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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004

Tavneos

Procedure number: EMA/REF/0000325221

INN/active substance: avacopan

Note:

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

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List of abbreviations

AAV	antineutrophil cytoplasmic antibody-associated vasculitis
AC	adjudication committee
AE	adverse event
ANCA	antineutrophil cytoplasmic antibody
AST	aspartate aminotransferase
AZA	azathioprine
BVAS	Birmingham Vasculitis Activity Score
C5aR1	complement 5a (C5a) receptor
CHMP	Committee on Human Medicinal Products (European Medicines Agency)
CI	confidence interval
CRO	contract research organisation
CSR	clinical study report
CYC	cyclophosphamide
DBL	data base lock
DILI	drug induced livery injury
DMP	data management plan
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
eTMF	electronic trial master file
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration (United States)
GC	glucocorticoid(s)
GCP	good clinical practice
GPA	granulomatosis with polyangiitis
ICH	International Council for Harmonisation
INR	International normalised ratio
IQR	interquartile range
IV	intravenous

KDIGO	Kidney Disease: Improving Global Outcomes
MAA	marketing authorisation application
MAH	marketing authorisation holder
MESI	medical event of interest
MMF	mycophenolate mofetil
MPA	microscopic polyangiitis
PASS	post-authorisation safety study
PMDA	Pharmaceuticals and Medical Device Agency (Japan)
PSUSA	periodic safety update report single assessment
QC	quality control
RTX	rituximab
RWE	real world evidence
SAP	statistical analysis plan
SmPC	summary of product characteristics
SoC	standard of care
SRAP	study results analysis plan
TMF	trial master file
US	United States
VBDS	vanishing bile duct syndrome
VDI	vasculitis damage index

1. Information on the procedure

In January 2026, the European Medicines Agency (EMA) became aware of new information, which raised questions regarding the data integrity of the ADVOCATE study, the pivotal trial supporting the marketing authorisation for Tavneos. The new information specifically pertained to the handling of the ADVOCATE study database prior to the regulatory approval of Tavneos. This raised serious questions as to whether amendments to the study data had taken place, whether such actions (if any) were consistent with the pre-specified protocol and statistical analysis plan for the study, and whether this new information could potentially impact the assessment of the results and the reliability of the ADVOCATE study that was previously conducted based on the information available to EMA at the time of the granting of a marketing authorisation for Tavneos by the European Commission (EC).

On 29 January 2026 the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the Committee for Medicinal Products for Human Use (CHMP) to assess the impact of the above concerns on the benefit-risk balance of Tavneos and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Tavneos (avacopan) is a centrally authorised medicinal product, which was granted a marketing authorisation in the European Union (EU) on 11 January 2022 based on an application in accordance with Article 8(3) of Directive 2001/83/EC.

Tavneos is an orally administered inhibitor of the complement 5a (C5a) receptor (C5aR1) and competitively inhibits the interaction between C5aR1 and C5a. The specific and selective blockade of C5aR1 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.

Tavneos, in combination with a rituximab or cyclophosphamide regimen, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). The recommended dose of Tavneos is 30 mg (3 hard capsules of 10 mg each) taken orally twice daily. The marketing authorisation holder (MAH) of Tavneos in the EU is Vifor Fresenius Medical Care Renal Pharma France.

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are the two main forms of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, which is a multisystem autoimmune condition that occurs due to production of anti-neutrophil cytoplasmic antibodies. The disease is characterised by generalised inflammation of small to medium sized blood vessels that can affect many different organ systems and commonly involves the kidneys. If left untreated, 80% of patients with GPA or MPA die within 2 years of disease onset and mortality is higher for patients with renal involvement.

In current clinical practice in the EU, in line with the 2022 European League Against Rheumatism (EULAR) recommendations for the management of ANCA-associated vasculitis, the following recommendation is included: "*Avacopan in combination with rituximab or cyclophosphamide may be considered for induction of remission in GPA or MPA, as part of a strategy to substantially reduce*

exposure to glucocorticoids" (Hellmich, 2024)[1]. In the Kidney Disease Improving Global Outcomes (KDIGO) 2024 clinical practice guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis (AAV), the following practice point linked to the induction of remission treatment is included: *"Avacopan may be used as an alternative to glucocorticoids. Patients with an increased risk of glucocorticoids toxicity are likely to receive the most benefit from avacopan. Patients with lower GFR may benefit from greater GFR recovery"* (ANCA Vasculitis Work Group, 2024)[2]. Based on the data provided by the MAH, it is estimated that approximately 2,410 patients in the EU currently receive avacopan treatment.

The marketing authorisation application (MAA) for Tavneos submitted by the applicant, Vifor Fresenius Medical Care Renal Pharma France, included one phase 3 clinical study (ADVOCATE, also known as Study CL010_168) and two supportive phase 2 clinical studies (CL002_168 and CL003_168). The ADVOCATE study (sponsor: ChemoCentryx) was considered the pivotal study for the assessment of the clinical efficacy of Tavneos in its therapeutic indication. In this study, avacopan+background therapy was non-inferior to prednisone+background therapy at week 26 (despite a lower dose of glucocorticoids in the avacopan arm) with respect to induction of remission, and superior to placebo+background therapy at week 52 for sustained remission. The absolute difference at week 52 was modest but statistically robust and of clinical relevance. On this basis, it was considered that the ADVOCATE study had met its primary objective, and that the efficacy of Tavneos in its therapeutic indication was established.

In January 2026, EMA became aware of new information which raised questions regarding the data integrity of the ADVOCATE study. The new information specifically pertained to the sponsor's handling of the ADVOCATE study database. This raised serious questions as to whether amendments to the study data had taken place, whether such actions (if any) were consistent with the pre-specified protocol and statistical analysis plan for the study, and whether this new information could potentially impact the reliability of the ADVOCATE study and the assessment of the results, previously conducted based on the information available to EMA at the time of the granting of a marketing authorisation for Tavneos by the EC.

On 29 January 2026, the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Tavneos, and to give its opinion on whether the relevant marketing authorisation should be maintained, varied, suspended or revoked.

In the context of the Article 20 procedure, the CHMP considered all available information and data concerning the data-handling of the ADVOCATE study, as well as all evidence supporting the benefit-risk balance of Tavneos. The MAH was requested to describe the handling of the database for the ADVOCATE study by the study sponsor prior to the regulatory approval of Tavneos in the EU. In addition, the MAH was invited to provide any further data in support of a favourable benefit-risk balance of their product in the approved indication, whether already provided at the time of the initial MAA or information that would have become available since the initial authorisation.

[1] Hellmich B, Sanchez-Alamo B, Schirmer JH, et al., 'EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update', Annals of the Rheumatic Diseases, Vol. 83, Issue 1, BMJ Publishing Group, London, 1 January 2024, pp. 30–47.
[2] Kidney Disease: Improving Global Outcomes (KDIGO) ANCA Vasculitis Work Group, 'KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis', Kidney International, Vol. 105, Issue 3 Supplement, Elsevier, New York, March 2024, pp. S71–S116.

2.2. Data on efficacy

2.2.1. ADVOCATE study

2.2.1.1. Study design

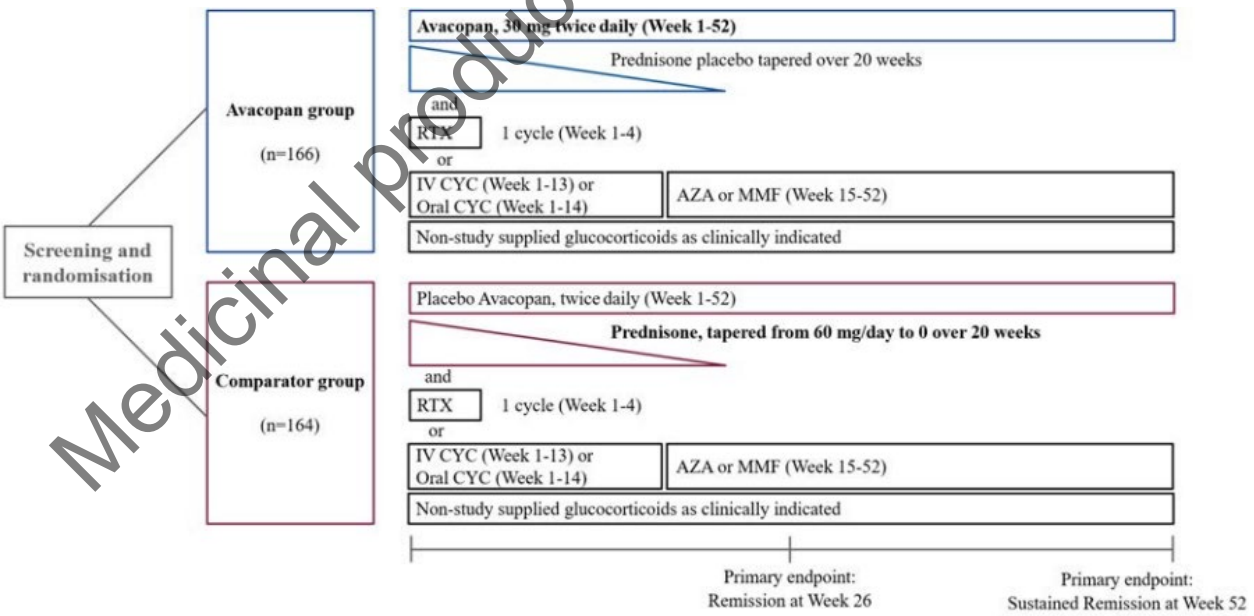
ADVOCATE (CL010_168) was a randomized, double-blind, active-controlled, phase 3 study to evaluate the safety and efficacy of avacopan in patients with ANCA-associated vasculitis treated concomitantly with rituximab or cyclophosphamide/azathioprine.

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).



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

Figure 1. ADVOCATE study schema

The first primary endpoint was remission at week 26, defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity), and no glucocorticoid (GC) use in the previous 4 weeks. The second primary endpoint was sustained remission at week 52, defined as remission at both weeks 26 and 52. 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: (1) non-inferiority at week 26, (2) non-inferiority at week 52, (3) superiority at week 52, and (4) superiority at week 26.

Important secondary endpoints were the GC toxicity index, BVAS remission at week 4, quality of life assessments, proportion of subjects with and time to relapse, change in estimated glomerular filtration rate (eGFR), reduction of proteinuria, and change in vasculitis damage index (VDI). None of these were multiplicity controlled.

The ADVOCATE study protocol established a blinded, independent adjudication committee (AC) to adjudicate BVAS scores and determine remission status and relapses. The adjudication committee's activities were governed by an adjudication committee charter (AC Charter). Additionally, the prespecified criteria and rules for adjudication regarding glucocorticoid use were, as stated in the version 1.0 of statistical analysis plan (SAP): *"Glucocorticoid use for purposes of assessing the primary endpoints are based on absence of glucocorticoid use, both study supplied and non-study supplied, for the 4 weeks prior to the endpoints at Week 26 and Week 52. Note that subjects are permitted to receive low doses of oral glucocorticoids (no more than 10 mg per day) for treatment of adrenal insufficiency and will be classified as responders for purposes of assessment of the primary endpoints if all other requirements for response are met".* These rules were later changed and reflected in the version 2.0 of the SAP (see 2.2.1.3.2.).

According to the clinical study report (CSR) submitted by the MAH as part of the MAA for Tavneos, the analysis of the efficacy endpoints was to be conducted when all randomized subjects completed at least the week 52 study visit. The database was frozen ('locked') on 20 November 2019 to conduct this analysis. This was the only database lock (DBL) described by the study sponsor in the CSR. Furthermore, the CSR indicated that treatment assignments for individual subjects remained blinded to the study team, investigators, and subjects until after the study database had been cleaned and locked.

2.2.1.2. Results of the ADVOCATE study as submitted in the marketing authorisation application (database lock - 20 November 2019)

The first primary endpoint, non-inferiority in BVAS remission at week 26, was achieved by 115/164 patients (70.1%) in the comparator group and 120/166 (72.3%) in the avacopan group (95% CI: -6.0, 12.8, p<0.0001 (non-inferiority) and 0.2387 (superiority)). The second primary endpoint, sustained remission at week 52, was achieved by 90/164 patients (54.9%) in the comparator group and 109/166 patients (65.7%) in the avacopan group (95% CI: 2.6, 22.3, p=<0.0001 (non-inferiority), 0.0066 (superiority)) (Table 1).

Table 1. Summary of primary efficacy results as submitted at the time of the MAA

	Comparator group (N=164)	**Avacopan group (N=166)**	**P-value for difference between groups[a]**
Primary endpoints			
Remission[b] at week 26, n (%)	115 (70.1)	120 (72.3)	<0.0001

Estimate of common difference in percentages	--	3.4	(non-inferiority) 0.2387 (superiority)
Two-sided 95% confidence interval for common difference	--	-6.0, 12.8	
Sustained remission[c] at week 52, n (%)	90 (54.9)	109 (65.7)	<0.0001 (non-inferiority) 0.0066 (superiority)
Estimate of common difference in percentages	--	12.5	
Two-sided 95% confidence interval for common difference	--	2.6, 22.3	

[a] One-sided P-values.
[b] Remission was defined as having a BVAS of zero at week 26 and not having received any glucocorticoids for ANCA-associated vasculitis within the 4 weeks prior to the week 26 visit.
[c] Sustained remission was defined as remission at week 26 and remission at week 52 (BVAS of 0 and not taking glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 52) and without relapse between week 26 and 52.
n=number of subjects with evaluable data; N=number of subjects in the treatment groups (Intent-to-Treat Population).

In the European Public Assessment report (EPAR) for Tavneos (EMA/708044/2021 Corr.1) adopted by the CHMP in the context of its scientific assessment of the MAA for this medicinal product, the CHMP noted that mixing of active and placebo, and placebo only comparators after the induction treatment regimens in the rituximab and cyclophosphamide strata, compromised the interpretation of the joint treatment effect estimate; especially since the obtained results in the two strata were different: the observed superiority in the joint analysis was driven by the rituximab stratum (Table 2).

Table 2. Remission at week 26 and sustained remission at week 52 by background treatment as submitted at the MAA

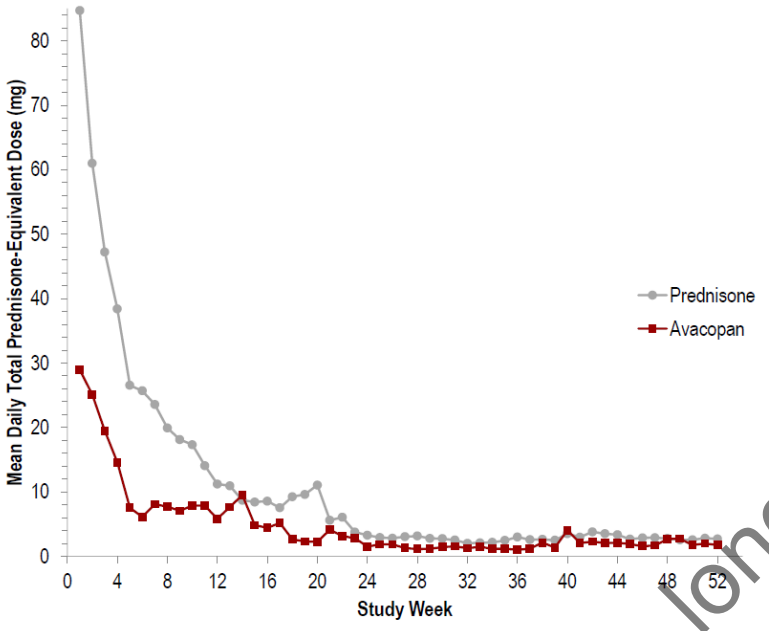
	Avacopan n/N (%)	**Comparator n/N (%)**	**Difference in %, 95% CI[a]**
Remission at week 26			
Patients receiving intravenous rituximab	83/107 (77.6)	81/107 (75.7)	1.9 (−9.5, 13.2)
Patients receiving intravenous or oral cyclophosphamide	37/59 (62.7)	34/57 (59.6)	3.1 (−14.7, 20.8)
Sustained remission 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.

Key secondary endpoints

In its assessment of the MAA for Tavneos (EPAR EMA/708044/2021 Corr.1), the CHMP further noted that the reduction in cumulative steroid dose between the active and control arms was considered clinically meaningful. The proportion of patients using GC beyond week 26 was 27.1% in the avacopan group vs 39% in the comparator group. There was an additional endpoint of cumulative steroid dose

that was reported to be 3846.9 mg in the comparator group and 1675.5 mg in the avacopan group. However, as confirmed by the CHMP in the above-mentioned EPAR, 1) a significant amount of steroids was needed also in the avacopan group, 2) in the comparator group, the majority of GC use was due to the protocol-mandated prednisone course that ended at end of week 20, and 3) the use of GCs was similar between study arms from end of week 26 to week 52 (Figure 2).



Source: Tavneos Summary of product characteristics (SmPC), section 5.1.

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

In patients with renal disease, the mean eGFR increase from baseline to week 52 was 4.1 mL/min/1.73 m^2 in the comparator group and 7.3 mL/min/1.73 m^2 in the avacopan group. The CHMP commented in the EPAR (EMA/708044/2021 Corr.1), that this difference in eGFR of around 3 mL/min/1.73 m^2 between the study arms was small, taking in account baseline of 56.6 ml/min/1.73 m^2 in the RTX stratum and 42.9 ml/min/1.73 m^2 in the CYC/AZA stratum. It was further noted that the secondary endpoint analysis on change in eGFR was not conducted between randomised groups, since change in eGFR was only compared between subjects who had renal disease at baseline.

Regarding other secondary endpoints, the CHMP further noted, during its assessment of the MAA for Tavneos, that 1) health-related quality-of-life increased markedly in both treatment arms during the study, and the differences in improvement between arms were small, 2) the incidence of relapse after remission had been achieved at week 26 was numerically higher in the comparator group (14 of 115 subjects, 12.2%) than in the avacopan group (9 of 120 subjects, 7.5%), and 3) regarding vasculitis damage index, both treatment groups showed a similar mean increase in least squares mean change in VDI from baseline to week 52 (1.17 in the avacopan group and 1.15 in the comparator group).

2.2.1.3. Data integrity and reliability

2.2.1.3.1. Sequence of key events related to data handling

Following the emergence of information raising concerns regarding the data handling, at the start of the present Article 20 referral procedure, the MAH was requested to describe in a detailed, clear, and precise manner the handling of the database for the ADVOCATE study prior to the granting of the MA for Tavneos in the EU. Based on the MAH's response, the sequence of key events can be summarised as follows:

1) The study database was cleaned in accordance with pre-specified procedure before DBL.
2) The database was locked on 05 November 2019 and unblinded in accordance with the Study Results Analysis Plan (SRAP).
3) Two of the unblinded sponsor-affiliated individuals (ChemoCentryx) reviewed unblinded efficacy results (provided by the clinical research organisation [CRO] Medpace on 08 November 2019) and learned that the primary endpoint of sustained remission at week 52 had failed and was not statistically significant (one-sided p-value 0.0513).
4) After seeing that the primary endpoint had failed, the sponsor initiated a new quality control (QC) of the adjudicated data.
5) The sponsor then reviewed unblinded subject level data, including treatment assignment and endpoint outcomes, and identified 9 subjects whose primary endpoint they thought were not consistent with pre-specified protocol definitions. They reran the statistical analysis of the primary endpoint on 13 November 2019 using revised remission status at week 26 and week 52 and found that superiority regarding sustained remission at week 52 could now be demonstrated.
6) After learning that re-adjudication of the 9 subjects from 'not in remission' to 'in remission' could flip the outcome of the study, the sponsor contacted the CRO who sent the patient profiles and original adjudication forms of these 9 subjects to the AC with a re-adjudication request. On 15 November 2019, the AC chair confirmed that they had re-adjudicated the subjects as requested. For sustained remission at week 52 (the primary efficacy endpoint demonstrating superiority in the MAA), 5 subjects had changed remission status all favouring avacopan (Table 3).

Table 3. Subjects with change in adjudication after initial database lock (05 November 2019)

Treatment	Week 26 remission (N=8)	Week 52 sustained remission (N=5)
Prednisone (N=164)	3 subjects	0 subjects
Avacopan (N=166)	5 subjects	5 subjects

7) After performing the post data lock change with the re-adjudicated remission statuses, the database was locked for a second time on 20 November 2019. The primary efficacy analysis was rerun and generated statistically significant results that were included in the CSR. These were the results submitted to EMA as part of the MAA for Tavneos to support efficacy (see section 2.2.1.2.). The initial DBL on 05 November 2019, and the unblinded re-adjudication performed afterwards, were not mentioned in the dossier submitted in the MAA. On the contrary, the CSR explicitly stated that the unblinding process outlined in the protocol had been followed. Lastly, as standard, the sponsor reported in the CSR that the study was

conducted in accordance with the International Council for Harmonisation (ICH) guidelines for good clinical practice (GCP), the principles of the Declaration of Helsinki, and applicable regulatory requirements.

The MAH put forward that the incorrect application of the predefined adjudication criteria in the 9 subjects led to an initial misclassification of remission data in these subjects and that re-adjudication was justified given these errors. According to the MAH, the reasons for the re-adjudications fell into the following categories:

a) how GC use for reasons unrelated to the treatment of AAV was accounted for in the adjudication,

b) how visit windows were applied in the adjudication, and

c) correction of a manual error.

Six (6) of the 9 subjects that were re-adjudicated after unblinding had a BVAS score of 0 but were initially classified as 'not in remission' due to GC use for other reasons than AAV. Other reasons included arthromyalgia, gout, lower respiratory tract infection, adrenal insufficiency, and arthralgia. It is noted that the subjects with lower respiratory tract infection and arthralgia were treated with 40 mg/day of glucocorticoids, which is more than the 10 mg/day prespecified as being 'low dose'.

Three (3) of the 9 subjects were re-adjudicated because they initially were mistakenly classified as not in remission because of missing data due to not attending their scheduled visit at week 26 although they had an unscheduled visit that occurred within the pre-defined permissible window for week 26 visits. According to the pre-specified criteria, subjects could be deemed 'in remission' if they had an unscheduled visit with BVAS score 0 within the permissible window (day 149 to day 228).

One (1) subject was re-adjudicated because of an apparent manual error (had no GC use and BVAS of 0 but was marked as not in remission).

Of note, 1 subject was re-adjudicated both because of an unscheduled early termination visit and GC use for other reason than AAV.

2.2.1.3.2. GCP compliance

The review of the information and data provided by the MAH identified several issues of GCP non-compliance in the ADVOCATE study. The main identified aspects of GCP-non-compliance are:

- A Study Results Analysis Plan (SRAP) prepared after the blinded data review meeting and 1 day before DBL mentions a QC review to be performed based on topline results by 3 named unblinded sponsor representatives. However, there is no documentation presented outlining the unblinded QC review performed by the sponsor representatives.

- At the request of the unblinded sponsor representatives performing the QC, a rerun of superiority tests at week 26 and week 52 was performed by an unblinded consultant statistician using modified response data for 11 patients to impute the current response data. The sponsor was informed about the *p*-value of the rerun. The unblinded consultant statistician's access to unblinded data and the activity to rerun superiority tests was not described in the SRAP.

After having seen the analysis results of the rerun, the list was reduced from 11 to 9 patients. Two (2) patients from the initial list were either deleted or imputed as non-responders, although the rationale for these changes could not be confirmed. Subsequently, a meeting was held between the sponsor and the CRO to initiate re-adjudication by the AC. There are no meeting minutes available from this

meeting. A post-DBL change approval form was signed, also this after the analysis results of the rerun were available. Thus, decisions to proceed with re-adjudications and data modifications were taken following the reruns of statistical analysis.

- The rules for permitted vs non-permitted concomitant GC treatment and thus classification of responders for purposes of assessment of the primary endpoints were changed late during the study and only in the SAP. The amended SAP (version 2.0) was dated after the blinded review meeting had been performed and approximately 1 week before DBL. The change had not been described in a protocol amendment and was thus not assessed by authorities, where relevant. The new rule as per SAP version 2.0 is described in the CSR, but it is not described as something that was changed compared to the protocol. The change to allow for a broader use of GCs affected 4 of the re-adjudicated cases, all on avacopan. From a Trial Master File (TMF) review performed by the MAH, it is not clear how those rules were communicated to the AC. It thus remains unclear if any action, such as final AC review, was taken due to the changed rules before the initial DBL. No such information was disclosed. Furthermore, the MAH described how the CRO on 24 October 2019 sent information to the sponsor regarding 4 patients and a request for review of remission status. The sponsor agreed that the patients could be considered in remission/sustained remission, but no corresponding request for re-adjudication was made prior to DBL. Instead, the issue with the above-mentioned patients was brought up again after the DBL following the unblinded review, and then re-adjudication was requested. This further points to an inconsequent application of rules affecting the primary endpoint.

- The AC charter states "*There will be no blinded BVAS-listing for review after un-blinding*" so it was not a preplanned option to perform re-adjudications following DBL and unblinding. There were thus no planned measures around how blinding would be maintained in such a situation. From the communication provided by the MAH in the context of the present Article 20 referral procedure, it is noted that there were verbal discussions between the unblinded sponsor representative and the AC Chair regarding re-adjudication and how to assess concomitant GC treatment and that the re-adjudications were solely performed by the AC Chair without involvement of other AC members. Thus, the robustness of the blinding during re-adjudications cannot be guaranteed.

- The initial DBL and unblinding, the re-classification of responders for purposes of assessment of the primary endpoints and the re-adjudications performed for a subgroup of patients, were not described in the CSR. Thus, events critical for data integrity were not disclosed and this is viewed as an intentional misrepresentation of data affecting the primary outcome of the study.

- According to the MAH, there were no changes made to the data in electronic data capture (EDC) following the initial DBL other than the re-adjudication results and one adverse event (AE)-coding following unblinding, however, based on the information submitted, it cannot be verified that there were no additional changes made.

The TMF review report describes that the EDC audit trail was reviewed in depth for a sample of 4 patients (same patients as mentioned above) and found accurate. This review was conducted up to the initial DBL (05 November 2019). The TMF review report mentions queries from adjudicators and sponsor, but it is not described which aspects were queried and whether these queries resulted in any change of primary endpoint data in the EDC by the investigators, and thus the potential impact on the results. There was no review presented of the audit trail as regards the primary endpoint data for all patients and across the whole study, thus no further information was provided regarding robustness of the data or any potential trends in data changes over time for the primary endpoint data.

- There are uncertainties regarding the AC processes that were followed.

Firstly, there is an apparent lack of independence of the AC. The chair, co-chair and all other AC members, except one, were principal investigators of the study. It is not sufficient that the adjudication of the results of the subjects from their own respective study sites where they were investigators was performed by other members of the AC. The other members were also investigators in the study and as such not independent. In the CSR, the following is stated: *"All BVAS data entered by the Investigators were adjudicated by an Adjudication Committee (AC), blinded to treatment assignment. This was done to ensure consistency across all study centers in scoring. The AC consisted of ANCA-associated vasculitis disease experts who adjudicated the data according to a charter*"; but similar to the protocol, the CSR does not mention that the AC consisted of study investigators.

The MAH acknowledged that there is limited clarity in the AC charter and other study documents regarding the activities of the AC. It is further stated in the TMF review report that there was lack of clarity regarding communication channels between sponsor, AC and CRO.

Secondly, the AC charter does not include the rule based on which the adjudication was expected to be conducted, for example related to GC dose. Hence, it appears that the rule could have been changed without any trace in official study documentation. The MAH clarified that there were instructions in study documents and reference to the protocol in the AC charter, although one relevant section was not cited (Section 12.6.2.3 stating "*Replacement glucocorticoids for adrenal insufficiency should not exceed 10 mg prednisone equivalent per day*"). In addition, as commented in TMF review done by MAH, "*while the rules for unscheduled visits were specified within the SAP, the AC was not always provided clear instructions to determine remission or sustained remission for subjects that had unplanned visits which would satisfy 26 or 52 week windows*". The results of the TMF review further comments that "*specific adjudication rules were documented in the SAP (e.g, used on unscheduled visit, visit window, GC use handling for other conditions like allergic reaction), although it is unclear how those rules were communicated to the AC*".

The AC charter does not include a transparent description of the data that was used as the basis of the adjudication and whether these data is based on case report form entries by the sites or whether it was processed in the interim by the Sponsor. This point applies in particular to concomitant non-study supplied glucocorticoid medications. The MAH agreed that certain aspects of the study documents were less explicit, especially those relating to GC use. The MAH also confirmed that the data was specified in the AC charter and data provided to the AC were sourced from the EDC.

The Data Management Plan (DMP) was updated very late (v5 on 30 Oct 2019) to include e.g. data cleaning step for adjudication. Therefore, it was unclear how the data sent to the adjudication had been quality controlled before, and updates or addition of final serious adverse event (SAE) reconciliation leaving only approximately 5-6 days to resolve any discrepancies before the DBL. The MAH clarified that SAE reconciliation had been included in the DMP from the beginning of the trial. However, the statement that final SAE reconciliation would occur prior to DBL (week 52 and week 60) to ensure that all discrepancies had been resolved was introduced only 5–6 days before DBL in the last DMP update. It remains unclear how data cleaning and QC processes were applied to the data submitted for adjudication prior to 30 October 2019 as it was introduced in the DMP on that date. In addition, other important study documents were updated late such as the AC charter and SAP (AC charter addendum 8 Oct 2019 and SAP v2 28 Oct 2019). The MAH briefly clarified the changes done and noted that SAP was updated before the study was unblinded and it is not uncommon to update SAP prior to primary analysis DBL (i.e. 8-9 days before, including e.g. clarification for glucocorticoid use for purposes of assessing the primary endpoints).

- The handling of prohibited and concomitant medications (the use of GC) is unclear, and it cannot be excluded that it may be subject to bias. The MAH clarified the intention of the used spreadsheets i.e. to

determine the study participants to be excluded from the Per Protocol Population. However, it remains unclear how these were created, including the source of the underlying information, how traceability was ensured, and what was the particularly prominent role of the sponsor's former chief medical officer in the process.

2.2.1.4. Results of the ADVOCATE study pre-readjudication (initial database lock – 05 November 2019).

The statistical analysis of the primary endpoints based on the remission status registered at initial DBL (as reviewed by the sponsor before deciding to perform additional QC and eventually request re-adjudication) of 9 subjects is shown in Table 4. These data were not included in the CSR or elsewhere in the dossier submitted as part of the MAA for Tavneos, but demonstrate that the study failed to show superiority of avacopan both in remission at week 26 (95% CI: -8.0, 11.4, p=0.3646) and in sustained remission at week 52 (95% CI: -1.7, 18.5, p=0.0513). Of note, based on the 05 November 2019 data, superiority of avacopan for sustained remission was not statistically significant in either of the rituximab or cyclophosphamide strata (although numerically higher remission rate for avacopan in the rituximab stratum: 67.3% in the avacopan arm and 56.1% in the control arm, 95% CI -1.7, 24.2).

Table 4. Summary of primary efficacy results as in the initial database lock (05 November 2019)

	Comparator group (N=164)	**Avacopan group (N=166)**	**P-value for difference between groups[a]**
Primary endpoints			
Remission[b] at week 26, n (%)	112 (68.3)	115 (69.3)	<0.0001 (non-inferiority) 0.3646 (superiority)
Estimate of common difference in percentages	--	1.7	
Two-sided 95% confidence interval for common difference	--	-8.0, 11.4	
Sustained remission[c] at week 52, n (%)	90 (54.9)	104 (62.7)	<0.0001 (non-inferiority) 0.0513 (superiority)
Estimate of common difference in percentages	--	8.4	
Two-sided 95% confidence interval for common difference	--	-1.7, 18.5	

[a] One-sided P-values
[b] Remission was defined as having a BVAS of zero at week 26 and not having received any glucocorticoids for ANCA-associated vasculitis within the 4 weeks prior to the week 26 visit.
[c] Sustained remission was defined as remission at week 26 and remission at week 52 (BVAS of 0 and not taking glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 52) and without relapse between week 26 and 52.
n=number of subjects with evaluable data; N=number of subjects in the treatment groups (Intent-to-Treat Population).

2.2.1.5. Post-hoc analysis

The MAH provided primary endpoint analyses after exclusion of the 9 subjects who were re-adjudicated. These results were consistent with the originally submitted endpoint analyses (i.e. non-inferiority for remission at week 26 [p<0.0001] and sustained remission at week 52 [p<0.0001] and superiority for sustained remission at week 52, one-sided *p*=0.013).

Additionally, the MAH provided a post hoc programmatic evaluation (without AC assessment) of remission at 26 weeks and sustained remission at 52 weeks. Regardless of using the initial adjudicated data (05 November 2019 DBL) or the data from programmatic identification of remission status, the results show non-inferiority of avacopan for remission at week 26 and sustained remission at week 52 but failed to show superiority for both these primary efficacy endpoints.

Lastly, the MAH presented a summary of the key results from a retrospective re-adjudication conducted by Duke Clinical Research Institute Clinical Events Classification group. In this re-adjudication, avacopan demonstrated non-inferiority to prednisone for remission at week 26 (67.1% vs 68.1%; difference 2.2%, 95% CI −7.5 to 11.9) and sustained remission at week 52 (61.4% vs 52.4%; difference 9.8%, 95% CI −0.3 to 19.9), with all lower confidence bounds remaining above the prespecified non-inferiority margin of −20%. Non-inferiority was supported by statistically significant one-sided p-values (<0.0001), while superiority was not demonstrated at either week 26 (p=0.3301) or week 52 (p=0.0282) at the prespecified threshold (0.025). Pre-specified sensitivity and subgroup analyses were consistent with the results of the 05 November 2019 DBL. Concordance analyses demonstrated agreement between adjudications performed by the Duke Clinical Research Institute Adjudication Committee and prior assessments, with agreement rates of 93.9% and 92.7% and Cohen's kappa values of 0.86 and 0.85 for week 26 and week 52 endpoints, respectively.

2.2.2. Additional studies

As described in the EPAR (EMA/708044/2021 Corr 1), the two phase 2 studies (CL002_168 and CL003_168) included a total of 109 patients. The first study, CL002_168, met its primary endpoint as avacopan, with or without reduced dose of prednisone, was non-inferior to the comparator (full dose prednisone) regarding BVAS response at day 85. There were, however, uncertainties regarding the statistical analyses affecting the reliability of these results. After 12 weeks of follow-up, the response rates for both avacopan groups were inferior to the comparator, questioning the efficacy of avacopan over time. There was also a concern on the clinical relevance of the primary endpoint, as there is a general consensus in clinical guidelines that the aim of vasculitis induction therapy is not the induction of response, but rather the induction of remission. For the secondary endpoint of BVAS remission, avacopan with or without low-dose prednisone appeared inferior to the comparator (Hellmich, 2024; Biddle, 2025; Santos Moreno, 2025; Chung 2021)[3,4,5,6]. The second phase 2 study, CL003_168, was primarily a safety study and did not provide additional supportive efficacy data for the proposed avacopan dose regimen.

In addition to the phase 2 studies part of the clinical development and presented as part of the MAA for Tavneos, during the Article 20 procedure, the MAH presented multiple real-world evidence (RWE) studies reported in the literature, including cohort studies (such as the Libra and Birmingham studies), case series and case reports, as well as a post-authorisation safety study (PASS) AVACOSTAR and a post marketing surveillance study in Japan. A meta-analysis of these studies reported in a recently

[3] Hellmich B, Sanchez-Alamo B, Schirmer JH, et al., 'EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update', Annals of the Rheumatic Diseases, Vol. 83, BMJ Publishing Group, London, 2024, pp. 30–47.
[4] Biddle K, Jade J, Wilson-Morkeh H, Adikari M, Al Yaghchi C, Anastasa Z, et al. British Society for Rheumatology Guideline Steering Group, 'The 2025 British Society for Rheumatology management recommendations for ANCA-associated vasculitis', Rheumatology, Vol. 64, Issue 8, Oxford University Press, Oxford, 1 August 2025, pp. 4470-4494.
[5] Santos Moreno P, García Salinas R, Caballero Uribe C, et al. 'Pan American League of Associations for Rheumatology recommendations for the management of rheumatoid arthritis', The Lancet Rheumatology, Vol. 8, Elsevier, London, 2025, pp. e53–e65.
[6] Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. '2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis', Arthritis Care & Research, Vol. 73, Issue 8, Wiley, Hoboken, NJ, 1 August 2021, pp. 1088–1105.

published systematic literature review (Berke et al. 2025) was also presented. The most relevant studies are summarised below.

2.2.2.1. AVACOSTAR (CS-AVA-2022-0016)

AVACOSTAR is an ongoing observational non-interventional PASS to evaluate the incidence of medical special events of interest in patients with AAV treated with avacopan. Among the secondary endpoints, this study also included some measures of avacopan effectiveness, including change in laboratory abnormalities (eGFR) over time and patterns of GC use in a real-world cohort. The study is expected to be completed by 2030. As of the interim data cut-off (11 September 2025), a total of 513 subjects were enrolled in the study, of which 504 were included in the full analysis set. Of these, 254 subjects were included in the avacopan group, and 250 subjects were included in the non-avacopan standard of care (SoC) arm. During the first induction period (up to 6 months after treatment start), all subjects received either rituximab and/or cyclophosphamide. Rituximab alone was administered to 49.6% of the avacopan group and 57.2% of the SoC group. Cyclophosphamide alone was used in 15.4% and 28.8% of subjects, respectively. Glucocorticoids were used by 83.5% of subjects in the avacopan group and 84.0% of those in the SoC group. The proportion of GC-free subjects (defined as being GC-free during the 3-month period preceding the timepoint) in the avacopan group vs non-avacopan SOC at 6 months was 62.8% vs 27.5% and 71.6% vs 37.9% at 12 months.

Kidney function was moderately impaired at baseline in both groups in AVACOSTAR. The eGFR improved over time in both groups, with a trend toward slightly greater increases in the avacopan group over the first 18 months—though later timepoints are limited by sparse data. At Month 6, mean eGFR improvement was 7.0 (14.8, n=168) mL/min/1.73 m² in the avacopan group versus 5.6 (16.7, n=137) in the SoC group. By month 12, improvements were 9.1 (15.0, n = 136) and 6.7 (17.7, n=92), respectively.

2.2.2.2. Paediatric study (EMA-0020230PIP01016-MO7, Study 14)

This is an ongoing phase 3, open-label, uncontrolled single-arm study to evaluate avacopan in combination with a rituximab or a cyclophosphamide-containing regimen in children from 6 years to < 18 years of age with active AAV. The study is expected to be completed by 2028. Background and concomitant medications included systemic GCs (prednisone or prednisolone in most patients, with tapering over time). Patient profiles of 16 enrolled subjects (10 subjects completed through week 26 and 2 subjects through week 52) were available.

2.2.2.3. Post-marketing real-world evidence (the LIBRA study and the Birmingham study)

<u>The LIBRA study</u>

This study evaluates the real-world comparative effectiveness of avacopan combined with SoC vs. SoC alone in United States adults with newly diagnosed or relapsing AAV. The LIBRA study has a retrospective cohort design that incorporates a prevalent new-user approach and sequential nested trial emulations utilising RWE data from two closed-claim databases.

The interim analysis report was available, in which one out of two prespecified RWE data sources was used: the Optum Market Clarity database (n ~197 million patients). The study period was 01 Oct 2015 to 30 Jun 2025. The interim analysis included 183 avacopan + SoC patients (each contributing to one index treatment episode, respectively) and 2,103 SoC patients (who contributed to 4,096 index treatment episodes in total). Index was defined as date of first avacopan claim, or date of first claim

for RTX/CYC or date of meeting a nephrologist or rheumatologist, respectively. A patient in the SoC arm could contribute more than one treatment episode if study entry criteria were repeatedly met.

Primary endpoints according to the study protocol v. 2.0 (dated 7 Apr 2026) were 1) time to first relapse, 2) glucocorticoid exposure expressed as the 30-day average prednisone-equivalent daily dose (PEDD) ≤7.5 mg at 90, 120, 180, 270, and 365 days post-index, and 3) incidence of major adverse kidney events (MAKE) within 12 months.

Based on the interim analysis report of the LIBRA study (dated 15 May 2026), the hazard ratio for time to first relapse between avacopan + SoC vs. SoC alone was 0.79 (95% CI: 0.58-1.10; weighted estimate). The reduction in GC exposure in patients treated with avacopan was modest. At day 120 post-index (i.e. at 1 out of 5 prespecified post-index timepoints), there was a slightly higher proportion of patients in the avacopan + SoC arm, compared to the SoC arm, achieving prednisone-equivalent daily dose ≤7.5 (Risk difference=9.9, 95% CI: 0.3-31.0). The incidence of major adverse kidney events was not quantified. Furthermore, the study results suggest no severe hepatotoxicity/drug-induced liver injury (DILI) or serious hypersensitivity reactions among patients treated with avacopan.

The Birmingham study

This was a retrospective cohort study in the United Kingdom that included a total of 126 patients with newly diagnosed or relapsing AAV. Seventy (70) of the patients in the cohort were treated with avacopan (+ protocolised minimal GC regimen alongside standard induction therapy RTX/CYC consisting of two weeks of oral GC). The comparative cohort consisted of 56 GC-treated patients. Dialysis-dependent patients were excluded.

The Birmingham study results presented are based on a study abstract (Azm Ul Hussain, 2026)[7]. No primary endpoint(s) were formally defined. The results do not imply differences in sustained remission (defined as achieving initial remission, maintaining a state of remission [BVAS of 0 and ≤5mg prednisolone for the preceding four weeks] at 12 months, and no clinical relapse during the intervening period) in the avacopan and GC-group, respectively. Furthermore, no differences were observed between the groups in relation to relapse-free survival at 12 months (nominal p=0.28). However, there were some indications of a lower cumulative oral prednisolone dose at 12 months in the avacopan group.

2.2.2.4. Ongoing randomised controlled trial on efficacy (AVASET)

A post-marketing commitment to perform a new study to evaluate safety and efficacy of avacopan was required by the U.S. Food and Drug Administration (FDA) as a condition for the initial approval of the medicinal product in the United States to evaluate safety outcomes, including hepatotoxicity, DILI), and serious hypersensitivity reactions. The ongoing study (PMR 4155-1, or AVASET) is also assessing efficacy outcomes (remission, sustained remission, relapse and quality of life) and is expected to enrol approximately 300 patients and have a duration of at least 5 years. The currently expected completion date is 2036. No data from this study is available.

2.2.2.5. Post-marketing surveillance data from Japan

This post-marketing surveillance study in Japan has been ongoing since June 2022. As 26 September 2025, a total of 448 patients, including those with active (325 patients) and non-active disease (123 patients), were included in the interim effectiveness analysis. By one year after starting

[7] Ul Hussain A, et al., 'Remission induction for ANCA-associated vasculitis with avacopan and minimal steroid dosing', UK Kidney Week 2026, UK Kidney Association, United Kingdom, 2026, Abstract 442.

avacopan, 8.5% of patients (38 of 448) experienced a relapse, while 410 patients remained relapse free. Among those patients with active disease at the time of avacopan initiation, the disease was no longer active for 185/244 patients (75.8%) at 6 months and 144/177 patients (81.4%) at 1 year.

In a population of 131 patients with active MPA or GPA who received avacopan as remission-induction therapy, whether at initial onset of disease or at relapse, kidney function, as measured by eGFR, remained generally stable over the course of 1 year. Patients with severely impaired renal function at baseline (eGFR <30 mL/min/1.73 m²) experienced the most notable change in eGFR, showing a gradual improvement from approximately 16 ml/min/1.73 m^2 at baseline to around 26 mL/min/1.73 m² over 12 months. Twenty-seven (27) patients who received avacopan after insufficient response to prior induction therapy and had eGFR data, remained generally stable throughout one year of avacopan treatment.

2.2.2.6. Meta-analysis (Berke et al. 2025)

A meta-analysis by Berke et al. was reported in a recently published systematic literature review, which identified 16 real-world studies (inclusion criteria: adults with GPA or MPA, minimum 5 patients included, at least 2 weeks of treatment, in English) comprising 447 patients evaluating the clinical outcomes of avacopan in patients with AAV (Berke, 2025)[8]. All studies were uncontrolled. The authors compared efficacy and safety outcomes reported in these studies with those of the main trial. Key endpoints included clinical remission and incidence of adverse events. The pooled remission rate at 6 months was 0.89 (95% CI: 0.84–0.93) (9 studies reported this endpoint), based on 215 patients, and 0.87 at 12 months (95% CI: 0.80–0.91) (7 studies reported this endpoint) based on 150 patients. As part of induction therapy, 61% of patients received pulse corticosteroids. Rituximab was used in 54% of cases, cyclophosphamide in 5%, and 32% received a combination of rituximab and cyclophosphamide. Complete steroid withdrawal rates varied widely, from 0% to 100%, with an average of 59% with cumulative GC dose ranging from 700-3,090 mg.

2.2.3. Discussion on efficacy

The data reviewed in the context of the present Article 20 referral procedure documents the handling and manipulation of the primary efficacy endpoint data of the ADVOCATE study. In summary, after reviewing unblinded efficacy data following an initial DBL (05 November 2019), the sponsor found that superiority at week 52 had not been demonstrated. Subsequently, 9 patients were re-adjudicated with knowledge of treatment outcomes, and reanalysis of the primary endpoint changed the result from non-significant to statistically significant. After performing the post-data lock change, the database was locked for a second time on 20 November 2019. These were the results submitted to EMA as part of the MAA for Tavneos to support efficacy.

This manipulation of the data of the ADVOCATE study, together with the lack of transparency and misrepresentation of the data handling process in the CSR used for the MAA for Tavneos, represent a serious breach of the ICH guidelines on GCP (e.g. ICH E6 Good Clinical Practice and ICH E9 Statistical Principles for Clinical Trials). Accordingly, the results from said study cannot be relied upon to demonstrate the clinical efficacy of Tavneos.

At start of the present review, the MAH recognised that the process leading to the identification of adjudication errors, and the timing in which it was conducted, included deviations from study-related

[8] Berke I, Keller F, Untersulzner C, et al., 'Systematic Review of Efficacy and Safety of Avacopan in Real-World Clinical Practice', Kidney International Reports, Vol. 11, Issue 4, Elsevier, New York, 2025, Article 103753.

guiding documents and did not appropriately adhere to ICH GCP guidelines. However, the MAH has presented two arguments in support of the reliability of the study results.

As a first claim, the MAH argued that the re-adjudication process followed was considered justified. Based on the review of the patient level data and the adjudication rules and endpoint definitions, it is not agreed that errors were made by the AC at the time of the original adjudications. Rather, it appears that the AC was not provided with all details necessary to conclude on remission (week 26) and sustained remission (week 52) according to what sponsor representatives retrospectively claimed to be the correct conclusions. The precise definition of the primary variable is critical and should be prespecified in the protocol, as it will be used in the statistical analysis (as per ICH E9). Failure to do so can impact the reliability of the study.

Regardless of the claim of the MAH that the re-adjudication was justified, the analysis of the data conducted after unblinding must be regarded as a post-hoc analysis initiated by unblinded personnel who had access to endpoint results that showed a failure to demonstrate superiority. Consequently, Type I error control of the ADVOCATE study can no longer be considered maintained, which negatively affects the confidence on the study results and the reliability of the study.

As a second claim, the MAH has argued that the data from the initial DBL, before the unblinding and re-adjudication, are compliant with GCP and that could therefore be relied upon to demonstrate the positive benefit-risk balance. In this respect, it bears noting that the impact of the above-explained GCP breach cannot be isolated to certain data of the study. The substantial failure to adhere to GCP rules for clinical research, i.e. ethical, scientific and quality standards, which evidently occurred in the period following the initial DBL, points to a general and unsound quality culture within the organisation(s) involved in the study conduct. As such, the GCP non-compliance undermines the integrity of data from the earlier part of the study as well, as said integrity cannot be guaranteed considering that the data is part of the same non-GCP compliant study and was managed by the same parties, mainly the sponsor and service provider.

The MAH also informed EMA that their staff were copied on historical correspondence exchanged between the sponsor and the MAH for the medicinal product in Japan concerning aspects of the Pharmaceuticals and Medical Devices Agency (PMDA) inspection in June 2021. This correspondence indicates that staff from the MAH in the EU had visibility of certain elements of the inspection discussions, including matters relating to re-adjudication and the initial DBL. The foregoing further shows a lack of transparency in trial-related communications, particularly given that the availability of this information was relevant to understanding access to unblinded data, trial decision-making, and the maintenance of data integrity.

According to the EMA document 'Points to consider on application with 1. meta-analyses; 2. one pivotal study' (CHMP/EWP/2330/99), when efficacy is supported primarily by a single pivotal study, the evidence is expected to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency. For the reasons explained above, the ADVOCATE study no longer fulfils these expectations and, therefore, cannot be relied upon.

Taken together, the serious breach to GCP with multiple aspects of non-compliance has direct impact on the integrity of the whole data and on the reliability of the results of the pivotal ADVOCATE study.

Further to the above, even if the results based on the initial DBL of 05 November 2019 were to be considered reliable as claimed by the MAH, these results showed that non-inferiority could be demonstrated for both remission at week 26 and sustained remission at week 52, but failed to demonstrate superiority at either timepoint (one-sided p-values 0.3646 and 0.0513, respectively).

Importantly, at the time of the assessment of the MAA for Tavneos, and as reflected in the EPAR (EMA/708044/2021 Corr 1), the demonstration of superiority at week 52 was considered a key and deciding factor supporting a positive benefit-risk balance for said medicinal product.

For the reasons explained above, it is now clear that superiority at week 52 was never demonstrated, as the data on superiority presented as part of the MAA for this medicinal product, which formed the basis of the original benefit-risk assessment at that time, were incorrect and misleading. Overall, as also explained above, the results based on the initial DBL of 05 November 2019 are not considered reliable and, in any case, failed to demonstrate superiority.

Additionally, the interpretation of the non-inferiority findings is complicated by the ADVOCATE study design as noted by the CHMP during the assessment of the MAA for Tavneos. In the prednisone arm, prednisone was tapered to zero by Week 20, while both treatment arms received background immunosuppressive treatment with either rituximab or cyclophosphamide followed by azathioprine. Therefore, for maintenance of remission the comparison was effectively between avacopan and placebo, particularly beyond the end of protocol-mandated prednisone treatment. Therefore, even if part of the study were to be considered reliable as claimed by the MAH, the inability to demonstrate superiority over placebo in this setting may be interpreted as a lack of efficacy. Of note, from the wording used in parts of the correspondence between sponsor representatives and the CRO shortly after unblinding, it appears likely that re-adjudication would not have been triggered had the superiority analysis been positive.

The MAH has also highlighted favourable findings in secondary endpoints of the ADVOCATE study and exploratory analyses, as well as supportive evidence from AVACOSTAR and other real-world studies.

With regard to the ADVOCATE secondary endpoints, it bears noting that these were not controlled for multiplicity and remain affected by the same limitations of study design and reliability that apply to the primary endpoints. Notably, from week 26 onwards, when the practical comparison was between avacopan and placebo, GC use was closely similar between treatment arms. Therefore, these analyses do not increase confidence in avacopan efficacy.

The post-marketing evidence provided by the MAH is also of limited value. The main relevant studies reported - AVACOSTAR, LIBRA, and the Birmingham studies - present methodological limitations inherent to observational research, including residual confounding, outcome misclassification, and incomplete clinical detail. In addition, the reported results demonstrate reductions in GC use but no convincing evidence of improved relapse-free survival or sustained remission. Accordingly, the post-marketing efficacy data are not considered sufficiently robust to compensate for the uncertainties surrounding the pivotal study. Likewise, the phase 2 studies part of the clinical development do not suffice to demonstrate the efficacy of avacopan.

Overall, due to the fluctuating course of AAV with multi-domain manifestations, and the current, rather complicated treatment regimens including other medications that affect the clinical response achieved, the isolated effect of avacopan on remission is not possible to assess in the absence of reliable randomised and blinded studies.

For the reasons explained above, efficacy of Tavneos is no longer considered to be demonstrated.

2.3. Data on safety

The safety profile of Tavneos is described in the summary of product characteristics (SmPC) and continuously monitored by routine pharmacovigilance activities. According to the Tavneos SmPC, 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%). Ongoing safety concerns for avacopan, as listed in the risk management plan, are the important identified risk of liver injury and the important potential risks of cardiovascular safety, serious infections and malignancy.

While the present Article 20 procedure was ongoing, new information related to the risk of liver injury was reported by the MAH, with reports of serious hepatic disorders including vanishing bile duct syndrome (VBDS) related to avacopan, including a number of cases with fatal outcome.

The pathogenesis of liver injury with avacopan is unknown. Avacopan is primarily metabolised in the liver via CYP3A4. Liver injury may be the result of direct toxicity from the administered drug or their metabolites, or injury may result from immune mediated mechanisms. In the clinical studies, exposure adjusted rates of treatment-emergent hepatic adverse events were 14.7 per 100 subject years with avacopan versus 12.3 with prednisone. Serious hepatic events occurred at 4.9 versus 3.2 per 100 subject years, respectively. Among the 10 serious cases in the avacopan group, 40% required hospitalization, none were fatal, 100% recovered without sequelae. The reported liver enzyme increases events in patients in both phase 2 and 3 studies were reversible and did not progress to liver failure.

After the marketing authorisation, liver-related events were discussed in multiple periodic safety update report single assessment (PSUSA) procedures (PSUSA/00010967/202309, PSUSA/00010967/202403), leading to several product information updates. The current SmPC includes information about liver events including fatal cases, stopping rules and frequency of liver monitoring, and labels DILI and VBDS as adverse drug reactions associated with Tavneos.

The new information related to liver injury referred above was reviewed by PRAC in the scope of the latest PSUSA (PSUSA/00010967/202509). It more robustly showed that most liver injury cases occurred within 3 months, mostly between 1 and 2 months, with only a few cases (mostly DILI cases) with a time-to-onset between 3 and 6 months. All VBDS events except one occurred within 3 months. As a conclusion, the PRAC agreed that a product information update was warranted to include more stringent monitoring advice during the first 3 months of treatment.

CHMP noted this serious risk and the PRAC recommendation for increased monitoring of the liver function. No new safety issues were identified in this procedure.

3. Stakeholders input

Submissions were also received from third parties, namely patients, patients' associations and healthcare professionals. Patients and patient associations shared their experiences and emphasised the value of maintaining Tavneos as a therapeutic option for GPA and MPA, citing the limitations of existing standard treatments and the burden associated with GC toxicity. They also highlighted the importance of considering patients' views in the context of the present procedure. Healthcare professionals stated that their clinical and real-world experience supports avacopan as an effective and generally well-tolerated treatment for AAV, highlighting its GC-sparing effect and clinically meaningful renal benefits - particularly in patients with severe kidney involvement - and expressing concern that restricting access could adversely affect patient outcomes despite the reliability issues regarding the ADVOCATE study data. Patients and healthcare professionals' representatives also presented their views during the oral explanation.

All data and information submitted was considered by the CHMP in reaching its conclusions.

4. Benefit-risk balance

The review of the data provided in the context of the Article 20 referral procedure has revealed serious breaches to GCP principles in the handling of primary endpoint data in the pivotal clinical study ADVOCATE.

The sponsor personnel reviewed unblinded efficacy data after an initial DBL (05 November 2019) and detected that superiority at week 52 had not been demonstrated. Thereafter, 9 patients were re-adjudicated based on knowledge of treatment outcomes, after which the primary analysis was rerun resulting in a change from a non-significant to a statistically significant result for superiority at week 52. The sponsor did not disclose the original analysis and post-unblinding data modifications in the initial MAA or post-authorisation procedures. On the contrary, the CSR specifically stated that the unblinding process outlined in the protocol has been followed. While the MAH has justified the re-adjudication on the grounds of errors in the initial adjudication, review of the patient level data and the adjudication rules and endpoint definitions do not support this statement. Further, the handling of the data as described is not compliant with the GCP principles (e.g. ICH E6 Good Clinical Practice and ICH E9 Statistical Principles for Clinical Trials). The impact of this breach cannot be isolated to a certain part of the data. Taken together, these issues lead to the conclusion that the study as a whole cannot be considered GCP compliant and reliable.

The ADVOCATE study was the single, pivotal study supporting the initial approval of Tavneos. In this study, according to the CSR submitted as part of the MAA, non-inferiority was shown for remission at week 26, while superiority compared to the comparator was documented at week 52 for sustained remission. At the time of the MA approval, it was considered that for remission at week 26, the interpretation of non-inferiority was complicated as both arms received additional immunosuppressive induction treatment. Therefore, an important deciding factor in favour of the positive benefit-risk balance at the time of the granting of the MA for Tavneos was based on superiority in the primary efficacy endpoint at week 52. For the reasons explained above, it is now clear that superiority at week 52 was never demonstrated. The data presented as part of the MAA for this medicinal product, which formed the basis of the original benefit-risk assessment at that time, were therefore incorrect and misleading in this respect.

The MAH has claimed that the data at initial DBL are GCP compliant and that they can be relied upon to demonstrate the positive benefit-risk balance. However, these data cannot be used to support the efficacy, since the study is non-GCP compliant, as described above. Furthermore, even if the results based on the initial DBL of 05 November 2019 were to be considered reliable as claimed by the MAH, the main efficacy result would be non-inferiority of avacopan (administered up to 52 weeks) compared with the comparator (placebo together with an initial 20-week prednisone course), at weeks 26 and 52. Further, the ADVOCATE secondary endpoints, such as the GC toxicity index, were not controlled for multiplicity and are affected by the same limitations of study design and reliability that apply to the primary endpoints.

Additional post-marketing evidence regarding the efficacy of avacopan, including the observational post-marketing safety study AVACOSTAR, is unconvincing, demonstrating limited or no clinically meaningful benefit, and is further constrained by the methodological limitations inherent to observational studies. While some studies may suggest a potential GC-sparing effect of avacopan, these findings are subject to significant limitations in study design and lack the robustness required to support efficacy of Tavneos. Overall, this evidence cannot replace the evidence from an adequately designed and GCP-compliant phase 3 study.

Regarding the safety profile of avacopan, a number of fatal cases of DILI and/or VBDS have been reported after the initial MA, and the last 3 PSUSAs resulted in updates to the product information accordingly, to minimise the serious risk of liver injury. In particular, in the last PSUSA, emerging safety information related to this risk led to the recommendation to introduce more stringent monitoring advice during the first 3 months of treatment.

On balance, considering that the pivotal study supporting the marketing authorisation is considered as not reliable due to the serious GCP breach, it is concluded that there is no longer demonstration of benefit outweighing the risks of Tavneos, in particular the serious hepatic risks.

CHMP acknowledges that Tavneos is indicated as an adjunctive treatment of a serious rare disease associated with high morbidity and mortality. It is also recognised that the therapeutic options are limited. Nevertheless, avacopan does not replace the established backbone therapy, namely rituximab or cyclophosphamide in combination with GCs. Therefore, in the absence of avacopan, effective treatment options for GPA and MPA remain available. This contextualises the therapeutic role of avacopan as an optimisation strategy rather than an indispensable treatment.

While it is acknowledged that the MAH has indicated the possibility of conducting a new post-authorisation efficacy study aiming to provide data on the efficacy of Tavneos in the future, this has no bearing on the present conclusion, which is based on the data available at present.

Lastly, it is noted that the validity of the marketing authorisation for Tavneos ends in January 2027 and the marketing authorisation will expire if not renewed, which would require demonstration of a positive benefit-risk balance. The MAH has no ongoing or planned alternative clinical study that is adequately designed to replace the ADVOCATE study to demonstrate a positive benefit-risk balance in a defined patient population, before the marketing authorisation is due to expire (as required per the 'Guideline on the processing of renewals in the centralised procedure', EMEA/CHMP/2990/00 Rev.4). Therefore, CHMP could not identify any condition that could be fulfilled to demonstrate a positive benefit-risk balance for Tavneos.

Overall, the CHMP considers that the benefit-risk balance of Tavneos is negative and that the particulars supporting the marketing authorisation are incorrect. Therefore, the revocation of the marketing authorisation is recommended.

5. Direct healthcare professional communications and communication plan

The Committee adopted the wording of a direct healthcare professional communication to inform the healthcare professionals of the conclusions of the review and upcoming unavailability of Tavneos as well as to inform of the adequate liver monitoring (in line with the outcome of the parallel procedure PSUSA/00010967/202509) until treatment with Tavneos is discontinued. The Committee also agreed on a communication plan.

6. Grounds for opinion

Whereas,

- The CHMP considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Tavneos.
- The CHMP reviewed the totality of the available data provided by the marketing authorisation holder in writing and in an oral explanation, including the new information pertaining to the data handling of the ADVOCATE study, the pivotal study supporting the initial marketing authorisation application for Tavneos. In addition, CHMP considered the views of patient representatives and healthcare professional representatives presented during the oral explanation, as well as written interventions received from third parties.
- The CHMP noted that the data provided at the time of the assessment of the marketing authorisation application for the ADVOCATE study were incorrect and misleading.
- The CHMP concluded that the ADVOCATE study was conducted in breach of good clinical practice principles. As a result of that breach, the results of the study cannot be relied upon to demonstrate efficacy. Further, the additional, available post-marketing authorisation data is not considered sufficient to provide confirmatory evidence which had initially been provided by the single pivotal study (ADVOCATE) to demonstrate the clinical benefit of Tavneos in its authorised indication.
- The CHMP also noted the known safety profile of Tavneos, in particular the serious hepatic risks. These risks are no longer outweighed by an established benefit.
- Furthermore, the CHMP could not identify any feasible condition that could be fulfilled to demonstrate a positive benefit-risk balance for Tavneos.

The Committee, as a consequence, considers that the benefit-risk balance of Tavneos is not favourable, and that the particulars supporting the marketing authorisation as provided for in Article 8 of Directive 2001/83/EC are incorrect.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the revocation of the marketing authorisation for Tavneos.