[b]	0.0002	
GTI Aggregate Improvement Score		
Week 13 (LSM ± SEM)	9.9 ± 3.45 (n=160)	23.2 ± 3.46 (n=161)
p-value[b]	0.003	
Week 26 (LSM ± SEM)	11.2 ± 3.48	23.4 ± 3.50

	(n=154)	(n=153)
p-value[b]	0.008	
BVAS of 0 at Week 4, n (%)	104 (62.7)	113 (68.9)
Estimate of treatment difference in % (95% CI)	-5.6 (-15.4, 4.2)	
p-value[a]	0.87	
SF-36v2 Physical Component Score		
Change from baseline to Week 26 (LSM ± SEM)	4.45 ± 0.73 (n=153)	1.34 ± 0.74 (n=147)
p-value[b]	0.002	
Change from baseline to Week 52 (LSM ± SEM)	4.98 ± 0.74 (n=147)	2.63 ± 0.75 (n=144)
p-value[b]	0.018	
SF-36v2 Mental Component Score		
Change from baseline to Week 26 (LSM ± SEM)	4.85 ± 0.83 (n=154)	3.27 ± 0.84 (n=147)
p-value[b]	0.16	
Change from baseline to Week 52 (LSM ± SEM)	6.39 ± 0.84 (n=148)	4.69 ± 0.85 (n=144)
p-value[b]	0.13	
EQ-5D-5L VAS		
Change from baseline to Week 26 (LSM ± SEM)	9.1 ± 1.38 (n=153)	5.5 ± 1.39 (n=150)
p-value[b]	0.053	
Change from baseline to Week 52 (LSM ± SEM)	13.0 ± 1.39 (n=149)	7.1 ± 1.41 (n=146)
p-value[b]	0.002	
EQ-5D-5L Index		
Change from baseline to Week 26 (LSM ± SEM)	0.0229 ± 0.0144 (n=152)	-0.0010 ± 0.0146 (n=146)
p-value[b]	0.217	
Change from baseline to Week 52 (LSM ± SEM)	0.0474 ± 0.0145 (n=149)	-0.0038 ± 0.0147 (n=145)
p-value[b]	0.009	
Relapses		
Relapses after achieving remission at Week 26, n (%)	9/120 (7.5)	14/115 (12.2)
p-value[b]	0.081	
Relapses after achieving BVAS=0 at any time, n (%)	16/158 (10.1)	33/157 (21.0)
p-value[b]	0.009	
eGFR (ml/min/1.73 m^2) in subjects with renal disease at baseline based on BVAS		
Baseline (mean ± SEM)	44.6 ± 2.42 (n=131)	45.6 ± 2.36 (n=134)
Change from baseline to Week 52 (LSM ± SEM)	7.3 ± 1.05 (n=119)	4.1 ± 1.03 (n=125)
p-value[b]	0.029	
UACR in subjects with renal disease (based on BVAS) and UACR of at least 10 mg/g creatinine at baseline		
Baseline (geometric mean, range), mg/g	432.9 (20-6461) (n=125)	312.2 (11-5367) (n=128)
Percent change from baseline to Week 52 (LSM ± SEM)	-74 ± 9.8 (n=109)	-77 ± 9.6 (n=114)
p-value[b]	0.40	
Urinary MCP-1:creatinine ratio in subjects with renal disease (based on BVAS) at baseline		
Baseline (geometric mean, range), pg/mg	983.8 (138-6145) (n=127)	947.8 (160-6525) (n=130)
Percent change from baseline to Week 52 (LSM ± SEM)	-73 ± 6.0 (n=106)	-71 ± 5.9 (n=108)
p-value[b]	0.22	
VDI		

Baseline (mean ± SEM)	0.66 ± 0.120 (n=165)	0.72 ± 0.109 (n=163)
Change from baseline to Week 52 (LSM ± SEM)	1.17 ± 0.091 (n=150)	1.15 ± 0.093 (n=151)
p-value[b]	0.87	

[a] One-sided p-value
[b] Two-sided p-value
[c] The secondary endpoints were not controlled for multiplicity

For the primary endpoints, the avacopan group was non-inferior to the prednisone group in achieving disease remission at Week 26 and superior to the prednisone group in achieving sustained remission at Week 52. At Week 26, 72.3% of patients in the avacopan group achieved remission compared to 70.1% of patients in the prednisone group (difference: 3.4%, 95% confidence interval [CI]: -6.0, 12.8; p<0.0001 for non-inferiority; p=0.2387 for superiority). The non-inferiority comparison was statistically significant, but superiority was not demonstrated. At Week 52, 65.7% of patients in the avacopan group achieved sustained remission compared to 54.9% of patients in the prednisone group (difference: 12.5%, 95% CI: 2.6, 22.3; p<0.0001 for non-inferiority; p=0.0066 for superiority). Both non-inferiority and superiority were demonstrated.

The results of the subgroup analyses were generally consistent with the findings of the primary analysis for remission at Week 26 across the analysed subgroups, including concomitant rituximab or cyclophosphamide, PR3 or MPO ANCA positivity, newly diagnosed or relapsing AAV, and GPA or MPA. For sustained remission at Week 52, the results in all subgroups were numerically in favour of avacopan. The efficacy of avacopan was more apparent in patients in the rituximab stratum, i.e., those who received rituximab induction therapy in the first 4 weeks and did not receive any maintenance therapies (71.0% in avacopan group vs 56.1% in prednisone group). For patients in the cyclophosphamide stratum who received maintenance therapies with azathioprine or mycophenolate mofetil/sodium, the difference in efficacy between the avacopan and prednisone groups was less apparent (55.9% vs 52.6%). Considering that the cyclophosphamide stratum was the smaller subset with wide 95% CI, and that the choice of induction therapy was based on investigators' discretion and not a randomisation variable, no firm conclusion could be made based on the subgroup analyses. Nonetheless, it was noted that a lower proportion of patients in the avacopan group (27.1%) required non-study supplied glucocorticoids compared to the prednisone group (39.0%) between Week 26 to Week 52. Specifically, a lower proportion of avacopan-treated patients required glucocorticoids for relapse during the same period, irrespective of background induction therapy. These findings suggested that the patients benefited from continued treatment after Week 26.

The secondary endpoints demonstrated nominally significant improvements across multiple measures that supported the primary efficacy results.

Glucocorticoid toxicity was assessed using the GTI, which comprised the Cumulative Worsening Score (CWS) that measures cumulative toxicity over time, and the Aggregate Improvement Score (AIS) that measures both improvement and worsening of toxicity over time. At both Weeks 13 and 26, the GTI-CWS and GTI-AIS demonstrated lower glucocorticoid-related toxicity symptoms in the avacopan group compared to the prednisone group. At Week 13, the least squares mean (LSM) of the GTI-CWS was 25.7 in the avacopan group compared to 36.6 in the prednisone group (p=0.014), and at Week 26, the LSM of the GTI-CWS was 39.7 and 56.6 in each group, respectively (p=0.0002). The LSM of the GTI-AIS was 9.9 in the avacopan group compared to 23.2 in the prednisone group (p=0.003) at Week 13, and 11.2 vs

23.4, respectively (p=0.008) at Week 26. A BVAS of 0 at Week 4 was observed in 62.7% of patients in the avacopan group compared to 68.9% in the prednisone group (p=0.87).

In terms of quality-of-life assessments, there was a greater improvement in the avacopan group compared to the prednisone group in the physical component score and several other physical domains of the SF-36v2 health-related quality of life assessment at Week 26 and/or Week 52 (p=0.002 and 0.018 for Week 26 and Week 52, respectively). The mental component score and other mental domains also showed numerically greater improvement in the avacopan group compared to the prednisone group. There was a greater improvement in the EQ-5D-5L VAS as well as EQ-5D-5L Index score from baseline in the avacopan group compared to the prednisone group at Week 52 (p=0.002 and 0.009, respectively).

The incidence of relapses after achieving remission at Week 26 was 7.5% in the avacopan group and 12.2% in the prednisone group (p=0.081). The incidence of relapse at any time during the study after BVAS=0 had been achieved was lower in the avacopan group compared with the prednisone group (10.1% vs 21.0%; p=0.009).

Kidney function, as measured by eGFR, showed greater improvement in the avacopan group compared to the prednisone group. At Week 52, the LSM change from baseline was 7.3 ml/min/1.73 m^2 in the avacopan group (from a baseline of 44.6 ml/min/1.73 m^2) and 4.1 ml/min/1.73 m^2 in the prednisone group (from a baseline of 45.6 ml/min/1.73 m^2; p=0.029). The extent of improvement in UACR was similar between treatment groups at Week 52. Urinary MCP-1:creatinine ratio decreased more in the avacopan group compared to the prednisone group by Week 13, but there was a similar decrease in the two treatment groups by Week 52. Both treatment groups showed a similar mean increase from baseline to Week 52 in the VDI.

Overall, the study met its primary endpoints, demonstrating that avacopan was non-inferior to the prednisone group for achieving disease remission at Week 26 and superior to the prednisone group in sustaining remission at Week 52, when administered in combination with rituximab or with cyclophosphamide followed by azathioprine/mycophenolate. The efficacy of avacopan in achieving sustained remission at Week 52 was primarily driven by the rituximab stratum (i.e., those who received rituximab induction therapy in the first 4 weeks and did not receive any maintenance therapies). While the benefit of avacopan in combination with cyclophosphamide followed by azathioprine/mycophenolate was less apparent, the overall proportion of patients requiring non-study supplied glucocorticoids between Week 26 to Week 52 was lower in the avacopan group compared to the prednisone group, indicating that the patients benefited from continued treatment after Week 26. Specifically, a lower proportion of patients in the avacopan group required non-study supplied glucocorticoids for treatment of relapse compared to the prednisone group, in both rituximab and cyclophosphamide strata. Therefore, the main advantage of avacopan as an add-on therapy to standard therapy is the reduction in cumulative glucocorticoid use, which was supported by the lower glucocorticoid-induced toxicity as measured by the GTI.

D ASSESSMENT OF CLINICAL SAFETY

The safety evaluation was based mainly on data from the Phase III study CL010_168, which comprised a total of 331 subjects (166 subjects in the avacopan group and 164 subjects in the prednisone group). Most subjects received avacopan or matching placebo for 184 to 365 days. The mean ± standard deviation (SD) exposure was 305.1 ± 118.36 days in the avacopan group and 320.8 ± 99.13 days in the prednisone group.

Overview of safety profile

	Avacopan (N=166)	Prednisone (N=164)
TEAE	164 (98.8%)	161 (98.2%)
SAE	70 (42.2%)	74 (45.1%)
TEAE leading to study medication discontinuation	27 (16.3%)	28 (17.1%)
TEAE leading to death	2 (1.2%)	4 (2.4%)

Treatment-emergent adverse events (TEAEs) were reported by 98.8% of patients in the avacopan group and 98.2% of patients in the prednisone group. The most frequently reported TEAEs in the avacopan group were nausea (23.5% in the avacopan group vs 20.7% in the prednisone group), peripheral oedema (21.1% vs 24.4%), and headache (20.5% vs 14.0%). Other events with a ≥2% higher incidence in the avacopan compared with the prednisone group included vomiting (15.1% vs 12.8%) and rash (11.4% vs 7.9%).

Serious adverse events (SAEs) were reported by 42.2% of patients in the avacopan group and 45.1% in the prednisone group. The most common SAE was ANCA-positive vasculitis (worsening) (7.2% in the avacopan group vs 12.2% in the prednisone group).

The incidence of TEAEs leading to discontinuation of study medication was comparable between the avacopan and prednisone groups (16.3% vs 17.1%). The incidence of hepatobiliary disorders leading to study medication discontinuation was 3.0% (5 of 166 subjects) in the avacopan group compared with none (0.0%) in the prednisone group.

Six patients died during the study, 2 (1.2%) in the avacopan group and 4 (2.4%) in the prednisone group; one additional death occurred during the screening period. In the avacopan group, the causes of death were GPA for 1 patient and pneumonia for the other; these patients were not receiving avacopan at the time of death. The two treatment discontinuations occurred on Day 236 in one patient who died on Day 315 and on Day 50 in the other patient who died on Day 160. None of the deaths in the avacopan group were assessed by the investigator to be treatment-related.

The adverse events of special interest (AESIs) included infection, low white blood cell (WBC) count, elevated hepatic function test, and hypersensitivity/angioedema.

Summary of AESIs

	Avacopan (N=166)	Prednisone (N=164)
Infection TEAE	113 (68.1%)	124 (75.6%)
TEAE associated with low WBC count	31 (18.7%)	39 (23.8%)
TEAE associated with hepatic function test abnormalities	22 (13.3%)	19 (11.6%)
Hypersensitivity TEAE	68 (41.0%)	70 (42.7%)

A lower proportion of patients in the avacopan group had TEAEs of infection (68.1% vs 75.6%), serious TEAEs of infection (13.3% vs 15.2%) and opportunistic infection (3.6% vs 6.7%), life-threatening TEAEs of infection (0.6% vs 1.2%), and infections resulting in death (0.6% vs 1.2%) compared with the prednisone group. Warnings on serious infections and recommendations for patient assessment have been included in the package insert.

There was also a lower incidence of TEAEs (18.7% vs 23.8%) and serious TEAEs associated with low WBC counts (2.4% vs 4.9%), as well as Grade 4 lymphopenia (2.4% vs 8.0%) and Grade 4 neutropenia (0% vs 1.2%) in the avacopan group compared with the prednisone

group. The package insert has included adequate warnings on low WBC count and recommendations for monitoring and dose modifications based on specific haematological parameters.

There was a slightly higher incidence of TEAEs (13.3% vs 11.6%) and serious TEAEs of elevated hepatic function test (5.4% vs 3.7%) in the avacopan group compared with the prednisone group. However, causality assessment was confounded by the reported use of other potentially hepatotoxic drugs such as co-trimoxazole, azathioprine, and alcohol, and viral aetiologies. The package insert has included warnings on elevated hepatic function test, with detailed recommendations for monitoring and criteria for treatment interruption and permanent discontinuation to manage the risk of hepatotoxicity.

The incidence of hypersensitivity reactions was similar between the avacopan (41.0%) and prednisone groups (42.7%). Two cases of angioedema were reported in the avacopan group, while none were reported in the prednisone group. Adequate warnings on angioedema and appropriate risk mitigation measures, including instructions for patient symptom reporting, have been included in the package insert.

Overall, the safety profile of avacopan was mainly characterised by elevated hepatic function test, hypersensitivity, infections, low WBC count, and gastrointestinal disorders. Adequate warnings and recommendations for management of the AEs, including laboratory monitoring and dose modifications, have been included in the package insert to mitigate the risks. The safety profile of avacopan was considered acceptable for the intended population.

E ASSESSMENT OF BENEFIT-RISK PROFILE

AAV is a rare, multisystem autoimmune condition characterised by inflammation of small to medium sized blood vessels, leading to organ damage and dysfunction. AAV primarily affects the kidneys, lungs and upper respiratory tract, but it can also involve the peripheral and central nervous system, skin, gut, and heart. Despite available therapies, a high relapse rate remains a concern in patients with AAV. Current therapies such as chronic glucocorticoid use are associated with significant adverse events. Hence, there is a need for treatment options with improved efficacy and/or safety.

The clinical benefit of avacopan as an adjunctive treatment in severe, active AAV in combination with standard therapy has been demonstrated in Study CL010_168. The results demonstrated statistically significant ($p<0.0001$) non-inferiority of avacopan versus prednisone for the endpoint of remission at Week 26 (72.3% vs 70.1%, respectively; difference: 3.4%, 95% CI: -6.0, 12.8). Superiority of avacopan versus prednisone was not demonstrated for this endpoint. At Week 52, both non-inferiority ($p<0.0001$) and superiority ($p=0.0066$) were demonstrated, with 65.7% of patients in the avacopan group compared to 54.9% in the prednisone group achieving sustained remission (difference: 12.5%, 95% CI: 2.6, 22.3). The efficacy of avacopan in achieving sustained remission at Week 52 was primarily driven by the rituximab stratum. While the effect size of avacopan in combination with cyclophosphamide followed by azathioprine/mycophenolate was smaller, the reduction in cumulative glucocorticoid use was supportive of efficacy of avacopan in both strata. The main advantage of avacopan as an add-on to standard therapy is the reduction in glucocorticoid use. This was further supported by the secondary endpoints measured by the GTI showing lower glucocorticoid-induced toxicity with avacopan treatment.

The safety profile of avacopan was considered acceptable for the intended population given the severity of the disease. The most notable safety concerns with avacopan were elevated hepatic function test, hypersensitivity, infections, low WBC count, and gastrointestinal disorders. Given the observed safety findings, warnings and recommendations for dose modifications have been included in the package insert as risk mitigation measures.

Overall, the benefit of avacopan as an adjunctive treatment of adult patients with severe, active ANCA-associated vasculitis (GPA or MPA) in combination with standard therapy outweighed the risk of adverse events associated with the treatment.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Tavneos as an adjunctive treatment of adult patients with severe, active ANCA-associated vasculitis (GPA or MPA) in combination with standard therapy, including glucocorticoids, was deemed favourable. Approval of the product registration was granted on 24 December 2024.

APPROVED PACKAGE INSERT AT REGISTRATION

Tavneos 10mg Hard Capsules

1. NAME OF THE MEDICINAL PRODUCT

Tavneos 10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 10 mg of avacopan.

Excipient with known effect

Each hard capsule contains 245 mg of macrogolglycerol hydroxystearate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Capsules with yellow body and light orange cap with “CCX168” in black ink.
One capsule has a length of 22 mm and a diameter of 8 mm (size 0).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tavneos is indicated as an adjunctive treatment of adult patients with severe , active anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] or microscopic polyangiitis [MPA]) in combination with standard therapy, including glucocorticoids.

4.2 Posology and method of administration

Treatment should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of GPA or MPA.

Posology

The recommended dose is 30 mg Tavneos (3 hard capsules of 10 mg each) taken orally twice daily, morning and evening, with food.

Tavneos should be administered in combination with a standard immunosuppression regimen including glucocorticoids as clinically indicated.

For details on doses of the immunosuppression regimen and concomitant glucocorticoids in the study, as well as data on efficacy and safety for the combinations, please see sections 4.8 and 5.1.

Clinical study data are limited to 52 weeks of exposure followed by 8 weeks of observation.

Missed doses

If a patient misses a dose, the missed dose is to be taken as soon as possible, unless within three hours of the next scheduled dose. If within three hours, then the missed dose is not to be taken.

Dose management

Treatment must be re-assessed clinically and temporarily stopped if:
- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is more than 3 times the upper limit of normal (ULN).

Treatment must be temporarily stopped if:
- ALT or AST > 5 × ULN,
- a patient develops leukopenia (white blood cell count < 2×10^9/L) or neutropenia (neutrophils < 1×10^9/L), or lymphopenia (lymphocytes < 0.2×10^9/L),
- a patient has an active, serious infection (i.e. requiring hospitalisation or prolonged hospitalisation).

Treatment may be resumed:
- upon normalisation of values and based on an individual benefit/risk assessment.

If treatment is resumed, hepatic transaminases and total bilirubin are to be monitored closely.

Permanent discontinuation of treatment must be considered if:
- ALT or AST > 8 × ULN,
- ALT or AST > 5 × ULN for more than 2 weeks,
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalised ratio (INR) > 1.5,
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%),
- an association between avacopan and hepatic dysfunction has been established.

Special populations

Elderly

No dose adjustment is required in elderly patients (see section 5.2).

Hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment (see section 5.2).

Avacopan has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations.

Renal impairment

No dose adjustment is needed based on renal function (see section 5.2).

Avacopan has not been studied in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis with an estimated glomerular filtration rate (eGFR) below 15 mL/min/1.73 m², who are on dialysis, in need of dialysis or plasma exchange.

Severe disease manifested as alveolar haemorrhage

Avacopan has not been studied in patients with severe disease manifested as alveolar haemorrhage.

Paediatric population

The safety and efficacy of avacopan in adolescents (12 to 17 years of age) have not yet been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made. The safety and efficacy of avacopan in children below 12 years of age have not yet been established. No data are available.

Method of administration

This medicinal product is for oral use.

The hard capsules are to be taken with food and swallowed whole with water and must not be crushed, chewed, or opened.

Grapefruit and grapefruit juice are to be avoided in patients treated with avacopan (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Liver function test increased

Serious adverse reactions of elevated hepatic transaminases with elevated total bilirubin have been observed in patients receiving avacopan in combination with cyclophosphamide (followed by azathioprine or mycophenolate) or rituximab and trimethoprim and sulfamethoxazole.
Liver function test (LFT) increased is considered as an adverse reaction (see section 4.8).

Avacopan must be avoided in patients with signs of liver disease, such as elevated AST, ALT, alkaline phosphatase (ALP), or total bilirubin > 3 times ULN.

Hepatic transaminases and total bilirubin must be obtained prior to initiation of therapy.

Patients must be monitored for hepatic transaminases and total bilirubin as clinically indicated and as part of the routine follow-up of patient's underlying condition (see section 4.2).

Blood and immune system

White blood cell (WBC) count must be obtained prior to initiation of therapy and patients must be monitored as clinically indicated and as part of the routine follow-up of patient's underlying condition (see section 4.2).

Treatment with avacopan must not be initiated if WBC count is less than 3500/μL, or neutrophil count less than 1500/μL, or lymphocyte count less than 500/μL.

Patients receiving avacopan must be instructed to report immediately any evidence of infection, unexpected bruising, bleeding, or any other manifestations of bone marrow failure.

Serious infections

Serious infections have been reported in patients receiving combination agents for treatment of GPA or MPA, including avacopan in combination with rituximab or cyclophosphamide (see section 4.8).

Patients must be assessed for any serious infections.

Avacopan has not been studied in patients with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infections. Before and during treatment, patients must notify their physician if they have been diagnosed with tuberculosis, hepatitis B, hepatitis C, or HIV infection.

Be cautious when treating patients with a history of tuberculosis, hepatitis B, hepatitis C, or HIV infection.

Avacopan does not decrease the formation of the membrane attack complex (C5b-9) or terminal complement complex (TCC). No cases of *Neisseria meningitidis* have been identified in the avacopan clinical programme. Monitor patients treated for ANCA-associated vasculitis according to standard practice for clinical signs and symptoms of *Neisseria* infections.

Pneumocystis jirovecii pneumonia prophylaxis

Pneumocystis jirovecii pneumonia prophylaxis is recommended for adult patients with GPA or MPA during avacopan treatment, as appropriate according to local clinical practice guidelines.

Immunisation

The safety of immunisation with live vaccines, following avacopan therapy has not been studied. Administer vaccinations preferably prior to initiation of treatment with avacopan or during quiescent phase of the disease.

Angioedema

Angioedema has been reported in patients receiving avacopan (see section 4.8).

Patients must notify their physician if they develop any symptoms such as swelling of the face, lips, or tongue, throat tightness, or difficulty breathing.

Avacopan must be withheld in cases of angioedema.

Interaction with strong CYP3A4 inducers

The use of strong CYP3A4 enzyme inducers (e.g., carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifampicin, and St. John's Wort) with avacopan is to be avoided (see section 4.5).
Patients anticipated to require long-term administration of these medicinal products are not to be treated with avacopan.
If short-term co-administration cannot be avoided in a patient already using avacopan, the patient must be closely monitored in case of any reoccurrence of disease activity.

Cardiac disorders

Patients with GPA or MPA are at risk of cardiac disorders such as myocardial infarction, cardiac failure, and cardiac vasculitis.

Serious adverse events (SAEs) of cardiac disorder have been reported in patients treated with avacopan. A treatment regimen based on the combination with cyclophosphamide followed by azathioprine may carry an increased risk for cardiac disorders as compared to a regimen based on the combination with rituximab.

Malignancy

Immunomodulatory medicinal products may increase the risk for malignancies. The clinical data are currently limited (see section 5.1).

Macrogolglycerol hydroxystearate content

This medicinal product contains macrogolglycerol hydroxystearate, which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

Avacopan is a substrate of CYP3A4. Co-administration of inducers or inhibitors of this enzyme may affect the pharmacokinetics of avacopan.

Effect of strong CYP3A4 inducers on avacopan

Co-administration of avacopan with rifampicin, a strong CYP3A4 enzyme inducer, resulted in a decrease in area-under-the-concentration time curve (AUC) and maximum plasma concentration (C_{max}) of avacopan by approximately 93% and 79%, respectively. Since this interaction may result in loss of efficacy of avacopan, the use of strong CYP3A4 enzyme inducers (e.g., carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifampicin, and St. John's Wort) with avacopan is to be avoided (see section 4.4). Patients anticipated to require long-term administration of these medicinal products are not to be treated with avacopan. If short-term co-administration cannot be avoided in a patient already using avacopan, the patient must be closely monitored for any reoccurrence of disease activity.

Effect of moderate CYP3A4 inducers on avacopan

Exercise caution when using moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, and modafinil) prescribed as concomitant medicinal product with avacopan and carefully evaluate the benefit/risk of avacopan.

Effect of strong CYP3A4 inhibitors on avacopan

Co-administration of avacopan with itraconazole, a strong CYP3A4 enzyme inhibitor, resulted in an increase in AUC and C_{max} of avacopan by approximately 2.2-fold and 1.9-fold, respectively. Therefore, strong CYP3A4 enzyme inhibitors (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole) should be used with caution in patients who are being treated with avacopan. Patients must be monitored for potential increase of side effects due to the increased exposure of avacopan.

Grapefruit and grapefruit juice can increase the concentration of avacopan; therefore, grapefruit and grapefruit juice are to be avoided in patients treated with avacopan.

Effect of avacopan on other medicinal products

Avacopan is a weak inhibitor of CYP3A4 *in vivo* and may increase the plasma exposures of concomitant medicinal products that are CYP3A4 substrates with a narrow therapeutic index (e.g., alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus). Be cautious when these medicinal products are used with avacopan. Patients must be managed according to the summary of product characteristics of the respective medicinal products with a narrow therapeutic index.

Effect of macrogolglycerol hydroxystearate on sensitive P-glycoprotein (P-gp) substrates

A clinically relevant effect of the excipient macrogolglycerol hydroxystearate on sensitive P-gp substrates with relatively low bioavailability (e.g., dabigatran etexilate) cannot be excluded. Exercise caution when using low-bioavailability P-gp substrates in patients who are being treated with avacopan.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Pregnancy

There are no data from the use of avacopan in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Avacopan is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Avacopan has not been measured in milk of lactating animals; however, avacopan has been detected in the plasma of nursing animal offspring without apparent offspring effects (see section 5.3).

A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy with avacopan, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of avacopan on human fertility. Animal data did not indicate any impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Tavneos has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are nausea (23.5%), headache (20.5%), white blood cell count decreased (18.7%), upper respiratory tract infection (14.5%), diarrhoea (15.1%), vomiting (15.1%), and nasopharyngitis (15.1%).

The most common serious adverse reactions are liver function abnormalities (5.4%) and pneumonia (4.8%).

Tabulated list of adverse reactions

The adverse reactions observed in the ANCA-associated vasculitis pivotal phase 3 study in patients treated with avacopan are listed in Table 1 by system organ class (SOC) and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1: Adverse reactions

System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Infections and infestations	Upper respiratory tract infection, Nasopharyngitis	Pneumonia, Rhinitis, Urinary tract infection, Sinusitis, Bronchitis, Gastroenteritis, Lower respiratory tract infection, Cellulitis, Herpes zoster, Influenza, Oral candidiasis, Oral herpes, Otitis media	
Blood and lymphatic system disorders		Neutropenia	
Nervous system disorders	Headache		
Gastrointestinal disorders	Nausea, Diarrhoea, Vomiting	Abdominal pain upper	
Hepatobiliary disorders	Liver function test increased*		
Skin and subcutaneous tissue disorders			Angioedema
Investigations	White blood cell count decreased**	Blood creatine phosphokinase increased	

* Alanine aminotransferase increased, total blood bilirubin increased, hepatic function abnormal, gamma glutamyl transferase increased, hepatic enzyme increased, transaminases increased.
****** Includes leukopenia.

Description of selected adverse reactions

Liver function test increased

In the pivotal phase 3 study in which 330 patients were dosed, 13.3% of patients in the avacopan group and 11.6% of patients in the prednisone group had an adverse reaction of elevated liver function test (LFT).
In the avacopan group, LFT increased was reported in the phase 3 study and included hepatitis (1.2%), hepatitis cholestatic (0.6%) of which one patient reported both hepatitis and hepatitis cholestatic as a diagnosis, hepatocellular injury (0.6%) in one patient diagnosed with asymptomatic hepatitis, cytolysis and anicteric cholestasis without hepatocellular insufficiency.

In the pivotal phase 3 study, adverse events of hepatobiliary disorders were more frequent in patients treated with a regimen based on a combination with cyclophosphamide followed by azathioprine (10.2%) as compared to those treated with a regimen based on a combination with rituximab (3.7%).

Study medicinal product was paused or discontinued permanently due to LFT increased in 5.4% of patients in the avacopan group and 3.0% of patients in the prednisone group. Serious adverse reactions of LFT increased were reported in 5.4% of patients in the avacopan group and 3.7% of patients in the prednisone group. All serious hepatic events resolved with either the withdrawal of avacopan and/or other potentially hepatotoxic medicinal products, including trimethoprim and sulfamethoxazole.

Neutropenia

In the pivotal phase 3 study, neutropenia was reported in 4 patients (2.4%) in each treatment group. A single case of agranulocytosis was reported each in the prednisone group and in the avacopan group.

The patient in the avacopan group was noted to have central neutropenia on a bone marrow biopsy which resolved spontaneously without additional treatment.

Creatine phosphokinase increased

In the pivotal phase 3 study, 6 patients (3.6%) in the avacopan group and 1 patient (0.6%) in the prednisone group had adverse reactions of increased creatine phosphokinase (CPK).

Hypersensitivity including angioedema

In the pivotal phase 3 study, 2 patients (1.2%) in the avacopan group had an adverse reaction of angioedema. One patient was hospitalised for the event. Avacopan was paused and both events resolved without sequelae. Avacopan was restarted in one patient and angioedema did not reoccur.

Gastrointestinal disorders

In the pivotal phase 3 study, adverse reactions of gastrointestinal disorders were observed in 74.6% of patients treated with avacopan and a regimen based on a combination with cyclophosphamide followed by azathioprine as compared to those treated with a regimen based on a combination with rituximab (53.3%).

Special populations

Paediatric population

A total of 3 adolescents were studied in the phase 3 study, one in the prednisone group and two in the avacopan group. There are no data in children below 12 years of age (see section 5.1).

Elderly patients

The safety profile was similar between patients ≥ 65 years of age and adult patients < 65 years of age in the clinical studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the local reporting system.

4.9 Overdose

Avacopan was studied in healthy subjects at a maximum total daily dose of 200 mg (given as 100 mg twice daily) for 7 days without evidence of dose limiting toxicities. In case of an overdose, it is recommended that the patient is monitored for any signs or symptoms of adverse effects, and appropriate symptomatic treatment and supportive care are provided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Complement inhibitors , ATC code: L04AJ05

Mechanism of action

Avacopan is a selective antagonist of the human complement 5a receptor (C5aR1 or CD88) and competitively inhibits the interaction between C5aR1 and the anaphylatoxin C5a.

The specific and selective blockade of C5aR1 by avacopan reduces the pro-inflammatory effects of C5a, which include neutrophil activation, migration, and adherence to sites of small blood vessel inflammation, vascular endothelial cell retraction and permeability.

Pharmacodynamic effects

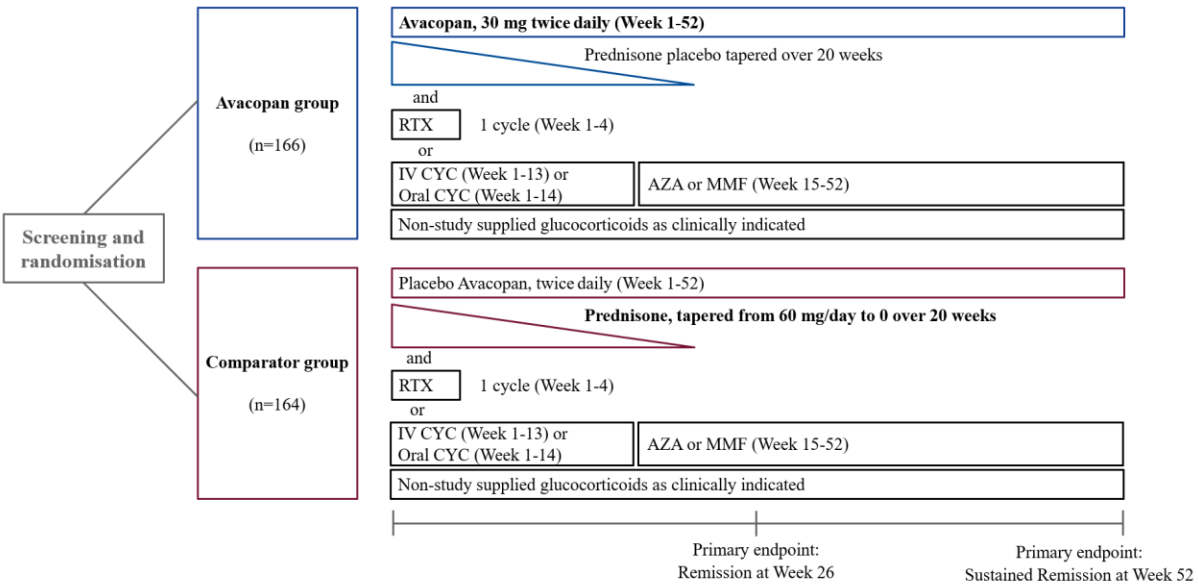
Avacopan blocks the C5a-induced upregulation of CD11b (integrin alpha M) on neutrophils taken from humans dosed with avacopan. CD11b facilitates neutrophil adherence to vascular endothelial surfaces, one of the steps in the vasculitis disease process.

Clinical efficacy and safety

A total of 330 patients aged 13 years or older with granulomatosis with polyangiitis (GPA) (54.8%) or microscopic polyangiitis (MPA) (45.2%) were treated in the active-comparator, randomised, double-blind, double-dummy, multicentre, pivotal phase 3 ADVOCATE study for 52 weeks.

The ADVOCATE study design is depicted in Figure 1.

Figure 1 ADVOCATE study design



AZA = azathioprine; CYC = cyclophosphamide; IV = intravenous; MMF = mycophenolate mofetil; RTX =rituximab

Patients were randomised in a 1:1 ratio to one of the two groups:

- Avacopan group (N=166): Patients received 30 mg avacopan twice daily for 52 weeks plus prednisone-matching placebo tapering regimen over 20 weeks,
- Comparator group (N=164): Patients received avacopan-matching placebo twice daily for 52 weeks plus prednisone (tapered from 60 mg/day to 0 over 20 weeks).

All patients in both groups received standard immunosuppressive regimens of either:

- Rituximab at the dose of 375 mg/m² for 4 weekly intravenous doses, or
- Intravenous cyclophosphamide for 13 weeks (15 mg/kg up to 1.2 g every 2 to 3 weeks), and then starting on week 15 oral azathioprine 1 mg/kg daily with titration up to 2 mg/kg daily (Mycophenolate mofetil 2 g daily was allowed in place of azathioprine. If mycophenolate mofetil was not tolerated or not available, enteric coated mycophenolate sodium could be given at a target dose of 1,440 mg/day), or
- Oral cyclophosphamide for 14 weeks (2 mg/kg daily) followed by oral azathioprine or mycophenolate mofetil/sodium starting at week 15 (same dosing regimen as intravenous cyclophosphamide).

For the first rituximab infusion, 100 mg methylprednisolone, or equivalent was given before starting the infusion with rituximab. Glucocorticoid pre-medication for the second, third, and fourth rituximab infusions was allowed.
Dose reductions or adjustments in cyclophosphamide, azathioprine, and mycophenolate were allowed to conform to standard approaches to maximize safety of these medicinal products.

The following study-supplied glucocorticoid tapering schedule was used (Table 2).

Table 2: Glucocorticoid tapering schedule – Prednisone dose (mg per day)

Study Day	**Avacopan**	**Comparator**	
	All	≥ 55 kg	< 55 kg
1 to 7	0	60	45
8 to 14	0	45	45
15 to 21	0	30	30
22 to 42	0	25	25
43 to 56	0	20	20
57 to 70	0	15	15
71 to 98	0	10	10
99 to 140	0	5	5
≥ 141	0	0	0

Non-study supplied glucocorticoids, unless strictly necessary due to a condition requiring the use of glucocorticoids (such as adrenal insufficiency), had to be avoided as much as possible during the study. However, patients who experienced worsening or a relapse of their ANCA-associated vasculitis during the study could be treated with a limited course of glucocorticoids.

Patients were stratified at time of randomisation to obtain balance across treatment groups based on 3 factors:

- Newly-diagnosed or relapsed ANCA-associated vasculitis,
- Proteinase-3 (PR3) positive or myeloperoxidase (MPO) positive ANCA-associated vasculitis,
- Receiving either intravenous rituximab, intravenous cyclophosphamide, or oral cyclophosphamide.

The two treatment groups were well balanced regarding baseline demographics and disease characteristics of patients (Table 3).

Table 3: Selected baseline characteristics in the pivotal phase 3 ADVOCATE study (Intent-to-Treat Population)

Demographic characteristic	**Avacopan (N = 166)**	**Comparator (N = 164)**
Age at screening		
Mean (SD), years	61 (14.6)	61 (14.5)
Range, years	13-83	15-88
ANCA-associated vasculitis status, n (%)		
Newly diagnosed	115 (69.3)	114 (69.5)
Relapsed	51 (30.7)	50 (30.5)
ANCA positivity, n (%)		
PR3	72 (43.4)	70 (42.7)
MPO	94 (56.6)	94 (57.3)
Type of ANCA-associated vasculitis, n (%)		
Granulomatosis with polyangiitis (GPA)	91 (54.8)	90 (54.9)
Microscopic polyangiitis (MPA)	75 (45.2)	74 (45.1)
BVAS score		
Mean (SD)	16.3 (5.87)	16.2 (5.69)
eGFR		
Mean (SD), mL/min/1.73 m^2	50.7 (30.96)	52.9 (32.67)
Prior Glucocorticoid Use (during Screening)		
n (%)	125 (75.3)	135 (82.3)
Mean (SD), prednisone-equivalent dose (mg)	654 (744.4)	728 (787.8)

ANCA = antineutrophil cytoplasmic autoantibody; BVAS = Birmingham Vasculitis Activity Score; MPO = myeloperoxidase; PR3 = proteinase-3, SD = standard deviation

The aim of the study was to determine if avacopan could provide an effective treatment for patients with ANCA-associated vasculitis, while also allowing for the reduction of glucocorticoids use without compromising safety or efficacy.

The primary objective was to evaluate the efficacy of the above described treatment regimens to induce and sustain remission in patients with ANCA-associated vasculitis based on the following two primary endpoints:

- the proportion of patients in disease remission defined as achieving a Birmingham Vasculitis Activity Score (BVAS) of 0 and not taking glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to week 26,
- the proportion of patients in sustained remission defined as remission at week 26 without relapse to week 52, and BVAS of 0 and not taking glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to week 52.

The two primary endpoints were tested sequentially for non-inferiority and superiority using a gatekeeping procedure to preserve the Type I error rate at 0.05.

Results from this study are showed in Table 4.

Table 4: Remission at week 26 and sustained remission at week 52 in the pivotal phase 3 ADVOCATE study (Intent-to-Treat Population)

	Avacopan N=166 n (%)	Comparator N=164 n (%)	Estimate of Treatment Difference in %[a]
Remission at week 26	120 (72.3)	115 (70.1)	3.4
95% CI	64.8, 78.9	62.5, 77.0	−6.0, 12.8
Sustained remission at week 52	109 (65.7)	90 (54.9)	12.5[b]
95% CI	57.9, 72.8	46.9, 62.6	2.6, 22.3

CI = confidence interval

[a] Two-sided 95% CIs are calculated by adjusting for randomisation stratification factors.

[b] superiority p value = 0.013 (2-sided)

The efficacy observed was consistent across pertinent subgroups, i.e., those with newly-diagnosed and relapsed disease, PR3 and MPO ANCA positive, GPA and MPA, and men and women. Efficacy results by background treatment are presented in Table 5.

Table 5: Remission at week 26 and sustained remission at week 52 in the pivotal phase 3 ADVOCATE study by background treatment (Intent-to-Treat Population)

	Avacopan n/N (%)	Comparator n/N (%)	Difference in %, 95% CI[a]
Remission at week 26			
Patients receiving intravenous rituximab	83/107 (77.6)	81/107 (75.7)	1.9 (−9.5, 13.2)
Patients receiving intravenous or oral cyclophosphamide	37/59 (62.7)	34/57 (59.6)	3.1 (−14.7, 20.8)
Sustained remission at week 52			
Patients receiving intravenous rituximab	76/107 (71.0)	60/107 (56.1)	15.0 (2.2, 27.7)
Patients receiving intravenous or oral cyclophosphamide	33/59 (55.9)	30/57 (52.6)	3.3 (−14.8, 21.4)

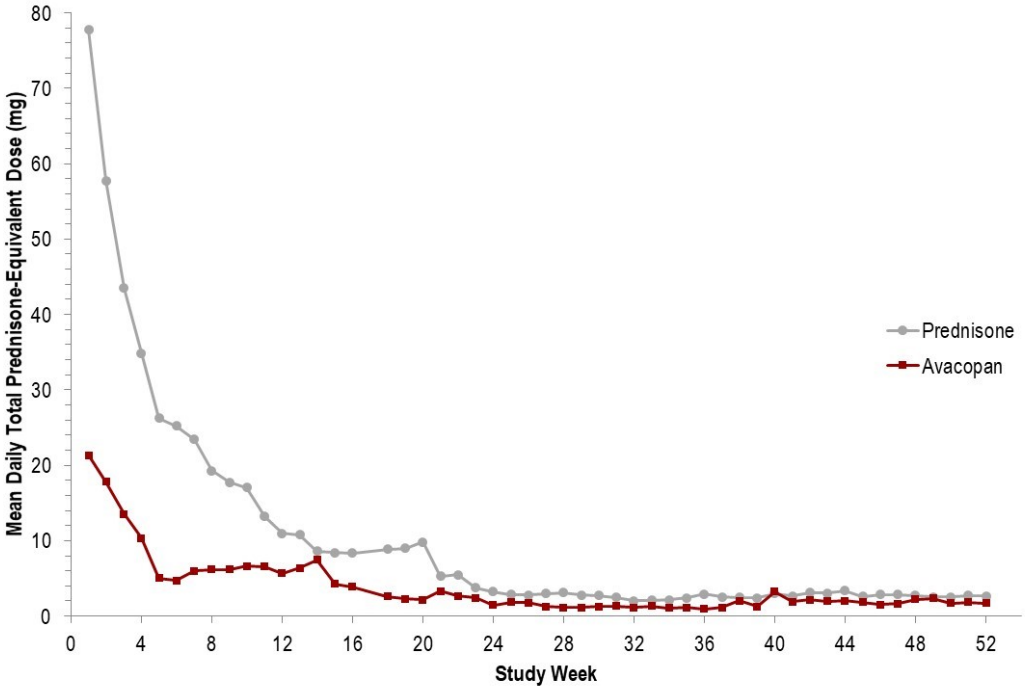
[a] Two-sided 95% confidence intervals (CI) are calculated for the difference in proportions (avacopan minus comparator) using the Wald method.

Glucocorticoid toxicity

In the pivotal phase 3 ADVOCATE study, the mean total cumulative prednisone-equivalent dose from day 1 to end-of-treatment was approximately 2.7-fold higher in the comparator group versus the avacopan group (3654.5 mg vs 1348.9 mg, respectively).

From baseline to week 26, 86.1 % of patients using avacopan received non-study supplied glucocorticoids. In the comparator group, the majority of glucocorticoids use was due to the protocol-defined prednisone course.

Figure 2: Total mean daily prednisone-equivalent glucocorticoid dose per patient by study week in the ADVOCATE study (Intent-to-Treat Population)



The Glucocorticoid Toxicity Index (GTI) assesses glucocorticoid-related morbidity, including measures of body mass index, glucose tolerance, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection. A higher GTI indicates greater glucocorticoid toxicity. The GTI contains the Cumulative Worsening Score (CWS) that captures cumulative toxicity over the course of time, and the Aggregate Improvement Score (AIS) that captures both improvement and worsening of toxicity over time.

The two GTI scores (CWS and AIS) of the avacopan group versus the comparator group are summarised in Table 6. The GTI measures were secondary endpoints in the study and not controlled for multiplicity

Table 6: Glucocorticoid Toxicity Index results in the pivotal phase 3 ADVOCATE study (Intent-to-Treat Population)

	Avacopan N = 166	**Comparator N = 164**	**Difference between Groups, 95% CI**
Cumulative Worsening Score (CWS)			
Week 13 (least squares mean)	25.7	36.6	−11.0 (−19.7, −2.2)
Week 26 (least squares mean)	39.7	56.6	−16.8 (−25.6, −8.0)
Aggregate Improvement Score (AIS)			
Week 13 (least squares mean)	9.9	23.2	−13.3 (−22.2, −4.4)
Week 26 (least squares mean)	11.2	23.4	−12.1 (−21.1, −3.2)

Paediatric population

A total of 3 adolescents were studied in the pivotal phase 3 ADVOCATE study, two in the avacopan group and one in the comparator group. One adolescent in the avacopan group discontinued treatment due to worsening renal vasculitis. The second adolescent patient who received avacopan completed treatment, achieved both remission at week 26 and sustained remission at week 52.
The adolescent in the comparator group discontinued treatment due to non-adherence to contraception.

5.2 Pharmacokinetic properties

Absorption

When administered without food, avacopan peak plasma concentration (C_{max}) occurs at a median time (t_{max}) of approximately 2 hours. Avacopan has shown an approximate dose-proportional increase in systemic exposure in the dose range of 10 to 30 mg.

Co-administration of 30 mg in capsule formulation with a high-fat, high-calorie meal increases the plasma exposure (AUC) of avacopan by approximately 72% and delays t_{max} by approximately 3 hours; however, the C_{max} is not affected.

Distribution

The reversible plasma protein binding (e.g., to albumin and α1-acid glycoprotein) of avacopan and metabolite M1 is greater than 99.9%. The apparent volume of distribution is high (Vz/F 3,000 – 11,000 L), indicating broad tissue distribution of the active substance.

Biotransformation

Avacopan is eliminated mainly through phase I metabolism. Following oral administration of radiolabelled avacopan, the bulk of the active substance-related materials was recovered in faeces in the form of phase I metabolites. One major circulating metabolite (M1), a mono-hydroxylated product of avacopan, was present at ~ 12% of the total active substance-related materials in plasma. This metabolite constitutes 30 to 50% of the parent exposure and has approximately the same activity as avacopan on C5aR1. Cytochrome P450 (CYP) 3A4 is the major enzyme responsible for the clearance of avacopan and for the formation and clearance of metabolite M1.

Avacopan is a weak inhibitor of CYP3A4 and CYP2C9 as indicated by a modest increase in the AUC of the probe active substances midazolam (1.81-fold) and celecoxib (1.15-fold), respectively.

In vitro, avacopan is not an inhibitor or an inducer of other CYP enzymes.

Avacopan showed negligible to weak inhibition of common transporters *in vitro*. Therefore, clinically relevant interactions are unlikely when avacopan is co-administered with substances that are substrates or inhibitors of these transporters.

Elimination

Based on population pharmacokinetic analysis, the total apparent body clearance (CL/F) of avacopan is 16.3 L/h (95% CI: 13.1 – 21.1 L/h). The median terminal elimination half-life is 510 hours (21 days) based on population pharmacokinetic analysis. When avacopan is stopped after steady state has been reached, the residual plasma concentration of avacopan is projected to decrease to ~ 20%, < 10%, and < 5% of the steady state maximum concentration approximately 4 weeks, 7 weeks, and 10 weeks, respectively, after the last dose.

Following oral administration of radiolabelled avacopan, about 77% and 10% of the radioactivity was recovered in faeces and urine, respectively, and 7% and < 0.1% of the radioactive dose was recovered as unchanged avacopan in faeces and urine, respectively. These results suggest that the main route of clearance of avacopan is metabolism followed by biliary excretion of the metabolites into faeces, and that direct excretion of avacopan into urine or faeces via bile is negligible.

Special populations

Elderly

Population pharmacokinetic analysis found no significant effect of age (among adults) on the plasma exposure of avacopan; however, there were limited pharmacokinetic data in patients over 75 years of age in clinical studies. No dose adjustment is necessary for elderly patients (see section 4.2).

Hepatic impairment

The pharmacokinetic properties of avacopan have been examined in 16 subjects with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. When compared to normal controls, no pharmacologically relevant differences in exposure (mean ratios of C_{max} and AUC ≤ 1.3) of avacopan or its major metabolite M1 was observed; therefore, no dose adjustment is necessary (see section 4.2).

Avacopan has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) (see section 4.2).

Renal impairment

Based on population pharmacokinetic analysis, the plasma exposure of avacopan is similar between patients with renal impairment and healthy subjects. Therefore, no dose adjustment is necessary based on renal function (see section 4.2).

Avacopan has not been studied in patients with ANCA-associated vasculitis with an eGFR below 15 mL/min/1.73 m², who are on dialysis, in need of dialysis or plasma exchange.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.

Fertility and early embryonic development

Avacopan produced no effects on male or female reproductive performance (fertility) or early development in hamsters at oral doses equivalent up to 6.8-fold the clinical AUC.

Embryo-foetal development

Avacopan was not teratogenic when dosed orally to hamsters and rabbits. In hamsters, an increased incidence of skeletal variations (short thoracolumbar supernumerary rib) was observed at exposure equivalent to 5.3-fold the clinical AUC. In rabbits, avacopan caused maternal toxicity (adverse clinical signs and abortions), but no foetal toxicity at 0.6-fold the clinical AUC.

Pre- and post-natal development

Avacopan did not result in adverse effects in female offspring when administered in hamsters at exposures up to 6.3-fold the clinical AUC during gestation and through lactation until weaning. In males, there was a slight delay in preputial separation at 3.7-fold the clinical AUC. This isolated finding was considered to be of low toxicological significance and was not associated with any impairment of reproductive performance.

Analysis of avacopan plasma levels in the lactating dams and the plasma levels in nursing offspring showed the presence of avacopan, suggesting that avacopan is likely secreted into the milk of lactating hamsters.

Carcinogenicity

The carcinogenic potential of avacopan was evaluated in a 2-year study in both rats and hamsters. In male rats, a slightly increased incidence of C-cell thyroid adenoma was noted in avacopan-treated rats; this increase was not statistically significant, and the incidence was within the historical control range. Avacopan was not carcinogenic in hamsters, the pharmacologically relevant species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Macrogolglycerol hydroxystearate
Macrogol (4000)

Capsule shell

Gelatin
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Polysorbate 80

Imprinting ink

Black iron oxide (E172)
Shellac
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C in the original bottle in order to protect from light.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with polypropylene child-resistant closure and induction seal.
Pack sizes of 30 or 180 hard capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRANT

Vifor Pharma Asia Pacific Pte Ltd
20 , McCallum Street, #20-01
Tokio Marine Centre
Singapore 069046

8. PRODUCT REGISTRATION NUMBER

SINXXXXX

9. DATE OF FIRST AUTHORISATION

Date of first authorisation:XXXXXX

10. DATE OF REVISION OF THE TEXT

17 Dec 2024