Report on the Deliberation Results

September 10, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Tavneos Capsules 10 mg
Non-proprietary Name	Avacopan (JAN*)
Applicant	Kissei Pharmaceutical Co., Ltd.
Date of Application	February 26, 2021

Results of Deliberation

In its meeting held on September 6, 2021, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

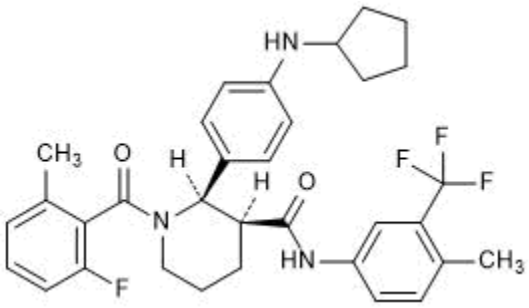
Review Report

August 26, 2021
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Tavneos Capsules 10 mg
Non-proprietary Name	Avacopan
Applicant	Kissei Pharmaceutical Co., Ltd.
Date of Application	February 26, 2021
Dosage Form/Strength	Hard capsules: Each capsule contains 10 mg of avacopan.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{33}H_{35}F_4N_3O_2$

Molecular weight: 581.64

Chemical name: (*2R,3S*)-2-[4-(Cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-*N*-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 430 of 2019 [*31 yaku*]; PSEHB/PED Notification No. 0304-1, dated March 4, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of microscopic polyangiitis and granulomatosis with polyangiitis, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition. The safety and efficacy of the product in clinical use should be further investigated via post-marketing surveillance.

Indications

Microscopic polyangiitis and granulomatosis with polyangiitis

Dosage and Administration

The usual adult dosage is 30 mg of avacopan orally administered twice daily after breakfast and dinner.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

August 6, 2021

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Tavneos Capsules 10 mg
Non-proprietary Name	Avacopan
Applicant	Kissei Pharmaceutical Co., Ltd.
Date of Application	February 26, 2021
Dosage Form/Strength	Hard capsules: Each capsule contains 10 mg of avacopan.
Proposed Indications	Microscopic polyangiitis and granulomatosis with polyangiitis

Proposed Dosage and Administration

The usual adult dosage is 30 mg of avacopan orally administered twice daily after breakfast and dinner.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Avacopan, an active ingredient of "Tavneos Capsules 10 mg," is an orally available selective complement C5a receptor (C5aR) antagonist discovered by ChemoCentryx, Inc. (US).

Microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) are characterized by production of anti-neutrophil cytoplasmic antibodies (ANCA), autoantibodies that recognize myeloperoxidase (MPO) and proteinase 3 (PR3) expressed on neutrophils as the antigens, are systemic necrotising vasculitis that mainly damages medium and small blood vessels, and are classified into ANCA-associated vasculitis together with eosinophilic granulomatosis with polyangiitis (EGPA) (Guidelines for Management of ANCA-associated Vasculitis 2017 [Japanese Clinical Practice Guideline]). MPA is defined as a small-vessel necrotising vasculitis pathologically without deposition of immune complex on the vascular wall and granuloma and presents with systemic symptoms such as fever and fatiguability and is complicated by lesions in various organs mainly comprising renal disorders. GPA is pathologically characterized by necrotising granulomatous lesions in the upper respiratory tract and lung, necrotising glomerulonephritis in the kidney, and systemic medium and small arterial necrotising vasculitis and initially presents with inflammation in the orbit, paranasal sinus, or middle ear, which is followed by inflammation in the lower respiratory tract including trachea, bronchus, and lung, further causing renal disorders (*Journal of Otolaryngology of Japan.* 2016;119:81-6). In addition, both diseases were designated as designated intractable diseases (Announcement Nos. 43 and 44) by Ministry of Health, Labour and Welfare (MHLW) Ministerial Announcement No. 393, dated October 21, 2014. In FY 2019, 9486 patients with MPA and 2879 patients with GPA were granted medical care recipient certificates for specific medical expenses.

Treatment of MPA and GPA basically comprises a combination of glucocorticoids (GCs) and immunosuppressive drugs. The standard remission induction therapy that is recommended is to use high dose GC and cyclophosphamide (CY) or rituximab (genetical recombination) (RTX) in combination, and the standard remission maintenance therapy that is recommended is to use low dose GC and azathioprine (AZA) in combination. Both GCs and immunosuppressive drugs are known to have a risk of serious adverse drug reactions including infections (Japanese Clinical Practice Guideline).

Although mechanisms of development of MPA and GPA have not been completely elucidated, complement 5a (C5a), a final product resulted from activation of the complement cascade, is considered to play an important role in the development. C5a primes circulating neutrophils via C5aR, and the C5a-primed neutrophils induce vasculitis (*Nat Rev Rheumatol.* 2014;10:463-73, *Nat Rev Nephrol.* 2017;13:359-67). Avacopan, which binds to C5aR and thereby inhibits effects of C5a, was expected to be effective in the treatment of MPA and GPA and thus underwent development operations.

Overseas, clinical development of avacopan for the treatment of MPA and GPA was started in September 2011. As of July 2021, its regulatory review is ongoing in the US and Europe. In Japan, clinical development of avacopan for the treatment of MPA and GPA was started in [redacted] 20[redacted]. The marketing application was submitted based on results from a global study including Japan.

Avacopan was designated as an orphan drug with the intended indications of "microscopic polyangiitis, granulomatosis with polyangiitis" on March 4, 2019 (Orphan Drug Designation No. 430 of 2019 [*31 yaku*]).

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

Avacopan, the drug substance, is registered in the master file (MF) under MF registration number 303MF10022 by Hovione LLC (US).

2.1.1 Characterization

The drug substance occurs as a white to light yellow solid. The general properties of the drug substance, including description, solubility, hygroscopicity, melting point, dissociation constant, partition coefficient, and [redacted], were determined. The drug substance has been found in at least 2 crystal forms (Form I [redacted] and Form II [redacted]), but it is confirmed that only in Form I ([redacted]) is formed in the commercial manufacturing process.

The chemical structure of the drug substance was elucidated by ultraviolet-visible absorption spectroscopy, infrared absorption spectroscopy, nuclear magnetic resonance (NMR) spectroscopy (^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR), mass spectrometry, single crystal X-ray diffractometry, X-ray powder diffraction, thermal analysis (differential scanning calorimetry), and elemental analysis.

2.1.2 Manufacturing process

See Supplement.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (infrared absorption spectroscopy, high performance liquid chromatography [HPLC]), purity (related substances [HPLC], [redacted] residual solvents (gas chromatography [GC]), [redacted]), [redacted], residue on ignition, and assay (HPLC).

2.1.4 Stability of drug substance

Table 1 shows major stability studies conducted on the drug substance. The results demonstrated that the drug substance is stable. In addition, the photostability testing shows that the drug substance is photostable.

Table 1. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	5 commercial batches	25°C	60%RH	Low-density polyethylene bag (double-layered) + high-density polyethylene drum	[redacted] months
Accelerated	5 commercial batches	40°C	75%RH		6 months

On the basis of the above, a retest period of [redacted] months has been proposed for the drug substance when stored at room temperature in the double-layered polyethylene bag placed in the high-density polyethylene drum in accordance with "Guideline on Evaluation for Stability Data" (ICH Q1E

guideline) (PFSB/ELD Notification No. 0603004, dated June 3, 2003). Long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is presented as hard capsules containing 10 mg of the drug substance and is a [redacted] formulation prepared by [redacted] the drug substance in [redacted] excipients. Excipients used in capsules of the drug product are polyoxyethylene hydrogenated castor oil 40 and macrogol 4000NF for the [redacted] capsules and gelatin and polysorbate 80 for the capsule [redacted].

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of [redacted], dissolving, capsule filling [redacted], and packaging and labeling. The process control items and process control values have been established in the processes for [redacted] and [redacted].

The quality control strategy has been constructed based on the following investigations using the quality-by-design technique (Table 2).

- Identification of critical quality attributes
- Identification of critical process parameters and critical material attributes based on quality risk assessment

Table 2. Outline of control strategy of drug product

Critical quality attributes	Control method
Description, strength, related substances, dissolution, uniformity of dosage units	Manufacturing process, specifications
Identification, [redacted], microbial limit	Specifications

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (HPLC, ultraviolet-visible absorption spectroscopy), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), microbial limit, dissolution (HPLC), and assay (HPLC).

Through the review process, the microbial limit was established.

2.2.4 Stability of drug product

Table 3 shows major stability studies conducted on the drug product. The results demonstrated that the drug product is stable. In addition, the photostability testing shows that the drug product is unstable to light.

Table 3. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 commercial batches	25°C	60%RH	Blister pack + aluminum-laminated bag + carton	[redacted] months
Accelerated	3 commercial batches	40°C	75%RH		6 months

On the basis of the above, a shelf life of [redacted] months has been proposed for the drug product when stored at room temperature in the blister pack (orange polypropylene film and aluminum foil) placed in the aluminum-laminated bag in the carton for protection from light in accordance with ICH Q1E guideline. Long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of the submitted data and the following review, PMDA concluded that the quality of the drug substance and drug product is appropriately controlled. The MF data for this product were separately submitted by the MF registrant. See Supplement for the results from the review on the MF data by PMDA.

2.R.1 Novel excipients

The drug product contains polyoxyethylene hydrogenated castor oil 40 and macrogol 4000NF as novel excipients that are not specified in any Japanese compendia.

2.R.1.1 Specifications and stability

On the basis of the submitted data, PMDA concluded that both novel excipients are acceptable in terms of the specifications and stability.

2.R.1.2 Safety

In view of the following safety evaluation results, PMDA concluded that both novel excipients are unlikely to raise safety concerns in terms of the amounts and method for their use.

- Polyoxyethylene hydrogenated castor oil 40

  In repeated oral dose toxicity studies of the concerned excipient in rats and dogs (up to 6 months), no systemic toxicity was observed at up to the maximum dose (5700 mg/kg in rats, 1500 mg/kg in dogs); in all of the bacterial reverse mutation test (Ames test), *in vitro* chromosomal aberration assay, and *in vivo* micronucleus assay, the concerned excipient tested negative. In the embryo-fetal development studies in mice and rats, no observed adverse effect level (NOAEL) for embryo-fetal development was >10000 mg/kg in mice and 2270 mg/kg in rats. On the basis of the above, the maximum daily intake ([redacted] mg/day) through administration of the drug product has an adequate safety margin. In addition, there is a preceding oral formulation, approved overseas though (NEORAL® Soft Gelatin Capsules), that contains this excipient (3645 mg/day) exceeding the maximum daily intake through administration of the drug product.

- Macrogol 4000NF

  Toxicity of orally administered macrogol increase with decreasing molecular weight (*J Am Pharm Assoc Sci Ed.* 1955;44:27-30). The maximum daily intake of macrogol 4000NF through administration of the drug product ([redacted] mg/day) is smaller than the daily intake (2310 mg/day) of macrogol 400 conforming to the Japanese Pharmacopoeia, of which the molecular weight is smaller than that of this novel excipient. Its use is therefore unlikely to raise safety concerns.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The applicant submitted results from primary pharmacodynamic studies in which the effect on binding between C5a and C5aR and the antagonistic effect on C5aR were investigated. The applicant also submitted results from secondary pharmacodynamic studies in which the inhibitory effect against various receptors and the effects on GC and CY were investigated. Furthermore, the applicant submitted results from safety pharmacology studies in which the effects on the central nervous, respiratory, and cardiovascular systems and renal functions were investigated.

In this section, human C5a and C5aR are simply expressed as C5a and C5aR. In addition, pharmacological parameters are expressed as the mean values.

3.1 Primary pharmacodynamics

3.1.1 Effect on binding between C5a and C5aR (CTD 4.2.1.1.1)

In a radioligand binding study using a human monocytic cell line (U937 cells), avacopan competitively inhibited binding between C5aR and ^{125}I-labeled C5a with the half maximal inhibitory concentration (IC_{50}) of 0.45 nmol/L.

3.1.2 Antagonistic effect against C5aR (CTD 4.2.1.1.1, 4.2.1.1.3, 4.2.1.1.5, and 4.2.1.1.7)

In various *in vitro* test systems, effects of avacopan and its human major metabolite M1 [see Section 6.2.1.3] on C5a-induced cell chemotaxis and an increase in intracellular Ca^{2+} concentration were investigated. Table 4 shows the results.

Table 4. Antagonistic effects of avacopan against C5aR in various test systems

Test system (cell type)	Evaluation item	A_2[a] (nmol/L)		Attached document CTD
		Avacopan	M1	
Human monocytic cell line (U937 cells)	Inhibition against C5a-induced cell chemotaxis	0.25	0.3	4.2.1.1.1 4.2.1.1.5
	Inhibition against a C5a-induced increase in intracellular Ca^{2+} concentration	0.1	—	
Neutrophils in human whole blood	Inhibition against C5a-induced cell chemotaxis	1.7	3	4.2.1.1.1 4.2.1.1.5
	Inhibition against a C5a-induced CD11b upregulation	—	7	4.2.1.1.5
Isolated human neutrophils	Inhibition against a C5a-induced increase in intracellular Ca^{2+} concentration	0.2[b]	—	4.2.1.1.1
Thioglycollate-induced intraperitoneal leukocyte recruitment in C5aR-KI mouse[1)]	Inhibition against C5a-induced cell chemotaxis	13	—	4.2.1.1.3
Neutrophils in whole blood from C5aR-KI mice orally treated with avacopan	Inhibition against a C5a-induced CD11b upregulation[c)]	4.75	—	4.2.1.1.7

-, Not measured
a) Concentration of avacopan required to shift the concentration-response curve established with C5a alone to the twice higher concentrations
b) IC_{50}
c) C5a (10 pmol/L to 1 μmol/L) was added to the whole blood collected from C5aR-KI mice 1 hour after oral administration of avacopan 0.1 to 5 mg/kg, and the amount of CD11b expressed on the surface of neutrophils was measured.

1) Knock-in mouse in which mouse C5aR gene was replaced with human C5aR gene

3.1.3 Antagonistic effects against C5aR of various animals (CTD 4.2.1.1.2, 4.2.1.1.5, 4.2.1.1.8, and 4.2.1.1.9)

Table 5 shows results from assays in which effects of avacopan and its metabolite M1 on C5a-induced cell chemotaxis were investigated using neutrophils or leukocytes and C5a[2)] of various animals.

Table 5. Effects of avacopan on C5a-induced cell chemotaxis in various animals

Animal species	Cell strain	A_2[a)] (nmol/L)		Attached document CTD
		Avacopan	M1	
Human	Neutrophils in whole blood	1.7	3	4.2.1.1.1 4.2.1.1.5
Cynomolgus monkey		18	2.6	4.2.1.1.2 4.2.1.1.8
Hamster	Leukocytes in whole blood	14	10	4.2.1.2.9
Rabbit		4000	3000	
Rat	Thioglycollate-induced intraperitoneal leukocyte recruitment	>10000	>1000	4.2.1.1.2
Mouse		>10000	>1000	4.2.1.1.8

a) Concentration of avacopan required to shift the concentration-response curve established with C5a alone to the twice higher concentrations

3.1.4 Effects on a C5a-induced decrease in neutrophils (CTD 4.2.1.1.3 and 4.2.1.1.4)

Avacopan was orally administered at 3 or 30 mg/kg to cynomolgus monkeys. Avacopan inhibited a decrease in neutrophils in blood induced by C5a, which was intravenously administered at 10 μg/kg 90 and 220 minutes post-dose, in a dose-dependent manner. Avacopan was orally administered at 0.03 to 30 mg/kg to C5aR-KI mice.[1)] Avacopan inhibited a decrease in leukocytes in blood induced by C5a, which was intravenously administered at 20 μg/kg 60 minutes post-dose, in a dose-dependent manner.

3.1.5 Effects on anti-MPO antibody-induced glomerulonephritis mouse model (CTD 4.2.1.1.6)

To C5aR-KI mice[1)] orally receiving avacopan at 0 (vehicle), 0.1, 1, or 37.5 mg/kg once daily or at 5 mg/kg twice daily, for 1 week, anti-MPO antibody was intravenously administered at 50 mg/kg on Day 2 to induce glomerulonephritis. Avacopan inhibited onset of glomerulonephritis and renal dysfunction at Week 1 in a dose-dependent manner. When compared with the vehicle, avacopan administered at 37.5 mg/kg once daily and at 5 mg/kg twice daily decreased the incidence of crescent formation in the glomeruli by 85% and 93%, respectively, and that of glomerular necrosis[3)] by 79% and 100%, respectively. Furthermore, when compared with the vehicle, avacopan administered at 37.5 mg/kg once daily and at 5 mg/kg twice daily improved scores for urine protein, leukocytes in urine, and urinary occult blood.[4)]

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2) The assays in human, cynomolgus monkey, hamster, and rabbit used recombinant human C5a, while assays in rat and mouse used recombinant mouse C5a.
3) Determined by histopathological image analysis
4) Score by the dip stick test (0-4 points for the presence of protein and leukocytes in urine; and 0-5 points for urinary occult blood)

3.2 Secondary pharmacodynamics

3.2.1 Effects on chemokine receptors (CTD 4.2.1.2.1 and 4.2.1.2.6)

Of 23 chemokine receptors[5)] investigated, only CCR5 and CCR10 were inhibited by avacopan with IC_{50} of 6.7 and 8.0 μmol/L, respectively. M1 up to 10 μmol/L, the maximum concentration tested, did not inhibit 17 chemokine receptors.[6)]

3.2.2 Effects on various receptors, ion channels, and transporters (CTD 4.2.1.2.2 and 4.2.1.2.6)

In an investigation of the effects on 55 types of receptors, ion channels, and transporters, avacopan (10 μmol/L) inhibited only Na^+ channel (site 2), and M1 (10 μmol/L) inhibited cannabinoid receptor 1, Na^+ channel (site 2), and Cl^- channel (GABA-gated) by ≥50%.

3.2.3 Effects on GC and CY (CTD 4.2.1.2.3 to 4.2.1.2.6)

Neither avacopan nor M1 (up to 10 μmol/L for both) bound to the GC receptor. In addition, neither avacopan nor M1 (0.01-10 μmol/L for both) inhibited GC metabolic enzymes (11β-HSD1 and 11β-HSD2) in human hepatic or renal microsomes. Furthermore, neither avacopan nor M1 (300 nmol/L for both) affected growth of human peripheral blood mononuclear cells or CY (0.5-1000 μmol/L)-induced inhibition against the cell growth.

3.3 Safety pharmacology

Table 6 shows results from safety pharmacology studies of avacopan. Because avacopan was found to have no pharmacological effect on C5aR in rats [see Section 3.1.3], results from studies in rats were evaluated together with those from repeated-dose toxicity studies in cynomolgus monkeys [see Section 5.2]. As a result of the evaluation, avacopan did not affect the central nervous system, respiratory system, or renal functions.

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5) CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR12, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CXCR7, C5L2 (C5aR2), C3aR, ChemR23, GPR1, and FPR1

6) CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR9, CCR12, CXCR1, CXCR2, CXR3, CXCR4, CXCR6, CXCR7, C3aR, and FPR1

Table 6. Outline of safety pharmacology study results

Item	Test system	Evaluation items and methods	Dose	Route of administration	Findings	Attached document CTD
Central nervous system	Rat (SD) (n = 6 males/group)	Autonomic response and behavioral observation (modified Irwin procedure), body temperature	Avacopan: 0,[a] 5, 25, 100 mg/kg	Oral	No effects NOAEL: 73 mg/kg[b]	4.2.1.3.2
Cardiovascular system	hERG-transfected HEK293 cells	hERG current (patch-clamp method)	Avacopan: 0.6, 1.2, 2.3, 6.9 µmol/L	*In vitro*	IC_{50}: >2.3 µmol/L[c] Inhibited by 4.5%-25.9% at 0.6-2.3 µmol/L	4.2.1.3.1
			M1: 1, 3, 10, 15.8 µmol/L		IC_{50}: >3 µmol/L[c] Inhibited by 15.4%-37.5% at 1-3 µmol/L	4.2.1.3.6 (reference)
	Cynomolgus monkey (4 males)	Blood pressure, heart rate, electrocardiogram, and clinical observation (telemetry method, unanesthetized)	Avacopan: 0,[a] 5, 15, 50 mg/kg	Oral	No effects NOAEL: 50 mg/kg	4.2.1.3.3
Respiratory system	Rat (SD) (n = 8 males/group)	Tidal volume, respiratory rate, and minute ventilation (unanesthetized)	Avacopan: 0,[a] 5, 25, 100 mg/kg	Oral	No effects NOAEL: 73 mg/kg[b]	4.2.1.3.4
Renal functions	Rat (SD) (n = 8 males/group)	Electrolyte, urine volume, water intake, plasma creatinine, and urinary parameters (total protein, urine specific gravity, osmolality, pH, creatinine, and urea nitrogen)	Avacopan: 0,[a] 5, 25, 100 mg/kg	Oral	No effects NOAEL: 100 mg/kg	4.2.1.3.5

a) Polyethylene glycol 400/ polyethylene glycol (15)-hydroxystearic acid ([redacted], v/v) used as a vehicle
b) Actual dose
c) The test article was not available at concentrations higher than this owing to its solubility.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects of avacopan

PMDA's view:

The submitted data suggested that avacopan inhibits biological activities of C5a medicated by binding to C5aR, and avacopan was potentially effective in the treatment of MPA and GPA, of which pathogenesis is considered related to the C5a-C5aR signaling pathway, from a pharmacological viewpoint.

3.R.2 Effects of avacopan on immune and coagulation systems

PMDA's view:

C5a-induced activation of the innate immune system and acquired immune system functions complementarily through the complement 3a (C3a)-complement 3a receptor (C3aR) signaling pathway, which is unaffected by avacopan (*Annu Rev Immunol.* 2005;23:821-52, *Immunity.* 2008;28:425-35). Toxicity studies of avacopan show no findings indicative of immunotoxicity or abnormality in the blood coagulation system [see Sections 5.2 and 5.4], but anti-C5 monoclonal antibody increases a risk of meningococcal infection by inhibiting C5 cleavage that leads to formation of the terminal complement complex, i.e., complement 5b, 6, 7, 8, and 9 complex (C5b-9) (*Blood.* 2017;130:891-99). PMDA will review the safety in the immune system in humans treated with avacopan based on not only the above findings but also clinical study results [see Section 7.R.3].

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The applicant submitted data on absorption, distribution, metabolism, and excretion, in the form of results from oral and intravenous administration studies in mice, rats, hamsters, rabbits, dogs, and monkeys. In pharmacokinetic studies, avacopan and ^{14}C-avacopan were used. Plasma concentrations of avacopan or its metabolite were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantification, 1 or 2 ng/mL), and radioactivity in samples was detected by a liquid scintillation counter or an HPLC system with a radioactivity detector. Unless otherwise specified, pharmacokinetic parameters are expressed as mean or mean ± standard deviation (SD).

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.2 to 4.2.2.2.4, 4.2.2.2.9, 4.2.2.2.11, and 4.2.2.2.13)

Table 7 shows pharmacokinetic parameters in mice, rats, rabbits, dogs, and monkeys orally or intravenously treated with a single dose of avacopan. Absolute bioavailability of avacopan orally administered was 17% and 87% in mice at 2.0 and 30 mg/kg, respectively, and 27%, 104%, and 55% in rats at 2.0, 30, and 100 mg/kg, respectively.

Table 7. Pharmacokinetic parameters after single oral or intravenous administration of avacopan

Animal species	Route of administration	Dose (mg/kg)	n	C_{max} (ng/mL)	$AUC_{0\text{-inf}}$ (ng·h/mL)	t_{max} (h)	CL (mL/min/kg)	Vd_{ss} (L/kg)	$t_{1/2}$ (h)
Mouse	Oral	2.0[a)]	3 females/ timepoint	75	240	1.0	—	—	2.9
		30[b)]	3 females/ timepoint	4630	18600	1.0	—	—	5.6
	Intravenous	0.5	3 females/ timepoint	—	343	—	26.6	1.5	1.8
Rat	Oral	2.0[a)]	2 males	186, 117	555, 314	1.0, 1.0	—	—	1.7, 2.9
		30[b)]	3 males	2530 ± 256	24600 ± 7450	1.5 ± 0.0	—	—	4.6 ± 0.8
		100[b)]	3 males	3810 ± 555	43300 ± 9730	1.7 ± 0.3	—	—	4.1 ± 0.2
	Intravenous	0.5	2 males	—	382, 413	—	22.2, 20.2	1.9, 1.7	2.0, 1.9
Rabbit	Oral	50[b)]	3 females	603 ± 53.9	3950 ± 674[c)]	4.0 ± 0.0	—	—	—
		100[b)]	3 females	727 ± 154	4300 ± 754[c)]	2.7 ± 1.2	—	—	—
		200[b)]	3 females	280 ± 144	3290 ± 1300[c)]	3.3 ± 1.2	—	—	—
		300[b)]	3 females	422 ± 81.8	2880 ± 741[c)]	3.3 ± 1.2	—	—	—
		1000[b)]	3 females	144 ± 16.3	1800 ± 473[c)]	4.0 ± 0.0	—	—	—
Dog	Intravenous	0.5	3 males	—	711 ± 112[c)]	—	11.9 ± 1.9	4.7 ± 1.9	14.2 ± 3.5
Monkey	Oral	15[b)]	3 males	815 ± 38.8	8840 ± 2550	5.3 ± 2.3	—	—	4.5 ± 0.5

-, Not determined
Mean ± SD, individual values for n = 2
a) 1% hydroxypropylmethylcellulose solution used as vehicle
b) Polyethylene glycol 400/polyethylene glycol (15)-hydroxystearic acid ([redacted], v/v) used as a vehicle
c) $AUC_{0\text{-}24}$

4.1.2 Repeated-dose studies (toxicokinetics) (CTD 4.2.2.2.6, 4.2.2.2.8, 4.2.2.2.12, 4.2.3.2.3, 4.2.3.2.4, and 4.2.3.2.7)

Table 8 shows pharmacokinetic parameters in repeated-dose toxicity studies in rats, hamsters, and monkeys in which avacopan was orally administered as multiple doses [see Section 5.2]. Exposures to avacopan and M1 increased less than dose-proportionally within a range from 30 to 100 mg/kg in a 26-week repeated-dose toxicity study in rats and a 13-week repeated-dose toxicity study in hamsters, while these increased dose-proportionally within a range from 10 to 30 mg/kg in the 13-week repeated-dose toxicity study in hamsters and throughout a dose range tested in a 44-week repeated-dose toxicity study in monkeys. No remarkable differences were observed between males and females of any animal species.

Table 8. Pharmacokinetic parameters after repeated oral administration of avacopan

Animal species	n	Sampling point (Day)	Dose (mg/kg/day)	Avacopan				M1			
				C_{max} (ng/mL)		AUC_{0-24} (ng·h/mL)		C_{max} (ng/mL)		AUC_{0-24} (ng·h/mL)	
				Male	Female	Male	Female	Male	Female	Male	Female
Rat	3/sex/ timepoint	1	5	515	672	5270	5450	34.5	44.7	409	323
			15	1780	1630	13400	15400	115	65.6	649	934
			100	4980	3870	53200	52600	95.9	130	1520	1720
			200[a)]	3120	2620	43600	32400	206	85.7	2390	1350
		182	5	1070	1190	9780	9360	138	45.4	1490	403
			15	4000	3650	29800	32300	292	67.2	1690	1100
			100	5430	11500	60400	85900	177	198	2420	2500
			200[a)]	6100	7370	82700	106000	545	214	7090	3780
Hamster	3/sex/ timepoint	1	10	893	632	5220	4240	34.5	22.9	319	230
			30	1940	1520	13400	12100	80.7	50.6	936	849
			100	4340	3500	25400	29800	90.4	122	1450	1730
			1000[b)]	1230	1530	16900	24400	49.0	102	944	1400
		91	10	1000	1420	6280	6610	39.9	35.1	427	352
			30	3060	4700	18000	21400	101	112	1300	1170
			100	4650	4790	40600	39200	186	159	2600	2350
			1000[b)]	1800	1890	31700	33400	133	110	2630	2240
Monkey	4/sex	1	5/7.25[c)]	159 ± 88.3	109 ± 61.0	799 ± 435	531 ± 182	82.1 ± 23.2	73.4 ± 18.0	867 ± 292	733 ± 237
	4/sex		15/22.5[c)]	537 ± 134	456 ± 186	3240 ± 1360	2980 ± 987	241 ± 108	259 ± 76.9	2470 ± 1190	2510 ± 437
	6/sex		30/45[c)]	377 ± 233	406 ± 280	3990 ± 2050	3990 ± 2550	192 ± 88.2	148 ± 67.4	3040 ± 1430	2110 ± 998
	4/sex	36	5/7.25[c)]	220 ± 48.8	299 ± 199	1380 ± 433	1490 ± 548	127 ± 39.6	131 ± 27.7	1300 ± 465	1240 ± 255
	4/sex		15/22.5[c)]	704 ± 213	905 ± 473	5740 ± 1570	7610 ± 4730	288 ± 98.1	325 ± 101	3540 ± 1270	4120 ± 1800
	6/sex		30/45[c)]	1130 ± 446	1230 ± 349	16300 ± 5920	14100 ± 4700	464 ± 144	394 ± 98.4	8100 ± 2710	6360 ± 1820
	4/sex	126	5/7.25[c)]	118 ± 52.3	150 ± 95.5	1030 ± 336	1200 ± 588	90.7 ± 21.8	97.1 ± 36.9	1030 ± 340	1130 ± 372
	4/sex		15/22.5[c)]	387 ± 141	608 ± 240	3920 ± 1490	6310 ± 2390	194 ± 49.6	227 ± 17.6	2590 ± 623	3150 ± 662
	6/sex		30/45[c)]	743 ± 376	1010 ± 371	7750 ± 3670	11100 ± 3500	239 ± 118	267 ± 46.9	4050 ± 1950	4590 ± 783
	4/sex	294	5/7.25[c)]	522 ± 204	267 ± 53.8	3930 ± 1950	2880 ± 1110	213 ± 89.1	140 ± 42.2	2540 ± 1210	2070 ± 880
	4/sex		15/22.5[c)]	1090 ± 252	1710 ± 1030	13700 ± 4970	19700 ± 11500	363 ± 53.2	445 ± 181	5430 ± 1110	6790 ± 2970
	6/sex		30/45[c)]	2200 ± 934	2470 ± 1230	26400 ± 9760	32200 ± 12800	538 ± 166	548 ± 128	9330 ± 3180	9840 ± 2470

Mean or mean ± SD
a) 100 mg/kg twice daily
b) 500 mg/kg twice daily
c) Dose during Weeks 1 to 25/dose during Weeks 26 to 44 (administration through a nasogastric tube during Weeks 1-5 and oral administration during Weeks 6-44)

4.1.3 *In vitro* membrane permeability (CTD 4.2.2.2.1)

An investigation using cell unilamellar membrane of human colorectal adenocarcinoma cell line (Caco-2) showed that the efflux ratio[7)] of avacopan 5 μmol/L was 1.08, indicating high membrane permeability.

4.2 Distribution

4.2.1 Plasma protein binding (CTD 4.2.2.3.1 to 4.2.2.3.3)

The plasma protein binding (equilibrium dialysis method) of avacopan or M1 at 2.5 to 50 μmol/L in plasma specimens from mice, rats, hamsters, rabbits, dogs, monkeys, and humans was all ≥99.9%. When avacopan or M1 at 5 or 10 μmol/L was added to human serum albumin or human α1-acid glycoprotein,

7) Ratio of a permeability coefficient from the basolateral surface to the apical surface with respect to that from the apical surface to the basolateral surface

their binding was reversible, and the binding of M1 to α1-acid glycoprotein was approximately 99%, while those of the other combinations were ≥99.9%.

4.2.2 Distribution in blood cells (CTD 4.2.2.3.5)

When avacopan or M1 at 5 μmol/L was added to whole blood specimens from mice,[8] rats, dogs, and humans, the erythrocyte/plasma concentration ratio was 0.45, 0.60, 0.27, and 0.42, respectively, for avacopan and 0.76, 0.37, and 0.30, respectively, for M1.

4.2.3 Tissue distribution (CTD 4.2.2.3.4)

Albino and pigmented rats (n = 1/sex/timepoint for both[9]) orally received a single dose of ^{14}C-avacopan, and radioactivity distribution in tissues was determined by quantitative autoradiography. Radioactivity concentrations reached the maxima at 4 or 8 hours post-dose in many tissues. The radioactivity concentrations was highest in the brown fat followed in descending order by the liver, white fat, adrenal gland, urinary bladder (male), Harderian gland (male), preputial gland (male), pancreas (female), myocardium (female), and salivary gland (female) in albino rats, and in the brown fat followed in descending order by the liver, white fat, adrenal gland, Harderian gland, pancreas, kidney and renal medulla/cortex (male), cecum (female), and small intestine (female) in pigmented rats.

In pigmented rats at 336 hours, low concentration radioactivity was detected in the adrenal gland, blood, uvea, fat, kidney, liver, preputial gland, spleen, skin, small intestine, uterus, and myocardium, but radioactivity was found to be below the lower limit of quantification in most of the tissues.

With respect to radioactivity distribution in melanin-containing tissues, radioactivity was eliminated from pigmented and non-pigmented skins in pigmented rats in a comparable manner, while radioactivity elimination from the uvea tended to be slower in pigmented rats than in albino rats, suggesting affinity of avacopan to the melanin-containing tissue in the eye. Its binding to the tissue, however, was considered to be reversible because the measured radioactivity decreased with time.

4.3 Metabolism

4.3.1 *In vitro* studies (CTD 4.2.2.4.1 to 4.2.2.4.5)

When avacopan 0.2 μmol/L was incubated with frozen hepatocytes from mice, rats, dogs, monkeys, and humans, the metabolic clearance rate was 20.6 ± 1.7, 45.3 ± 4.5, 36.0 ± 1.2, 33.4 ± 2.7, and 10.9 ± 0.7 μL/10^6 cells/min, respectively.

When avacopan was incubated with hepatocytes or liver microsomes prepared from rats, hamsters, rabbits, dogs, monkeys, and humans, 11 metabolites including M1, M3, and M6 were detected in addition to unchanged avacopan.

Avacopan or M1 was incubated with human liver microsomes in the presence of an inhibitor specific to each of the cytochrome P450 (CYP) isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19,

[8] Specimens from mice were tested only with avacopan.
[9] Albino rats underwent the autoradiography at 1, 2, 4, 8, 24, and 72 hours, and pigmented rats underwent it at 1, 2, 4, 8, 24, 72, 168, and 336 hours.

CYP2D6, and CYP3A4[10]) to determine their subsequent inhibition against metabolism of avacopan and M1. The results suggested that CYP3A4 and CYP2B6 are involved in metabolism of avacopan, and CYP3A4, CYP2B6, CYP2C8, and CYP2C19 are involved in metabolism of M1, respectively.

When avacopan or M1 was incubated with a recombinant human CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4), avacopan was metabolized into at least 9 metabolites including M1, M3, and M6, and M1 was metabolized into at least 5 metabolites including M3 and M26, suggesting that formation of any metabolite is associated with CYP3A4, and the other CYP isoforms are also involved in formation of the metabolites (Table 9).

Table 9. Metabolites of avacopan or M1 and contribution of CYP isoforms to their formation

Metabolite	Contribution (%) of each CYP isoform to formation of each metabolite													
	Avacopan							M1[a)]						
	3A4	1A2	2B6	2C9	2C19	2D6	2C8	3A4	1A2	2B6	2C9	2C19	2D6	2C8
M1	68.9	2.5	0.2	0.1	9.0	17.6	1.7							
M3	84.3	0	0	0	0	13.8	1.9	56.5	0	2.8	0	10.3	19.5	10.7
M6	9.5	3.2	19.5	3.3	30.6	17.7	16.1							
M26	100	0	0	0	0	0	0	100	0	0	0	0	0	0
M8/M17/M18	90.8	0	0	0.4	2.6	4.4	1.9							
M9	92.0	0	3.0	0	2.3	2.8	0							
M10/M11	98.3	0	0	0	0	1.7	0	92.7	0.1	0	0.5	0.2	2.5	3.9
M16	100	0	0	0	0	0	0	92.2	0	0	0	0	1.7	6.1
M19	100	0	0	0	0	0	0	100	0	0	0	0	0	0

a) None of M1, M6, M8/M17/M18, and M9 were detected as metabolites of M1.

4.3.2 *In vivo* studies (4.2.2.4.6 and 4.2.2.4.7)

Table 10 shows metabolites found in samples from rats or monkeys that orally received a single dose of ^{14}C-avacopan 15 mg/kg.

Table 10. Metabolite profile of avacopan in various animal species

Animal species	Dosage regimen	Test article	n	Plasma	Bile	Feces	Urine	Attached document CTD
Rat	15 mg/kg Single oral dose	^{14}C-avacopan	3/sex/ timepoint	Up to 168 hours post-dose Unchanged avacopan, M1, M3, M6, M15		Up to 72 hours post-dose Unchanged avacopan, M15, M3, M25, M1, M6[a)]	Up to 72 hours post-dose M3,[b)] M15[b)]	4.2.2.4.6
			3/sex[c)]/ timepoint		Up to 48 hours post-dose M2, M24, M3, M5, M25, M6, unchanged avacopan			4.2.2.4.6
Monkey	15 mg/kg Single oral dose	^{14}C-avacopan	3/sex	Up to 168 hours post-dose M1, unchanged avacopan, M10/M11, M12		Up to 96 hours post-dose Unchanged avacopan, M1, M10/M11, M16, M23, M9	Up to 120 hours post-dose Unchanged avacopan, M1, M10/M11, M16	4.2.2.4.7

a) Detected only in males, b) Detected only in females, c) Bile-duct-cannulated rats

Figure 1 shows the postulated metabolic pathways of avacopan based on the above investigation.

[10)] The following inhibitors against CYP isoforms were used: Furafylline for CYP1A2, thiotepa for CYP2B6, quercetin for CYP2C8, sulfaphenazole for CYP2C9, ticlopidine for CYP2C19, quinidine for CYP2D6, and ketoconazole for CYP3A4

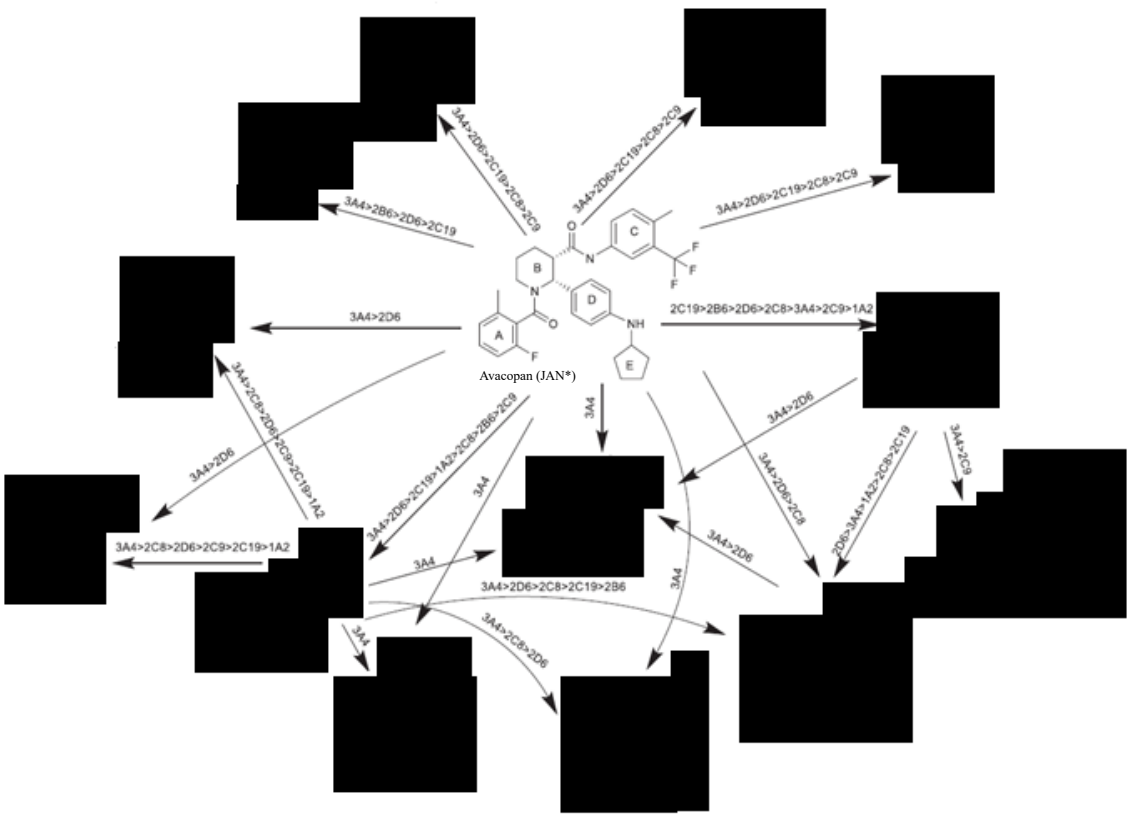

Figure 1. Postulated metabolic pathways of avacopan

4.4 Excretion

4.4.1 Fecal and biliary excretion (CTD 4.2.2.3.4 and 4.2.2.5.1)

Albino rats (n = 3/sex) orally received a single dose of ^{14}C-avacopan 15 mg/kg. The mean total recovery of radioactivity up to 168 hours post-dose was 97.1% in males and 97.7% in females, urinary recovery of radioactivity was 2.71% in males and 1.05% in females, and fecal recovery of radioactivity was 92.6% in males and 96.1% in females. Major metabolites excreted up to 72 hours post-dose (the percentage of total radioactivity administered) were M3 (10.0% in females)[11] and M15 (2.51% in females)[11] in urine and unchanged avacopan (21.5% in males, 19.5% in females), M15 (12.5%, 17.2%), M3 (9.83%, 12.0%), and M25 (7.62%, 6.08%) in feces.

Bile duct-cannulated rats (n = 3/sex) orally received a single dose of ^{14}C-avacopan 15 mg/kg. The mean total recovery of radioactivity up to 120 hours post-dose was 93.9% in males and 97.3% in females, biliary recovery of radioactivity was 27.2% in males and 24.6% in females, urinary recovery of radioactivity was 0.940% in males and 1.04% in females, and fecal recovery of radioactivity was 62.7% in males and 70.9% in females. Major metabolites excreted into bile up to 48 hours post-dose (the percentage of total radioactivity administered) were M2 (12.8% in males, 32.3% in females), M24 (12.0%, 15.5%), M3 (7.82%, 5.69%), M5 (5.89%, 6.92%), M25 (3.13%, 3.67%), and unchanged avacopan (1.00%, 1.45%).

[11] Not detected in males

Cynomolgus monkeys (n = 3/sex) orally received a single dose of ^{14}C-avacopan 15 mg/kg. The mean total recovery of radioactivity up to 168 hours post-dose was 71.0% in males and 72.1% in females, urinary recovery of radioactivity was 3.78% in males and 4.31% in females, and fecal recovery of radioactivity was 29.1% in males and 24.8% in females. Major metabolites excreted in these samples (the percentage of total radioactivity administered) were unchanged avacopan (26%), M1 (3.7%), M10/M11 (2.1%), and M16 (1.6%) in urine up to 120 hours post-dose and unchanged avacopan (31.0%), M1 (14.6%), M10/M11 (9%), M16 (3.3%), M23 (1.9%), and M9 (1.7%) in feces up to 96 hours post-dose. From cage washings, however, radioactivity (38.1% in males, 35.5% in females) presumably derived from watery stool attributable to PEG-400 in vehicle was recovered. The applicant therefore explained that the actual values for the total recovery and fecal excretion were potentially higher than the above values.

4.5 Pharmacokinetic drug-interactions

4.5.1 Enzyme inhibition and induction (CTD 4.2.2.6.1 to 4.2.2.6.7)

Inhibitory effect of avacopan and M1 against CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was investigated using human liver microsomes.[12)] No clinically relevant inhibitory effect was observed except for the inhibitory effect of M1 against CYP2C9 (IC_{50}, 4.7 μmol/L). Time-dependent inhibitory effect of avacopan and M1 against CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was investigated.[13)] Both avacopan and M1 inhibited CYP3A4 in a time-dependent manner.

Induction effects of avacopan (0.03-30 μmol/L) and M1 (10 μmol/L) on enzymatic activities of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) and induction effect of avacopan (0.03-30 μmol/L) on messenger ribonucleic acid (mRNA) expression of these isoforms were investigated.[14)] Avacopan and M1 did not induce either the enzymatic activity or mRNA expression of CYP1A2 and CYP2B6. The enzymatic activity of CYP3A4, on the other hand, decreased in the presence of avacopan or M1, but the mRNA expression increased 1.11 to 7.51 times in the presence of avacopan compared with that in the absence of avacopan (the increased mRNA expression corresponds to 30%-40% of that induced by rifampicin, the positive control), suggesting that avacopan induces CYP3A4.

4.5.2 Inhibition against and substrate potential for drug transporters (CTD 4.2.2.6.8)

Inhibitory effect of avacopan and M1 against transporters was investigated using Madin-Darby canine kidney (MDCK)II cells expressing human multi drug resistance associated protein (MDR)1/P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP), MDCKII-Fin cells expressing human multidrug and toxin extrusion protein (MATE)1 and MATE2-K, and human embryonic kidney 293 (HEK293) cells expressing human organic anion transporter (OAT)1, OAT3, organic anion transporting

12) The following substrates for CYP isoforms were used: Phenacetin for CYP1A2, bupropion for CYP2B6, paclitaxel for CYP2C8, diclofenac for CYP2C9, *S*-mephenytoin (avacopan)/omeprazole (M1) for CYP2C19, dextromethorphan for CYP2D6, and midazolam and testosterone CYP3A4.

13) The following substrates for CYP isoforms were used: Phenacetin for CYP1A2, bupropion for CYP2B6, amodiaquine for CYP2C8, diclofenac for CYP2C9, *S*-mephenytoin for CYP2C19, dextromethorphan for CYP2D6, and midazolam for CYP3A4.

14) The following substrates for CYP isoforms were used: Phenacetin for CYP1A2, bupropion for CYP2B6, and testosterone for CYP3A4.

polypeptide (OATP)1B1, OATP1B3 or organic cation transporter (OCT)2. Avacopan and M1 did not inhibit any of the transporters.[15)]

Investigation using MDCKII cells expressing human MDR1/P-gp or BCRP and HEK293 cells expressing OATP1B1 and OATP1B3[16)] suggested that M1 is a substrate for MDR1/P-gp. Because urinary excretion of avacopan and M1 little contributes to elimination, their substrate potential for MATE1, MATE2-K, OAT1, OAT3, and OCT2 was not investigated.

4.5.3 Other drug-interactions (CTD 4.2.1.2.4, 4.2.1.2.5, and 4.2.2.6.9)

Drug-interactions with prednisolone, CY, AZA, and mycophenolic acid, drugs generally prescribed for treatment of ANCA-associated vasculitis, were investigated.

Avacopan and M1 did not inhibit either of the activities of 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and type 2 (11β-HSD2), enzymes involved in metabolism of GC. Prednisone in human plasma and a percentage of the unbound prednisolone fraction (equilibrium dialysis method) remained unaffected by avacopan 1 μmol/L.

In an *in vitro* study, avacopan (300 nmol/L) and M1 (300 nmol/L) did not inhibit antiproliferative effect of CY on peripheral blood mononuclear cells.

The applicant discussed that AZA and mycophenolic acid were unlikely to cause drug-interactions with avacopan because these drugs are metabolized by non-CYP metabolic enzymes.

4.R Outline of the review conducted by PMDA

The applicant's explanation about placental transfer and excretion into milk for avacopan:

- Placental transfer

Placental transfer of avacopan has not been investigated, but an embryo-fetal development toxicity study of avacopan in hamsters showed an increased incidence of short supernumerary ribs at an exposure approximately 5 times the clinical exposure [see Section 5.5], and thus the possibility that avacopan crossed the placenta to affect the fetuses cannot be ruled out.

In addition, avacopan is considered likely to cross the blood-placental barrier and enter fetuses through simple diffusion because avacopan has high membrane permeability [see Section 4.1.3] and does not serve as a substrate for exporters (MDR1/P-gp and BCRP), which are expressed on the brush border membrane in the placenta and interfere with transfer of drugs into the fetuses [see Section 4.5.2].

Additionally in view of results from embryo-fetal development studies in hamsters and rabbits [see Section 5.5], the package insert is planned to include a cautionary statement that use in pregnant women is not recommended.

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15) The following substrates for transporters were used: Digoxin for P-gp, prazosin for BCRP, metformin for MATE1, MATE2-K and OCT2, tenofovir for OAT1, methotrexate for OAT3, estradiol-17β glucuronide for OATP1B1, and cholecystokinin octapeptide for OATP1B3.

16) The following inhibitors of transporters were used: Valspodar for P-gp, Ko143 for BCRP, rifampicin for OATP1B1 and OATP1B3.

- Excretion into milk

Excretion of avacopan into milk has not been investigated, but a reproductive and developmental toxicity study of avacopan in hamsters showed that avacopan was found in plasma specimens from both orally-treated maternal animals on Postpartum Day 15 and their offspring by plasma avacopan concentration measurement [see Section 5.5]. Avacopan is therefore considered likely to enter milk from lactating hamsters. Accordingly, the package insert is planned to include a cautionary statement that appropriateness of continued lactation should be considered for lactating women by weighing the treatment with the benefit of breast feeding.

PMDA's view:

PMDA accepted the applicant's explanation. The above review and submitted non-clinical pharmacokinetic study results gave a grasp of the body's handling of avacopan to a certain extent.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted toxicity data, in the form of results from single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies (immunotoxicity and phototoxicity studies and evaluation on impurities). Unless otherwise specified, polyethylene glycol 400/polyethylene glycol (15)-hydroxystearic acid ([redacted], v/v) was used as a vehicle.

5.1 Single-dose toxicity

In oral or nasogastric dose toxicity studies in rats and cynomolgus monkeys, an approximate lethal dose and acute toxicity were evaluated (Table 11). The approximate lethal doses in rats and cynomolgus monkeys were determined to be >100 mg/kg and >120 mg/kg, respectively. No acute symptoms were observed in either rats or cynomolgus monkeys. In a 26-week repeated-dose toxicity study in rats [see Section 5.2], the first dose of avacopan 200 mg/kg/day did not lead to deaths or acute symptoms either.

Table 11. Outline of single-dose toxicity study and evaluation results

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female rats (SD)	Oral	0, 5, 25, 100	None	>100	4.2.3.1.1
Male and female cynomolgus monkeys	Nasogastric	3,[a] 50,[a] 65,[a] 80,[b] 120[b]	None	>120	4.2.3.2.10

a) 4-day treatment, b) 2-day treatment

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies in rats were conducted (Table 12). Although abnormal values and findings listed in Table 12 were observed in rats treated with avacopan, all of these were considered to be of low toxicological significance because of no related changes.

In the 26-week repeated oral dose toxicity study in rats, the NOAEL was determined to be 200 mg/kg/day for both males and females, and at this NOAEL, $AUC_{0\text{-}24h}$ (82700 ng·h/mL in males and

106000 ng·h/mL in females) was approximately 12 times (males) and approximately 15 times (females) the clinical exposure ($AUC_{0\text{-}24h}$, 6932 ng·h/mL).[17)]

Table 12. Outline of rat repeated-dose toxicity study results

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (SD)	Oral gavage	4 weeks (once daily) + 2-week recovery period	0, 5, 25, 100	≥25: High prothrombin time (male) Recovery period None	100	4.2.3.2.1
Male and female rats (SD)	Oral gavage	13 weeks (once daily) + 4-week recovery period	0, 3, 15, 100	≥3: Salivation[a)] (male and female) Recovery period None	100	4.2.3.2.2 4.2.2.4.8
Male and female rats (SD)	Oral gavage	26 weeks + 6-week recovery period	0,[c)] 5,[c)] 15,[c)] 100,[c)] 0,[d)] 200[d)]	≥15: High white blood cell count (female) ≥100: High blood lymphocyte count[b)] (male and female), low blood calcium value (female) 200: High urinary volume (male), low mean cell volume and low mean cell hemoglobin, high ALT (female) Recovery period None	200	4.2.3.2.3

a) Except females at 3 mg/kg, b) Except females at 100 mg/kg, c) Once daily administration, d) Twice daily administration

Repeated oral or nasogastric dose toxicity studies in cynomolgus monkeys were conducted (Table 13). Although mildly high liver/body weight ratio was observed in the 4-week repeated-dose toxicity study as an abnormal finding in cynomolgus monkeys treated with avacopan, it was considered to be of low toxicological significance because of no related changes.

In the 44-week repeated dose toxicity study in cynomolgus monkeys, the NOAEL was determined to be 30/45 mg/kg/day for both males and females, and at this NOAEL, $AUC_{0\text{-}24h}$ (26400 ng·h/mL in males and 32200 ng·h/mL in females) was approximately 3.8 times (males) and approximately 4.6 times (females) the clinical exposure ($AUC_{0\text{-}24h}$, 6932 ng·h/mL). The exposure ($AUC_{0\text{-}24h}$) to the metabolite M1 in the avacopan high dose group was 9330 ng·h/mL in males and 9840 ng·h/mL in females.

Table 13. Outline of cynomolgus monkey repeated-dose toxicity study results

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female cynomolgus monkeys	Oral gavage	4 weeks (once daily) + 2-week recovery period	0, 5, 15, 50	50: Mildly high liver/body weight ratio (female) Recovery period None	50	4.2.3.2.5
Male and female cynomolgus monkeys	Oral gavage	20 weeks (once daily) + 4-weeks recovery period	0, 5, 15, 30	None Recovery period None	30	4.2.3.2.6 4.2.2.4.8
Male and female cynomolgus monkeys	Nasogastric[a)]/ oral gavage[b)]	44 weeks + 6-weeks recovery period	Up to Week 25 0,[c)] 0,[d)] 5,[c)] 15,[c)] 30[d)] Weeks 26-44 0,[c)] 0,[d)] 7.25,[c)] 22.5,[c)] 45[d)]	None Recovery period None	30/45	4.2.3.2.7

a) Weeks 1-5, b) Weeks 6-44, c) Once daily administration, d) Twice daily administration

[17)] Plasma exposure in patients with ANCA-associated vasculitis orally treated with avacopan 30 mg twice daily

5.3 Genotoxicity

Genotoxicity of avacopan was investigated in an Ames test and a forward gene mutation assay in mouse lymphoma cells *in vitro* as well as in a bone marrow micronucleus assay in rats *in vivo* (Table 14). Avacopan was determined to be negative for genotoxicity. In the bone marrow micronucleus assay in rats, the maximum exposure was observed at 500 mg/kg/day. C_{max} (5060 ng/mL) at this dose was approximately 14.5 times the clinical exposure (C_{max}, 349 ng/mL).

Table 14. Outline of genotoxicity study results

Type of study		Test system	Metabolic activation (treatment duration)	Concentration or dose	Test results	Attached document CTD
In vitro	Ames test	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvr*A	S9-/+	0, 33.3, 100, 333, 1000, 3330, 5000 µg/plate	Negative	4.2.3.3.1.1 4.2.3.7.5.1
	Forward mutation assay	L5178Y TK$^{+/-}$ mouse lymphoma cells	S9- (24 hours)	0, 1.56, 3.13, 25.0, 50.0, 100, 200, 300, 400, 500 µg/mL	Negative	4.2.3.3.1.2
			S9-/+ (4 hours)	0, 0.781, 1.56, 3.13,[a] 6.25, 12.5, 25.0,[a] 50.0, 100, 200, 300,[a] 400, 500 µg/mL	Negative	
In vivo	Rat micronucleus test	Male rat (SD) bone marrow		0, 500, 1000, 2000 mg/kg/day (oral, repeatedly for 2 days)	Negative	4.2.3.3.2.1 4.2.2.2.5

Vehicle for *in vitro* studies: Dimethyl sulfoxide (DMSO)
a) S9+ only

5.4 Carcinogenicity

An oral dose carcinogenicity study in rats was conducted (Table 15). No tumorigenesis related to avacopan occurred. Tumor lesions listed in Table 15 that did not occur in the vehicle control group or tended to occur more frequently than in the vehicle control group were considered unlikely to be related to avacopan because the data fell within a range of historical control data of this animal species.

The above results indicated that the non-carcinogenic dose is 100 mg/kg. In this study, the maximum exposure was observed at avacopan 30 mg/kg/day, and $AUC_{0\text{-}24h}$ after 4-week repeated administration at this dose (25600 ng·h/mL in males and 33400 ng·h/mL in females) was approximately 3.7 times (males) and approximately 4.8 times (females) the clinical exposure ($AUC_{0\text{-}24h}$, 6932 ng·h/mL). The maximum exposure ($AUC_{0\text{-}24h}$) to the metabolite M1 was observed at avacopan 100 mg/kg/day (males) and 10 mg/kg/day (females) and the values were 1440 ng·h/mL (males) and 3670 ng·h/mL (females).

Table 15. Outline of rat carcinogenicity study results

Test system	Route of administration	Treatment duration	Major lesions		Dose (mg/kg/day)					Non-carcinogenic dose (mg/kg/day)	Attached document CTD
					Control I	Control II	Avacopan				
					0	0	10	30	100		
				n/sex	57/sex	57/sex	57/sex	57/sex	57/sex		
Male and female rats (SD)	Oral gavage	2 years	Tumor lesion							100	4.2.3.4.1.1
			Thyroid/C cell adenoma	Male	7	6	9	9	13		
				Female	5	5	8	10	4		
			Adrenal gland/malignant pheochromocytoma	Male	2	1	0	0	1		
				Female	0	1	0	3	0		
			Skin/fibrosarcoma	Male	1	1	5	3	0		
				Female	1	0	0	1	1		
			Haemolymphoreticular tumour	Male	1	0	4	2	0		
				Female	2	2	1	0	0		
			Haemolymphoreticular tumour/ histiocytic sarcoma	Male	0	0	3	1	0		
				Female	1	2	0	0	0		
			Proliferative lesion								
			Thyroid/C cell hyperplasia	Male	6	6	6	7	11		
				Female	14	11	10	16	10		
			Other findings								
			Survival rate (%)	Male	45.6	35.1	36.8	36.8	47.4		
				Female	35.1	50.9	49.1	45.6	45.6		

Control I, Polyethylene glycol 400/polyethylene glycol (15)-hydroxystearic acid ([redacted], v/v); Control II, Water

An oral dose carcinogenicity study in hamsters was conducted (Table 16). No tumorigenesis related to avacopan occurred. Tumor lesions listed in Table 16 that did not occur in the vehicle control group or tended to occur more frequently than in the vehicle control group were considered unlikely to be related to avacopan because the data fell within a range of historical control data of this animal species. Non-tumor lesions observed were increased incidence and severity of mineralization in the ovary in the avacopan groups.

The above results indicated that the non-carcinogenic dose of avacopan is 100 mg/kg/day, and $AUC_{0\text{-}24h}$ at Week 26 at this dose (42000 ng·h/mL in males and 35600 ng·h/mL in females) is approximately 6.1 times (males) and approximately 5.1 times (females) the clinical exposure ($AUC_{0\text{-}24h}$, 6932 ng·h/mL). The exposure ($AUC_{0\text{-}24h}$) to the metabolite M1 in the avacopan 100 mg/kg/day group was 2850 ng·h/mL (males) and 2500 ng·h/mL (females).

Table 16. Outline of hamster carcinogenicity study results

Test system	Route of administration	Treatment duration	Major lesions		Dose (mg/kg/day)					Non-carcinogenic dose (mg/kg/day)	Attached document CTD
					Control I	Control II	Avacopan				
					0	0	10	30	100		
				n/sex	65/sex	65/sex	65/sex	65/sex	65/sex		
Male and female hamsters (Golden Syrian)	Oral gavage	2 years	Tumor lesion							100	4.2.3.4.1.2
			Adrenal gland/cortical adenoma	Male	5	21	13	7	8		
				Female	10	11	9	10	8		
			Thyroid/C cell adenoma or carcinoma	Male	0	1	0	1	2		
				Female	3	3	9	6	3		
			Parathyroid gland/adenoma	Male	2	1	0	3	2		
				Female	9	18	16	17	12		
			Uterus/adenoma	Male	—	—	—	—	—		
				Female	1	0	1	1	4		
			Malignant lymphoma (pleomorphic)	Male	0	0	1	0	0		
				Female	0	3	0	1	3		
			Vagina/squamous papilloma	Male	—	—	—	—	—		
				Female	0	2	3	2	4		
			Other findings								
			Ovary/mineralization	Male	—	—	—	—	—		
				Female	2	4	5	15	32		
			Survival rate (%)	Male	30.8	63.1	40.0	40.0	40.0		
				Female	33.8	30.8	40.0	27.7	30.8		

Control I, Polyethylene glycol 400/polyethylene glycol (15)-hydroxystearic acid ([redacted], v/v); Control II, Water

5.5 Reproductive and developmental toxicity

The following oral studies were conducted: Fertility and early embryonic development to implantation in male and female hamsters, embryo-fetal development in hamsters and rabbits, and effects on pre- and postnatal development, including maternal function, in hamsters (Table 17). In the study for embryo-fetal development in hamsters, an increased incidence of short supernumerary ribs was observed in the avacopan groups. In the study for embryo-fetal development in rabbits, an increased number of maternal animals with abortion observed is considered as a change secondary to toxicity in the maternal animals. In the study for effects on pre- and postnatal development, including maternal function, in hamsters, glans penis·preputial separation delayed was observed in the F_1 offspring but was considered to be of low toxicological significance because no findings related to changes in reproductive hormone were observed in any other toxicity studies.

At the NOAEL for fertility and early embryonic development (1000 mg/kg/day in both males and females), $AUC_{0\text{-}24h}$ (47340 ng·h/mL in males and 35100 ng·h/mL in females[18]) was approximately 6.8 times (males) and approximately 5.1 times (females) the clinical exposure ($AUC_{0\text{-}24h}$, 6932 ng·h/mL). At the NOAEL (1000 mg/kg/day in hamsters and 200 mg/kg/day in rabbits) in the studies for embryo-fetal development, the maximum exposures ($AUC_{0\text{-}24h}$, 36400 ng·h/mL in hamsters on Gestation Day 12 and 4180 ng·h/mL in rabbits on Gestation Day 18) were approximately 5.3 times (hamsters) and approximately 0.6 times (rabbits) the clinical exposure ($AUC_{0\text{-}24h}$, 6932 ng·h/mL). The maximum exposure ($AUC_{0\text{-}24h}$) to the metabolite M1 in the studies for embryo-fetal development was 1680 ng·h/mL in hamsters and 780 ng·h/mL in rabbits. In the study for effects on pre- and postnatal development, including maternal function, the maximum exposure was observed at 100 mg/kg/day of avacopan, and $AUC_{0\text{-}24h}$ at this dose (43800 ng·h/mL [on Postpartum Day 15]) was approximately 6.3 times the clinical exposure ($AUC_{0\text{-}24h}$, 6932 ng·h/mL).

[18] Plasma exposure at the NOAEL (1000 mg/kg) at Week 4 in the 13-week repeated oral dose toxicity study in hamsters [see Section 5.6.4]

Table 17. Outline of reproductive and developmental toxicity study results

Type of study	Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Study for fertility and early embryonic development to implantation	Male and female hamsters (Golden Syrian)	Oral gavage	Male: From 28 days before mating to day before necropsy Female: From 15 days before mating to Gestation Day 12	0,[a] 10,[a] 30,[a] 100[a] 0,[b] 1000[b]	Parent animal None Reproductive function None Early embryonic development None	Parent animal (general toxicity): 1000 Parent animal (reproductive function): 1000 Fertility and early embryonic development: 1000	4.2.3.5.1.1
Study for embryo-fetal development	Female hamster (Golden Syrian)	Oral gavage	From Gestation Day 6-12 Caesarean section: Gestation Day 15	0,[a] 10,[a] 30,[a] 100[a] 0,[b] 1000[b]	Maternal animal None Embryo-fetal development 1000: Increased incidence of maternal animals and fetuses with short supernumerary ribs	Maternal animal (general toxicity/reproductive function): 1000 Embryo-fetal development: 1000	4.2.3.5.2.1
	Female rabbit (NZW)	Oral gavage	Gestation Day 6-18 (once daily) Caesarean section: Gestation Day 29	0, 10, 30, 200	Maternal animal 200: Decreased feces, emaciation, red ejected tissue, red aborted mass, high number of animals with abortion Embryo-fetal development None	Maternal animal (general toxicity/reproductive function): 30 Embryo-fetal development: 200	4.2.3.5.2.2
Study for effects on pre- and postnatal development, including maternal function	Female hamster (Golden Syrian)	Oral gavage	Maternal animal: Gestation Day 6 to Postpartum Day 20	0,[a] 10,[a] 30,[a] 100[a] 0,[b] 1000[b]	Maternal animal None F_1 offspring ≥30: Glans penis·preputial separation delayed	Maternal animal (general toxicity): 1000 Maternal animal (reproductive function): 1000 F_1 offspring (general toxicity): 1000	4.2.3.5.3.1

a) Once daily administration, b) Twice daily administration (avacopan, 500 mg/kg × 2)

5.6 Other studies

5.6.1 Immunotoxicity

In an immunotoxicity study in rats (Table 18), avacopan did not affect antibody production of immunoglobulin (Ig)G and IgM in response to keyhole limpet hemocyanin (KLH). In the 44-week repeated-dose toxicity study in monkeys (Table 13), antibody production of IgG and IgM in response to KLH and lymphocyte subset were not affected either.

Table 18. Outline of immunotoxicity study results

Test system	Test method	Major findings	Attached document CTD
Male and female rats (Fisher)	Avacopan was orally administered at 0, 3, 15, and 100 mg/kg once daily for 4 weeks. On Day 15, animals were immunized with KLH, and then anti-KLH antibody concentrations were measured on Days 20 (IgM) and 29 (IgG).	None	4.2.3.7.2.1

CY 10 mg/kg was orally administered as the positive control.

5.6.2 Phototoxicity

Avacopan absorbs light between 290 and 370 nm, and its molar extinction coefficient is 2989 L mol^{-1} cm^{-1} at 290 nm. In view of these results, a neutral red uptake (NRU) phototoxicity study in mouse fibroblasts was conducted (Table 19), and avacopan was considered to be negative for phototoxicity.

Table 19. Outline of phototoxicity study results

Type of study	Test system	Test method	Major findings	Attached document CTD
Phototoxicity	Mouse fibroblast (BALB/c 3T3)	0,[a] 0.18, 0.32, 0.56, 1.0, 1.78, 3.16, 5.62, 10 µg/mL Exposed to UVA 5 J/cm^2 and UVB 21-22 mJ/cm^2	None (photo irritation factor, 1,[b] 1[b]; mean photo effect, −0.002, 0.000)	4.2.3.7.7.1

a) Vehicle, Phosphate buffered saline (PBS) solution containing 1% DMSO
b) Expressed in substitute figures because of unavailability of calculated figures owing to the absence of toxicity

5.6.3 Toxicologic evaluation of metabolite

In humans treated with avacopan 30 mg twice daily, M1 was identified as a metabolite accounting for >10% of the total exposure to drug-related substances [see Section 6.2.1.3]. The safety of M1 was characterized and evaluated in the 44-week repeated oral dose toxicity study in cynomolgus monkeys, the carcinogenicity study in rats, and the study for embryo-fetal development in hamsters where the exposure was at least 50% of the clinical exposure. No toxicological findings specific to the metabolite were observed.

5.6.4 Toxicologic evaluation of impurities

Of impurities found in the proposed manufacturing process of the drug substance, Impurity A, Impurity B, and Impurity C were identified as specified impurities.[19] Impurity A (same structure as metabolite [redacted]) was subjected to an Ames test, and it was negative for mutagenicity. Because mutagenicity of Impurity B was denied by *in silico* evaluation, and Impurity C is an enantiomer of avacopan, both impurities were considered to be non-mutagenic. Impurity A was identified as an impurity requiring qualification,[19] and a 13-week repeated oral dose toxicity study in hamsters was conducted using the drug substance that contained the concerned impurity at 0.2% (Table 20). Abnormal findings in hamsters treated with the drug substance containing the impurity were increased blood triglyceride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and inorganic phosphorus, but the increased triglyceride is likely to be a change related to the selective antagonistic effect on C5aR (*Immunology.* 2016;221:822-32, *PLos ONE.* 2013;8:e62531), and the other abnormal values did not accompany related changes. All of these findings were considered to be of low toxicological significance. No other potential mutagenic impurities were found in the drug substance. Impurities in the drug substance do not raise any safety concerns.

Potential impurities generated in the manufacturing process of avacopan were evaluated for mutagenicity *in silico*, and 14 chemical compounds are identified as potential impurities of which mutagenicity could not be ruled out. For others, Impurity D and Impurity E were identified as known genotoxic impurities. Of the potential impurities, Impurity F, an intermediate in the manufacturing process, was subjected to the Ames test, and it was negative for mutagenicity. For the potential impurities

[19] Revision of the Guideline on Impurities in New Drug Products (PFSB/ELD Notification No. 0624001, dated June 24, 2003)

of which mutagenicity could not be ruled out and the known genotoxic impurities, their exposure in humans would be kept below the toxicological threshold for potential mutagenic impurities by controlling the manufacturing process. The above results indicated that the potential impurities in avacopan are unlikely to raise a safety concern.

Table 20. Outline of repeated oral dose toxicity study results with the drug substance containing impurities

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female hamsters (Golden Syrian)	Oral gavage	13 weeks + 4-week recovery period	0,[a)] 10,[a)] 30,[a)] 100[a)] 0,[b)] 1000[b)]	≥100: Increased blood triglyceride (male and female) 1000: Increased blood AST, ALT, and inorganic phosphorus (male)	1000	4.2.3.2.4

a) Once daily administration, b) Twice daily administration (avacopan, 500 mg/kg × 2)

5.R Outline of the review conducted by PMDA

5.R.1 Mineralization in the ovary

The applicant's explanation about the increased incidence of mineralization in the ovary in hamsters treated with avacopan in the carcinogenicity study:

The cause for the development remains unknown but the concerned finding is unlikely to be adverse because there are no findings related to dystrophic changes (degeneration or necrosis of cells), abnormal laboratory test values suggestive of hypercalcemia, or mineralization in organs or tissues other than the ovary; and no similar finding at exposure above the clinical exposure was observed in the carcinogenicity study in rats or 44-week repeated-dose toxicity study in monkeys.

PMDA accepted the applicant's explanation.

5.R.2 Effects on fetal skeletogenesis

The applicant's explanation about the increased incidence of short supernumerary ribs in hamsters treated with avacopan in the study for embryo-fetal development:

The applicant will include a cautionary statement concerning this finding in the package insert in view of the cause remaining unclear, although it is considered unlikely to be adverse because short supernumerary ribs are absorbed in the vertebral arch during development (*J Appl Toxicol.* 1988;8:91-4, *J Toxicol Envioron Health B Crit Rev.* 2004;7:437-49) and thus the abnormal finding is not suggestive of teratogenicity (*Teratology.* 1973;8:309-16); and there is no public information suggesting any relationship between the selective antagonistic effect on C5aR and teratogenicity at present.

PMDA accepted the applicant's explanation.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The applicant submitted results from studies on food effect (Studies CCX1101 [CTD 5.3.3.1.1] and CL007_168 [CTD 5.3.1.1.1]) as evaluation or reference data.

Plasma concentrations of avacopan or its metabolites were determined by LC-MS/MS (lower limit of quantification, 0.2 or 1 ng/mL). Unless otherwise specified, measured values and pharmacokinetic parameters are expressed as mean or mean ± SD.

6.1.1 Effects of food (Reference CTD 5.3.1.1.1, Study CL007_168 [[redacted] to [redacted]]; CTD 5.3.3.1.1, Study CCX1101 [[redacted] to [redacted]])

An open-label, 2-treatment, 2-period crossover study was conducted in healthy non-Japanese adults to investigate the pharmacokinetics after a single oral administration of avacopan 30 mg in the fasted state or in the fed state with a high-fat meal.[20)] Table 21 shows pharmacokinetic parameters.

Table 21. Pharmacokinetic parameters after a single oral administration of avacopan 30 mg

Analyte	Dosing state	n	C_{max} (ng/mL)	$AUC_{0\text{-}t}$ (ng·h/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	Least squares geometric mean ratio [90% CI] (fed with high-fat meal/fasted)		
								C_{max}	$AUC_{0\text{-}t}$	$AUC_{0\text{-}inf}$
Avacopan	Fed with high-fat meal	16	132 ± 32.5	1460 ± 418	1710 ± 490	6.00 [2.00, 8.01]	97.6 ± 40.1	1.08 [0.92, 1.27]	1.71 [1.51, 1.93]	1.72 [1.47, 2.00]
	Fasted	16	123 ± 35.5	902 ± 440	1050 ± 621[a)]	2.01 [1.50, 4.00]	73.5 ± 35.5[a)]			
M1	Fed with high-fat meal	16	20.8 ± 4.31	532 ± 147	632 ± 175	6.00 [2.51, 12.00]	55.6 ± 17.3	0.49 [0.45, 0.54]	0.87 [0.83, 0.91]	0.89 [0.86, 0.93]
	Fasted	16	42.2 ± 8.91	613 ± 182	707 ± 194	3.00 [2.00, 4.01]	51.3 ± 22.1			

Mean ± SD; t_{max} expressed as median [range]
a) n = 14

A randomized, single-blind study was conducted in healthy Japanese adults to investigate the pharmacokinetics after a single oral administration of avacopan 30 mg in the fasted state or in the fed state with a low-fat meal.[21)] Table 22 shows pharmacokinetic parameters.

Table 22. Pharmacokinetic parameters after a single oral administration of avacopan 30 mg

Analyte	Dosing state	n	C_{max} (ng/mL)	$AUC_{0\text{-}last}$ (ng·h/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	Least squares geometric mean ratio [90% CI] (fed with low-fat meal/fasted)		
								C_{max}	$AUC_{0\text{-}last}$	$AUC_{0\text{-}inf}$
Avacopan	Fed with low-fat meal	8	139 ± 43.0	1086 ± 394	1380 ± 504	2.50 [1.50, 3.00]	109 ± 50.6	1.08 [0.96, 1.22]	1.93 [1.85, 2.02]	2.11 [1.92, 2.32]
	Fasted	8	129 ± 40.7	559 ± 203	653 ± 245	1.50 [1.00, 2.00]	44.3 ± 18.7			
M1	Fed with low-fat meal	8	34.1 ± 10.0	608 ± 233	699 ± 229	3.00 [2.50, 4.00]	45.2 ± 14.8	0.60 [0.55, 0.66]	1.11 [1.01, 1.21]	1.12 [1.03, 1.21]
	Fasted	8	56.1 ± 13.1	539 ± 164	631 ± 211	2.25 [2.00, 2.50]	31.1 ± 8.41			

Mean ± SD; t_{max} expressed as median [range]

6.2 Clinical pharmacology

The applicant submitted results from a Japanese phase I study in healthy adults (Study CCX1101 [CTD 5.3.3.1.1]), a foreign phase II study in patients with ANCA-associated vasculitis (Study CL003_168 [CTD 5.3.5.1.2]), a global phase III study (Study CL010_168 [CTD 5.3.5.1.3]), and QT/corrected QT interval (QTc) evaluation study (Study CL014_168 [CTD 5.3.5.4.1]) as evaluation data. The applicant

20) Fat accounts for approximately 50% of the total calories.
21) Fat accounts for approximately 30% of the total calories.

also submitted results from a foreign phase I study in healthy non-Japanese adults (Study CL001_168 [CTD 5.3.3.1.2]), study in patients with hepatic impairment (Study CL013_168 [CTD 5.3.2.2.1]), interaction study (Study CL008_168 [CTD 5.3.3.4.1]), mass balance study (Study CL004_168 [CTD 5.3.4.1.1]) and population pharmacokinetic analysis as reference data.

6.2.1 Studies in healthy adults

6.2.1.1 Japanese phase I study (CTD 5.3.3.1.1, Study CCX1101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

In the randomized, single-blind study in healthy adults, the pharmacokinetics after a single oral administration of avacopan 10, 30, or 100 mg in the fasted state was investigated, and the pharmacokinetic parameters are shown in Table 23. Table 24 shows pharmacokinetic parameters after twice-daily oral administration of avacopan 30 or 50 mg for 7 days.

Table 23. Pharmacokinetic parameters after a single administration of avacopan (healthy adults)

Analyte	Dose (mg)	Population	n	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V_z/F (L/kg)
Avacopan	10	Japanese	8	38.1 ± 7.29	123 ± 46.8	1.5 [1.0, 3.0]	4.08 ± 1.31	1.36 ± 0.356	7.83 ± 3.12
		Non-Japanese	8	40.4 ± 9.42	139 ± 55.7	1.5 [1.0, 2.0]	4.77 ± 1.48	1.16 ± 0.38	7.42 ± 2.32
	30	Japanese	8	129 ± 40.7	653 ± 245	1.5 [1.0, 2.0]	44.3 ± 18.7	0.870 ± 0.363	48.7 ± 15.6
		Non-Japanese	8	119 ± 42.2	686 ± 234	2.0 [1.5, 2.5]	48.8 ± 24.9	0.705 ± 0.307	40.9 ± 11.8
	100	Japanese	8	522 ± 86.3	4150 ± 1010	2.0 [1.5, 3.0]	81.4 ± 12.7	0.407 ± 0.114	46.4 ± 9.30
M1	10	Japanese	8	18.0 ± 3.69	152 ± 53.3	1.75 [1.5, 3.0]	16.0 ± 5.14	—	—
		Non-Japanese	8	17.1 ± 2.92	178 ± 45.8	2.0 [1.5, 2.5]	26.3 ± 10.8	—	—
	30	Japanese	8	56.1 ± 13.1	631 ± 211	2.25 [2.0, 2.5]	31.1 ± 8.41	—	—
		Non-Japanese	8	42.1 ± 7.91	509 ± 136	2.5 [2.0, 3.0]	30.1 ± 12.8	—	—
	100	Japanese	8	170 ± 15.4	2610 ± 491	2.5 [2.0, 4.0]	41.0 ± 9.02	—	—

Mean ± SD; t_{max} expressed as median [range]; -, Not calculated

Table 24. Pharmacokinetic parameters after multiple administration of avacopan (healthy adults)

Analyte	Dose (mg)	Population	Day of measurement	n	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V_z/F (L/kg)
Avacopan	30	Japanese	1	8	139 ± 28.1	648 ± 178	2.5 [2.0, 4.0]	6.22 ± 2.16	0.640 ± 0.194	5.93 ± 3.02
			7	8	252 ± 55.2	1550 ± 472	2.75 [2.0, 4.0]	150 ± 33.1	0.330 ± 0.110	72.8 ± 36.3
		Non-Japanese	1	8	106 ± 32.6	485 ± 158	2.5 [1.5, 4.0]	6.91 ± 2.89	0.765 ± 0.228	7.50 ± 3.11
			7	8	184 ± 45.2	1020 ± 267	2.5 [2.0, 3.0]	154 ± 44.6	0.428 ± 0.093	91.3 ± 17.1
	50	Japanese	1	8	205 ± 45.1	1000 ± 78.0	2.5 [2.0, 6.0]	7.82 ± 3.00	0.627 ± 0.108	7.25 ± 3.58
			7	8	478 ± 120	2800 ± 765	2.5 [2.0, 4.0]	145 ± 46.4	0.300 ± 0.066	62.1 ± 23.5
M1	30	Japanese	1	8	37.0 ± 5.60	249 ± 37.5	2.5 [2.0, 4.0]	14.0 ± 3.74	—	—
			7	8	81.1 ± 14.7	718 ± 160	4.0 [2.5, 4.0]	63.8 ± 5.02	—	—
		Non-Japanese	1	8	30.0 ± 4.15	195 ± 28.6	3.5 [2.0, 4.0]	12.9 ± 4.09	—	—
			7	8	56.7 ± 9.83	497 ± 95.6	4.0 [3.0, 4.0]	63.8 ± 7.51	—	—
	50	Japanese	1	8	56.0 ± 9.39	392 ± 54.5	3.5 [2.5, 6.0]	15.8 ± 4.18	—	—
			7	8	132 ± 14.5	1220 ± 186	4.0 [2.5, 6.0]	66.3 ± 14.5	—	—

Mean ± SD; t_{max} expressed as median [range]; -, Not calculated

6.2.1.2 Foreign phase I study (Reference CTD 5.3.3.1.2, Study CL001_168 [December 2009 to September 2010])

In the randomized, single-blind study in healthy non-Japanese adults, the pharmacokinetics after a single oral administration of a liquid preparation[22] of avacopan 1, 3, 10, 30 or 100 mg in the fasted state was investigated, and the pharmacokinetic parameters are shown in Table 25. Table 26 shows pharmacokinetic parameters after twice-daily oral administration of avacopan capsules[23] 30 or 50 mg for 7 days.

Table 25. Pharmacokinetic parameters after a single administration of liquid preparation of avacopan (healthy adults)

Analyte	Dose (mg)	n	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Avacopan	1	5	1.84 ± 0.889	6.14 ± 3.25	1.0 [1.0, 1.5]	2.03 ± 0.721	195 ± 79.7	518 ± 131
	3	6	9.17 ± 1.98	25.2 ± 9.58	1.0 [1.0, 1.5]	1.92 ± 1.02	131 ± 38.5	324 ± 99.7
	10	6	25.3 ± 5.71	130 ± 39.4	1.5 [1.5, 2.0]	22.9 ± 7.33	87.0 ± 40.8	2620 ± 722
	30	6	78.7 ± 35.6	643 ± 218[a)]	1.8 [1.0, 2.0]	81.2 ± 26.0[a)]	51.1 ± 16.6[a)]	5600 ± 1610[a)]
	100	6	197 ± 157	2030 ± 1070	1.8 [1.0, 6.0]	64.0 ± 22.1	62.4 ± 34.0	5260 ± 2370

Mean ± SD; t_{max} expressed as median [range]; -, Not calculated
a) n = 5

Table 26. Pharmacokinetic parameters after multiple administration of avacopan capsules (healthy adults)

Analyte	Dose (mg)	Day of measurement	n	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Avacopan	30	1 (a.m.)	6	97.2 ± 16.4	380 ± 89.3	2.0 [1.0, 2.0]	—	—	—
		1 (p.m.)	6	274 ± 69.9	695 ± 171	2.0 [2.0, 2.0]	—	—	—
		7 (a.m.)	6	161 ± 22.9	880 ± 230	2.0 [2.0, 3.0]	—	—	—
		7 (p.m.)	6	191 ± 60.2	966 ± 243	2.0 [1.0, 4.0]	129 ± 30.7	5.86 ± 2.09	1080 ± 436
	50	1 (a.m.)	6	202 ± 66.1	820 ± 274	2.0 [2.0, 2.0]	—	—	—
		1 (p.m.)	6	423 ± 204	1400 ± 728	2.0 [2.0, 3.0]	—	—	—
		7 (a.m.)	6	425 ± 156	2340 ± 885	2.0 [2.0, 3.0]	—	—	—
		7 (p.m.)	6	359 ± 139	2180 ± 811	2.5 [2.0, 4.0]	120 ± 19.5	4.05 ± 1.02	695 ± 165

Mean ± SD; t_{max} expressed as median [range]; -, Not calculated

6.2.1.3 Mass balance study (Reference CTD 5.3.4.1.1, Study CL004_168 [[redacted] to [redacted]])

Mass balance in healthy non-Japanese adults (6 subjects) after a single oral administration of ^{14}C-avacopan 100 mg was investigated. C_{max} of avacopan in plasma, radioactivity in plasma, and radioactivity in whole blood was 432 ± 129 ng/mL, 997 ± 201, and 588 ± 122 ng eq/mL, respectively, with t_{max} (median) of 2.50, 3.00, and 3.00 hours, respectively, and $t_{1/2}$ was 225 ± 105, 127 ± 30.0, and 111 ± 60.0 hours, respectively. The mean C_{max} ratio of total radioactivity in plasma to that in whole blood was 0.6. The total recovery rate of radioactivity up to 336 hours post-dose was 86.7% ± 4.04%, and 9.5% ± 0.88% and 77.2% ± 3.71% of the administered radioactivity were recovered in the urine and fecal, respectively. The recovery rates of unchanged avacopan in urine and feces were 0.02% and 6.7%, respectively; metabolites accounted for most of the radioactivity in the urine and feces. Of the 7

[22] Liquid preparations using Vehicle A or Vehicle B were administered to 3 subjects each (for 1 mg, a liquid preparation using Vehicle A was administered to 2 subjects).
[23] Capsules using Vehicle C or Vehicle D (identical formulation as avacopan) were administered to 3 subjects each.

identified metabolites in plasma, only M1 accounted for >10% of the total plasma exposure as a single metabolite.

6.2.2 Studies in patients with ANCA-associated vasculitis

6.2.2.1 Foreign phase II study (CTD 5.3.5.1.2, Study CL003_168 [February 2015 to July 2016])

In a randomized, double-blind, parallel-group study in patients with ANCA-associated vasculitis [see Section 7.1.2], pharmacokinetic parameters 1 day after twice-daily oral administration of avacopan 10 mg or 30 mg are shown in Table 27. Time course of plasma trough concentration during multiple oral administration of avacopan are shown in Table 28.

Table 27. Pharmacokinetic parameters 1 day after administration of avacopan (patients with ANCA-associated vasculitis)

Analyte	Dose (mg)	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-6} (ng·h/mL)
Avacopan	10 mg	13	51.2 ± 32.0	2.00 [1.00,4.00]	146 ± 79.7
	30 mg	16	177 ± 92.0	2.00 [0.92,3.00]	542 ± 257
M1	10 mg	13	12.1 ± 6.12	3.00 [1.00,4.00]	41.2 ± 18.9
	30 mg	16	31.6 ± 17.7	2.05 [1.00,6.00]	112 ± 46.1

Mean ± SD; t_{max} expressed as median [range]

Table 28. Time course of plasma trough concentration (ng/mL) during multiple administration of avacopan (patients with ANCA-associated vasculitis)

Analyte	Dose (mg)	n	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12
Avacopan	10 mg	13	15.9 ± 10.1 (11)	20.9 ± 9.12 (10)	28.7 ± 15.2 (12)	42.5 ± 28.9 (8)	59.4 ± 32.9 (6)	44.8 ± 28.8 (6)	59.3 ± 28.0 (10)	65.4 ± 32.0 (7)
	30 mg	16	105 ± 87.7 (15)	111 ± 55.6 (12)	108 ± 74.0 (13)	161 ± 106 (10)	169 ± 139 (10)	220 ± 169 (11)	225 ± 150 (10)	238 ± 158 (12)
M1	10 mg	13	13.1 ± 4.68 (11)	15.5 ± 5.56 (10)	17.6 ± 6.72 (12)	21.2 ± 8.59 (8)	26.2 ± 6.44 (6)	22.5 ± 9.88 (6)	27.3 ± 6.88 (10)	30.0 ± 6.21 (7)
	30 mg	16	51.4 ± 32.8 (15)	58.1 ± 23.4 (12)	56.9 ± 28.2 (13)	75.1 ± 40.8 (10)	66.8 ± 51.0 (10)	77.6 ± 41.5 (11)	82.7 ± 49.0 (10)	87.8 ± 50.3 (12)

Mean ±SD (number of patients measured)

6.2.2.2 Global phase III study (CTD 5.3.5.1.3, Study CL010_168 [March 2017 to November 2019])

In a randomized, double-blind, parallel-group study in patients with MPA or GPA [see Section 7.2], time course of plasma trough concentration during twice-daily oral administration of avacopan 30 mg are shown in Table 29.

Table 29. Time course of plasma trough concentration (ng/mL) during multiple administration of avacopan 30 mg (patients with MPA or GPA)

Analyte	Population	n	Week 1	Week 2	Week 4	Week 7	Week 13	Week 26	Week 39	Week 52
Avacopan	Overall population	142	83.0 ± 40.8 (97)	122 ± 61.7 (102)	164 ± 79.9 (90)	187 ± 83.5 (75)	229 ± 108 (92)	252 ± 125 (80)	260 ± 153 (63)	271 ± 199 (62)
	CY/AZA combination population	48	72.5 ± 30.8 (29)	118 ± 53.3 (33)	144 ± 58.8 (37)	187 ± 92.2 (32)	217 ± 112 (33)	234 ± 131 (28)	244 ± 178 (23)	222 ± 150 (22)
	RTX combination population	94	87.5 ± 43.9 (68)	124 ± 65.6 (69)	179 ± 89.4 (53)	187 ± 77.6 (43)	235 ± 106 (59)	262 ± 115 (52)	269 ± 139 (40)	298 ± 218 (40)
	Japanese subgroup	11	139 ± 72.1 (8)	198 ± 73.2 (9)	265 ± 72.8 (8)	262 ± 46.1 (3)	451 ± 156 (4)	322, 447	314	364 ± 80.4 (3)
M1	Overall population	142	50.0 ± 20.9 (97)	65.1 ± 26.4 (102)	77.3 ± 34.9 (90)	78.3 ± 32.2 (75)	95.8 ± 39.0 (92)	101 ± 45.9 (80)	99.3 ± 47.9 (63)	101 ± 52.6 (60)
	CY/AZA combination population	48	46.5 ± 17.9 (29)	63.1 ± 22.9 (33)	68.1 ± 26.5 (37)	74.1 ± 30.2 (32)	89.5 ± 40.1 (33)	93.3 ± 44.9 (28)	88.4 ± 42.4 (23)	85.4 ± 44.1 (22)
	RTX combination population	94	51.5 ± 22.0 (68)	66.0 ± 28.1 (69)	83.6 ± 38.7 (53)	81.4 ± 33.7 (43)	99.3 ± 38.2 (59)	105 ± 46.4 (52)	105 ± 50.2 (40)	110 ± 55.6 (38)
	Japanese subgroup	11	91.5 ± 24.2 (8)	110 ± 29.1 (9)	136 ± 36.0 (8)	138 ± 27.1 (3)	173 ± 38.2 (4)	158, 158	143	157 ± 56.8 (3)

Mean ± SD (number of patients measured), individual values for n = 2

6.2.3 Studies on intrinsic factors

6.2.3.1 Study in subjects with hepatic impairment (Reference CTD 5.3.2.2.1, Study CL013_168 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The pharmacokinetics was investigated in non-Japanese subjects with mild to moderate hepatic impairment (Child-Pugh A or B) and non-Japanese subjects with normal hepatic function after a single oral administration of avacopan 30 mg, and the pharmacokinetic parameters of avacopan are shown in Table 30.

Table 30. Pharmacokinetic parameters of avacopan after a single oral administration of avacopan 30 mg

Analyte	Severity of hepatic impairment	n	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng·h/mL)	Least squares geometric mean ratio [90% CI] (hepatic impairment/normal hepatic function)	
					C_{max}	$AUC_{0\text{-last}}$
Avacopan	Moderate	8	106 ± 31.7	1000 ± 317	0.83 [0.66, 1.03]	1.02 [0.78, 1.33]
	Mild	7[a)]	110 ± 24.1	1050 ± 239	0.87 [0.70, 1.10]	1.09 [0.83, 1.44]
	Normal	8	125 ± 24.8	988 ± 317		
M1	Moderate	8	42.0 ± 12.4	818 ± 306	0.84 [0.66, 1.06]	1.17 [0.90, 1.52]
	Mild	7[a)]	47.2 ± 11.0	788 ± 211	0.95 [0.75, 1.22]	1.15 [0.88, 1.51]
	Normal	8	49.6 ± 12.1	694 ± 210		

Mean ± SD

a) Excluding 1 subject with exposure approximately twice greater than that in the other subjects

6.2.4 Study for pharmacokinetic interaction (Reference CTD 5.3.3.4.1, Study CL008_168 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Drug interactions between avacopan and other concomitant drugs were investigated. Table 31 and Table 32 show least squares geometric mean ratios of pharmacokinetic parameters of avacopan or concomitant drugs administered in combination to those administered alone. Combination of itraconazole, a potent CYP3A4 inhibitor, increased exposure to avacopan (approximately twice for both C_{max} and $AUC_{0\text{-inf}}$), and combination of rifampicin, a potent CYP3A4 inducer, remarkably decreased the exposure to avacopan (by 79% for C_{max} and by 93% for $AUC_{0\text{-inf}}$). Combination of either midazolam, a CYP3A4 substrate, or celecoxib, a CYP2C9 substrate, increased exposure to the substrate yet only less than twice for both C_{max} and $AUC_{0\text{-inf}}$.

Table 31. Effects of concomitant drugs on pharmacokinetic parameters of avacopan

Dosage regimen		No. of subjects analyzed	Analyte	Least squares geometric mean ratio [90% CI]	
Test drug	Concomitant drug			C_{max}	$AUC_{0\text{-}inf}$
Avacopan 30 mg twice daily	Itraconazole 200 mg once daily	16	Avacopan	1.87 [1.70, 2.06]	2.19 [2.00, 2.41][a)]
			M1	1.03 [0.95, 1.11]	1.19 [1.11, 1.28][a)]
Avacopan 30 mg single dose	Rifampicin 600 mg once daily	16	Avacopan	0.21 [0.18, 0.25]	0.074 [0.058, 0.095]
			M1	0.27 [0.23, 0.31]	0.074 [0.062, 0.089]

a) $AUC_{0\text{-}tau}$

Table 32. Effects of avacopan on pharmacokinetic parameters of concomitant drug

Dosage regimen		No. of subjects analyzed	Least squares geometric mean ratio [90% CI]	
Test drug	Concomitant drug		C_{max}	$AUC_{0\text{-}inf}$
Midazolam 2 mg single dose	Avacopan 30 mg twice daily	16	1.55 [1.41, 1.69]	1.81 [1.65, 1.98]
Celecoxib 200 mg single dose	Avacopan 30 mg twice daily	16	1.64 [1.34, 2.00]	1.15 [1.03, 1.28]

6.2.5 Study for QT/QTc (CTD 5.3.5.4.1, Study CL014_168 [[redacted] 20[redacted] to [redacted] 20[redacted]])

In a placebo-controlled, randomized, double-blind, parallel-group study in healthy non-Japanese adults, an effect of avacopan on QT interval was investigated. Avacopan 30 mg was orally administered twice daily for 7 days, followed by twice-daily oral administration of avacopan 100 mg for 7 days or a single oral administration of the placebo or moxifloxacin 400 mg (positive control). A difference of changes in QT interval corrected with Fridericia formula (QTcF) from baseline between the avacopan and placebo groups (ΔΔQTcF) (least squares mean) fell within a range from −1.0 to 4.9 msec at any measurement timepoint,[24)] and the upper limit of 90% confidence interval (CI) of ΔΔQTcF was <10 msec at all the timepoints.

An exposure-response analysis was performed using plasma concentrations of avacopan and M1 as well as changes in QTcF from baseline obtained in this study. C_{max} (geometric means) of avacopan and M1 and ΔΔQTcF (least squares mean [90% CI]) after the twice-daily administration of avacopan 30 mg or 100 mg were 203.0 ng/mL for avacopan, 83.1 ng/mL for MI, and 1.46 [−0.17, 3.09] msec in the avacopan 30 mg group and 779.8 ng/mL for avacopan, 231.4 ng/mL for MI, and 0.82 [−2.41, 4.05] msec in the avacopan 100 mg group. As presented above, ΔΔQTcF is unlikely to exceed 10 msec, and avacopan is thus considered to be negative for a risk of QT interval prolongation.

6.3 Population pharmacokinetic analysis (CTD 5.3.3.5.1 and 5.3.4.2.1)

A population pharmacokinetic analysis was performed using plasma concentration data on avacopan and M1 obtained from 7 clinical studies[25)] in healthy adults or patients with ANCA-associated vasculitis (5682 sampling timepoints for avacopan and 5409 for M1 in 368 subjects in total) (Phoenix NLME ver.8.2).

The basic model for both avacopan and M1 was described as a 3-compartment model with the zero-order absorption and biotransformation, and covariates[26)] selected for avacopan were body weight, age, ALT value, and estimated glomerular filtration rate (eGFR) for CL/F and body weight and albumin for

24) Measurement was performed at 0.5, 1, 2, 3, 4, 5, 6, 9, 12, and 24 hours post-dose.
25) Phase I studies (Studies CCX1101, CL007_168, CL008_168, and CL013_168), phase II studies (Studies CL002_168 and CL003_168), and phase III study (Study CL010_168)
26) Potential covariates investigated were age, sex, race, body weight, BMI, eGFR and other renal and hepatic function parameters.

V/F; and covariates selected for M1 were body weight, age, and eGFR for CL/F and body weight for V/F.

The population pharmacokinetic parameters [95% CI] estimated from the final model were CL/F of 16.3 [13.1, 21.1] L/h and V/F of 345 [290, 421] L for avacopan and CL/F of 28.5 [26.5, 31.1] L/h and V/F of 840 [837, 974] L for M1.

6.4 Exposure-response analysis (CTD 5.3.4.1.1)

An exposure-response relationship was analyzed using data on the C5a-induced neutrophil CD11b upregulation and plasma avacopan concentration obtained from Study CL001_168, and the percent C5aR inhibition was expressed in the following formula.

$$\% \text{ C5aR inhibition} = (1 - [1 / \text{x-fold shift}]) \times 100$$

Figure 2 shows concentration-response curves in which the C5a-induced neutrophil CD11b upregulation is plotted against C5a concentration after administration of avacopan 30 mg twice daily or the placebo. For the plasma avacopan concentration at 2 hours post-dose, administration of avacopan 30 mg shifted the concentration-response curve to the 20-times higher concentration (corresponding to approximately 95% C5aR inhibition). The mean plasma avacopan concentration at 2 hours post-dose during the twice-daily administration of avacopan 30 mg for 7 days was 150.9 ng/mL, which was suggested as the concentration required to inhibit C5aR by approximately 95%.

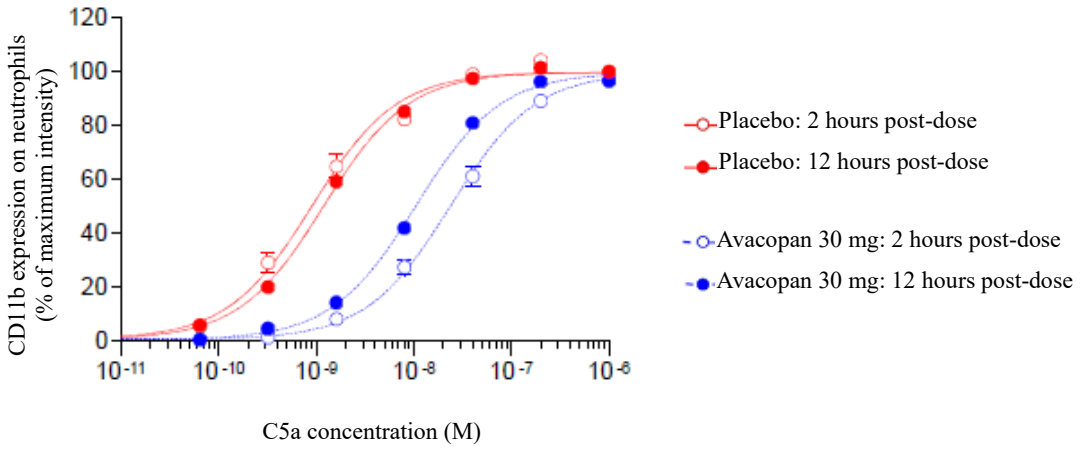

Figure 2. Concentration-response curves for the C5a-induced neutrophil CD11b upregulation after administration of avacopan 30 mg twice daily or placebo

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic differences in pharmacokinetics of avacopan

The applicant's explanation about ethnic differences in pharmacokinetics of avacopan:

In the Japanese phase I study (Study CCX1101) [see Section 6.2.1.1], exposures to avacopan and M1 after multiple doses of avacopan 30 mg tended to be higher in Japanese subjects than in non-Japanese subjects. Distributions of observed exposures in Japanese subjects (range of C_{max} after 7-day administration, 169-335 ng/mL for avacopan and 61.1-98.9 ng/mL for M1; range of AUC_{tau} after 7-day

administration, 712-2340 ng·h/mL for avacopan and 449-891 ng·h/mL for M1) almost overlapped with those in non-Japanese subjects (range of C_{max} after 7-day administration, 144-278 ng/mL for avacopan and 44.3-77.4 ng/mL for M1; range of AUC_{tau} after 7-day administration, 803-1600 ng·h/mL for avacopan and 381-670 ng·h/mL for M1). In addition, race was not selected as a significant covariate in the population pharmacokinetic analysis either [see Section 6.3]. The difference in exposure between Japanese and non-Japanese subjects was not clinically significant in light of no clear difference in the safety between Japanese and non-Japanese subjects [see Section 7.R.3].

PMDA accepted the above applicant's explanation and considers it presumably unproblematic from a pharmacokinetic viewpoint to use results from a global study including Japanese patients with MPA or GPA as data documenting the efficacy and safety of avacopan.

6.R.2 Necessity of dose adjustment for patients with renal impairment

The applicant's explanation about necessity of dose adjustment for patients with renal impairment:
A total of 367 subjects were included in 7 clinical studies used in the population pharmacokinetic analysis. According to renal functions, this population comprised 128 subjects with normal renal functions, 85 subjects with mild renal impairment, 90 subjects with moderate renal impairment, 62 subjects with severe renal impairment (including subjects on dialysis), and 3 subjects with unknown renal functions. In the concerned population pharmacokinetic analysis, eGFR was selected as a covariate for avacopan, and moderate and severe renal impairment was estimated to decrease CL/F of avacopan by 15% to 34% and 34% to 49%, respectively. Of patients with ANCA-associated vasculitis enrolled in the phase III studies, on the other hand, at least 85% of the patients had mild to severe renal impairment. Relationships of $AUC_{0\text{-}12h}$, C_{max}, and C_{min} of avacopan at steady state with severity of renal impairment were investigated by empirical Bayesian inference using the constructed population pharmacokinetic model, and the estimate of each pharmacokinetic parameter, irrespective of severity of renal impairment, did not exceed 1.25 times that in the subgroup with normal renal function. Therefore, the dose adjustment of avacopan according to severity of renal impairment was not required.

PMDA accepted the above explanation.

6.R.3 Pharmacokinetic interactions involving avacopan

The applicant's explanation:
In view of pharmacokinetic profiles after concomitant use of avacopan with rifampicin, itraconazole, midazolam, or celecoxib [see Section 6.2.4], the package insert will provide a cautionary statement concerning interactions with drugs acting as a potent CYP3A4 inducer or inhibitor. In addition, concerning the decreases in C_{max} and $AUC_{0\text{-}inf}$ of avacopan by 79% and 93% after concomitant use with rifampicin (Table 31), the applicant discusses about the causes as described below, taking account of effects of rifampicin on drug metabolic enzymes and transporters other than its inducing effect on CYP3A4 and the contribution of M1, which inhibits human C5aR as with avacopan.

Rifampicin is known to induce CYP3A4, CYP2C8, CYP2C9, CYP2C19, and MDR1/P-gp, and induce or inhibit OATP1B1 and OATP1B3 ("Guideline on drug interaction for drug development and appropriate provision of information" [PSEHB/PED Notification No. 0723-4, dated July 23, 2018], *Clin*

Pharmacol Ther. 2011;89:234-42). Avacopan, on the other hand, is metabolized mainly by CYP3A4, and CYP2D6 and CYP2C19 are also suggested to contribute to metabolism of avacopan [see Section 4.3.1]. Avacopan was not a substrate of OATP1B1, OATP1B3, MDR1/P-gp, or BCRP [see Section 4.5.2]. That is, avacopan does not act as a substrate of any of the drug transporters induced or inhibited by rifampicin, and thus the decreased exposure to avacopan after concomitant use of rifampicin is considered mainly attributable to its CYP3A4 induction.

M1 is known to be generated and further metabolized by CYP3A4 [see Section 4.3.1]. Concomitant use with rifampicin also decreased C_{max} and $AUC_{0\text{-}inf}$ of M1 by 73% and 93% (Table 25); the decrease in exposure to M1 was similar to that in exposure to avacopan. The applicant therefore considers it unnecessary to take separately account of contribution of M1 to the drug effect.

The above findings indicated that the decreased exposure to avacopan after concomitant use of rifampicin is considered mainly attributable to the CYP3A4 induction. The package insert will provide a cautionary statement about interactions with drugs acting as a potent or even moderate CYP3A4 inducer, although the effects of the moderate CYP3A4 inducer on pharmacokinetics of avacopan have not been investigated.

PMDA's view:
Although the effects of a moderate CYP3A4 inducer on pharmacokinetics of avacopan have not been investigated, the package insert should provide cautionary statements about interactions with not only potent CYP3A4 inducers and inhibitors but also moderate CYP3A4 inducers, taking account of explanation that concomitant use of rifampicin decreased C_{max} and $AUC_{0\text{-}inf}$ of avacopan by 79% and 93%, respectively, and the concerned decreased exposure is mainly caused by CYP3A4.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results from studies listed in Table 33.

Table 33. List of major clinical studies for efficacy and safety

Region	Study ID	Phase	Study population	No. of subjects enrolled	Dosage regimen	Main endpoints
Foreign	Study CL002_168	II	Patients with MPA, patients with GPA, or patients with renal limited vasculitis	(a) 22 (b) 22 (c) 23	With concomitant immunosuppressive drugs,[a] (a) Avacopan 30 mg twice daily oral administration (b) Avacopan 30 mg twice daily oral administration + low dose prednisone[b] (c) Placebo + high dose prednisone[c]	Efficacy Safety
Foreign	Study CL003_168	II	Patients with MPA, patients with GPA, or patients with renal limited vasculitis	(a) 13 (b) 16 (c) 13	With concomitant immunosuppressive drugs,[d] (a) Avacopan 10 mg twice daily oral administration + high dose prednisone[e] (b) Avacopan 30 mg twice daily oral administration + high dose prednisone[e] (c) Placebo twice daily oral administration + high dose prednisone[e]	Efficacy Safety
Global	Study CL010_168	III	Patients with MPA or patients with GPA	(a) 166 (b) 165	With concomitant immunosuppressive drugs,[f] (a) Avacopan 30 mg twice daily oral administration (b) High dose prednisone[g]	Efficacy Safety

a) Intravenous CY, intravenous CY/AZA, or RTX
b) Prednisone was orally administered according to the predetermined tapering regimen in which the dose was started at 20 mg/day (for patients weighing ≥55 kg) or 15 mg/day (for patients weighing <55 kg) and then gradually reduced to 0 mg over a period of 14 weeks.
c) Prednisone was orally administered according to the predetermined tapering regimen in which the dose was started at 60 mg/day (for patients weighing ≥55 kg) or 45 mg/day (for patients weighing <55 kg) and then gradually reduced to 0 mg over a period of 20 weeks.
d) Intravenous CY/AZA, or RTX
e) Prednisone was orally administered according to the predetermined tapering regimen in which the dose was started at 60 mg/day and then gradually reduced to 0 mg over a period of 20 weeks.
f) CY (intravenous or oral)/AZA, or RTX
g) Prednisone was orally administered according to the predetermined tapering regimen in which the dose was started at 60 mg/day (for patients aged ≥18 years and weighing ≥55 kg), 45 mg/day (for patients aged ≥18 years and weighing <55 kg or patients aged <18 years and weighing >37 kg), or 30 mg/day (for patients aged <18 years and weighing ≤37 kg) and then gradually reduced to 0 mg over a period of 20 weeks.

7.1 Phase II studies

7.1.1 Foreign phase II study (CTD 5.3.5.1.1, Study CL002_168 [September 2011 to November 2016])

A randomized, double-blind, parallel-group study was conducted to evaluate efficacy and safety of avacopan in patients with MPA, patients with GPA, or patients with renal limited vasculitis (target sample size, 60 patients [20 per group]) requiring treatment with CY or RTX, using the tapering prednisone regimen as the comparator in 11 countries or regions including Germany, France, and the UK. Table 34 shows the main inclusion criteria for this study.

Table 34. Main inclusion criteria

1. Diagnosis of MPA, GPA, or renal limited vasculitis, consistent with Chapel Hill Consensus Conference definitions (revised in 2012)
2. Newly-diagnosed or relapsed disease requiring treatment with CY or RTX
3. Perinuclear or cytoplasmic ANCA positive in an indirect immunofluorescence assay, or anti-MPO or anti-PR3 antibody positive in an enzyme-linked immunosorbent assay; for patients positive only in the indirect immunofluorescence assay, there should be the past record of a positive result in the enzyme-linked immunosorbent assay.
4. At least 1 major item, at least 3 non-major items, or at least 2 renal items of proteinuria and hematuria on the BVAS version 3 are met.
5. eGFR ≥20 mL/min/1.73 m^2
6. Aged ≥18 years

This study consisted of Steps 1 to 3 (each comprising a 12-week treatment period and a 12-week follow-up period). Of the regimens below, (b) or (c) was applied to Step 1, and (a) or (c) was applied to Step

2.[27] Throughout the study period, intravenous CY was concomitantly used.[28] To Step 3,[27] (a), (b), or (c) was applied, and throughout the study period, a regimen of intravenous CY followed by AZA[29] or RTX[30] was concomitantly used. In all steps, rescue treatment with GC was allowed for worsened symptoms.[31][32]

(a) Avacopan 30 mg was orally administered twice daily for 12 weeks (avacopan group).

(b) Avacopan 30 mg was orally administered twice daily for 12 weeks during an oral prednisone tapering regimen in which its dose was started at 20 mg/day (for patients weighing ≥55 kg) or 15 mg/day (for patients weighing <55 kg) and then gradually reduced to 0 mg over a period of 14 weeks as predetermined (avacopan + low dose prednisone group).

(c) Prednisone was orally administered according to the predetermined tapering regimen in which its dose was started at 60 mg/day (for patients weighing ≥55 kg) or 45 mg/day (for patients weighing <55 kg) and then gradually reduced to 0 mg over a period of 20 weeks (high dose prednisone group).

All of 67 patients randomized until Step 3[33] (22 in the avacopan group, 22 in the avacopan + low dose prednisone group, 23 in the high dose prednisone group) received the study drug at least once and were included in the safety analysis population. Of these, 63 patients (21 in the avacopan group, 22 in the avacopan + low dose prednisone group, 20 in the high dose prednisone group) excluding 4 patients who did not provide the Birmingham vasculitis activity score (BVAS) assessment result after administration of the study drug were included in the intent to treat (ITT) population, and the ITT was used as the efficacy analysis population. Discontinuation occurred in 18.2% (4 of 22) of patients in the avacopan group, 13.6% (3 of 22) of patients in the avacopan + low dose prednisone group, and 21.7% (5 of 23) of patients in the high dose prednisone group, and main reasons for discontinuation were adverse events (9.1% [2 of 22] of patients in the avacopan group, 9.1% [2 of 22] of patients in the avacopan + low dose prednisone group, 8.7% [2 of 23] of patients in the high dose prednisone group) and consent withdrawal (4.5% [1 of 22] of patients in the avacopan group, 13.0% [3 of 23] of patients in the high dose prednisone group).

Table 35 shows results on the proportion of patients achieving disease response at Week 12, the primary efficacy endpoint [for the definitions, see Section 10].

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27) Treatment was started when both of the following criteria were met in the preceding step: (a) Not more than 1 unknown serious adverse drug reaction judged to be highly related to avacopan by the data monitoring committee occurred in patients treated with avacopan; (b) the data monitoring committee judged that disease activity of ANCA-associated vasculitis with renal impairment was controlled without use of a rescue drug (GC) in the majority of patients treated with avacopan.

28) CY was intravenously administered at 15 mg/kg (up to 1.2 g) at the start of treatment and Weeks 2, 4, and 8, and then at an investigator's specified dose at Weeks 12, 16, 20, and 24.

29) CY was intravenously administered at 15 mg/kg (up to 1.2 g) at the start of treatment and Weeks 2, 4, 8, and 12, and then AZA was orally administered at 2 mg/kg/day between Weeks 14 and 24.

30) RTX was intravenously administered at 375 mg/m^2 at the start of treatment and Weeks 1, 2, and 3.

31) If any of the following (a) to (d) is met: (a) Worsened eGFR values were observed for more than 3 consecutive days, and the investigator assessed that the renal function would continue worsening without additional therapeutic intervention; (b) the eGFR value decreased from baseline by more than 10 mL/min during the treatment or follow-up period; (c) symptoms on the non-renal major items on the BVAS were continued or newly developed; and (d) rescue treatment with GC was considered most beneficial for the patient by a physician.

32) Methylprednisolone 500 mg was intravenously administered once daily for 3 days, and then GC was orally administered according to the local standard of care treatment.

33) In Step 3, disease stage (newly diagnosed or relapsed), ANCA type (anti-MPO or anti-PR3 antibody positive), and base treatment (CY or RTX) were used as stratification factors.

Table 35. Proportion of patients achieving disease response at Week 12 (ITT population, last observation carried forward [LOCF])

	Avacopan	Avacopan + low dose prednisone	High dose prednisone
Proportion of patients achieving disease response	81.0 (17/21)	86.4 (19/22)	70.0 (14/20)
Difference from high dose prednisone [90% CI]	11.0 [-11.0, 32.9]	16.4 [-4.3, 37.1]	

% (Number of patients), Patients receiving rescue treatment were handled as non-responders

During the whole study period, adverse events occurred in 95.5% (21 of 22) of patients in the avacopan group, 95.5% (21 of 22) of patients in the avacopan + low dose prednisone group, and 91.3% (21 of 23) of patients in the high dose prednisone group. Table 36 shows the major events.

No deaths occurred.

Serious adverse events occurred in 45.5% (10 of 22) of patients in the avacopan group, 36.4% (8 of 22) of patients in the avacopan + low dose prednisone group, and 21.7% (5 of 23) of patients in the high dose prednisone group. A causal relationship to the study drug could not be ruled out for the events reported by 2 patients (renal dysfunction and hepatic enzyme increased/pancreatic enzymes increased in 1 patient each) in the avacopan group and 1 patient (pneumonia) in the high dose prednisone group.

Adverse events leading to discontinuation occurred in 13.6% (3 of 22) of patients in the avacopan group, 4.5% (1 of 22) of patients in the avacopan + low dose prednisone group, and 8.7% (2 of 23) of patients in the high dose prednisone group.

Adverse drug reactions occurred in 54.5% (12 of 22) of patients in the avacopan group, 31.8% (7 of 22) of patients in the avacopan + low dose prednisone group, and 43.5% (10 of 23) of patients in the high dose prednisone group.

Table 36. Adverse events reported by ≥5.0% of patients in any group (whole period, safety analysis population)

Term	Avacopan (n = 22)	Avacopan + low dose prednisone (n = 22)	High dose prednisone (n = 23)
Hypertension	6 (27.3)	2 (9.1)	2 (8.7)
Nausea	5 (22.7)	7 (31.8)	6 (26.1)
Nasopharyngitis	5 (22.7)	4 (18.2)	5 (21.7)
Vomiting	5 (22.7)	4 (18.2)	1 (4.3)
Arthralgia	5 (22.7)	3 (13.6)	2 (8.7)
Headache	4 (18.2)	3 (13.6)	3 (13.0)
Fatigue	4 (18.2)	0	3 (13.0)
Epistaxis	3 (13.6)	4 (18.2)	2 (8.7)
Diarrhoea	3 (13.6)	3 (13.6)	3 (13.0)
Rash	3 (13.6)	1 (4.5)	1 (4.3)
Chills	3 (13.6)	1 (4.5)	0
Purpura	3 (13.6)	0	1 (4.3)
Oral herpes	3 (13.6)	0	1 (4.3)
Constipation	2 (9.1)	3 (13.6)	5 (21.7)
Cough	2 (9.1)	3 (13.6)	2 (8.7)
Vasculitis	2 (9.1)	3 (13.6)	2 (8.7)
Rhinitis	2 (9.1)	2 (9.1)	1 (4.3)
Respiratory tract infection	2 (9.1)	2 (9.1)	0
Oedema peripheral	2 (9.1)	1 (4.5)	5 (21.7)
Abdominal pain upper	2 (9.1)	1 (4.5)	2 (8.7)
Alanine aminotransferase increased	2 (9.1)	1 (4.5)	1 (4.3)
Pyrexia	2 (9.1)	0	3 (13.0)
Bronchitis	2 (9.1)	0	1 (4.3)
Hypercholesterolaemia	2 (9.1)	0	1 (4.3)
Neck pain	2 (9.1)	0	0
Asthenia	2 (9.1)	0	0
Paraesthesia	1 (4.5)	3 (13.6)	3 (13.0)
Dyspepsia	1 (4.5)	2 (9.1)	2 (8.7)
Insomnia	1 (4.5)	2 (9.1)	1 (4.3)
Viral upper respiratory tract infection	1 (4.5)	2 (9.1)	0
Musculoskeletal chest pain	1 (4.5)	2 (9.1)	0
Pain in extremity	1 (4.5)	2 (9.1)	0
Muscle spasms	1 (4.5)	1 (4.5)	5 (21.7)
Back pain	1 (4.5)	1 (4.5)	5 (21.7)
Blood creatinine increased	1 (4.5)	1 (4.5)	2 (8.7)
Renal vasculitis	1 (4.5)	1 (4.5)	2 (8.7)
Hyperhidrosis	1 (4.5)	0	2 (8.7)
Nocturia	0	3 (13.6)	1 (4.3)
Decreased appetite	0	3 (13.6)	0
Dyspnoea exertional	0	2 (9.1)	2 (8.7)
Abdominal discomfort	0	2 (9.1)	1 (4.3)
Upper respiratory tract infection	0	2 (9.1)	0
Breath sounds abnormal	0	1 (4.5)	2 (8.7)
Deep vein thrombosis	0	1 (4.5)	2 (8.7)
Anaemia	0	1 (4.5)	2 (8.7)
Anxiety	0	0	3 (13.0)
Viral infection	0	0	2 (8.7)
Abdominal pain	0	0	2 (8.7)
Erythema	0	0	2 (8.7)
Dizziness	0	0	2 (8.7)
Tremor	0	0	2 (8.7)

Number of patients (%)

7.1.2 Foreign phase II study (CTD 5.3.5.1.2, Study CL003_168 [February 2015 to July 2016])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate efficacy and safety of avacopan in patients with MPA, patients with GPA, or patients with renal limited

vasculitis (target sample size, 45 patients [15 per group]) requiring treatment with CY or RTX in the US and Canada. Table 37 shows the main inclusion criteria for this study.

Table 37. Main inclusion criteria

1. Diagnosis of MPA, GPA, or renal limited vasculitis, consistent with Chapel Hill Consensus Conference definitions (revised in 2012)
2. Newly-diagnosed or relapsed disease requiring treatment with CY or RTX
3. Perinuclear or cytoplasmic ANCA positive in an indirect immunofluorescence assay, or anti-MPO or anti-PR3 antibody positive in an enzyme-linked immunosorbent assay; for patients positive only in the indirect immunofluorescence assay, there should be the past record of a positive result in the enzyme-linked immunosorbent assay.
4. At least 1 major item, at least 3 non-major items, or at least 2 renal items on the BVAS version 3 are met.
5. eGFR ≥20 mL/min/1.73 m^2
6. Aged ≥18 years

This study consisted of the 12-week treatment period and 12-week follow-up period. Avacopan 10 mg or 30 mg or the placebo was orally administered twice daily for 12 weeks during an oral prednisone tapering regimen in which its dose was started at 60 mg/day and then gradually reduced to 0 mg over a period of 20 weeks as predetermined. Throughout the study period, a regimen of intravenous CY followed by AZA[34] or RTX[35] was concomitantly used. Rescue treatment with GC was allowed for worsened symptoms.[36][37]

All of 42 patients randomized[38] (13 in the avacopan 10 mg group, 16 in the avacopan 30 mg group, 13 in the placebo group) received the study drug at least once and were included in the safety analysis population. Of these, 40 patients (12 in the avacopan 10 mg group, 15 in the avacopan 30 mg group, 13 in the placebo group) excluding 2 patients who did not provide the BVAS assessment result after administration of the study drug were included in the ITT population, and the ITT was used as the efficacy analysis population. Discontinuation occurred in 7.7% (1 of 13) of patients in the avacopan 10 mg group and 6.3% (1 of 16) of patients in the avacopan 30 mg group, and reasons for discontinuation were adverse events for all the cases.

Table 38 shows results on the proportion of patients achieving disease response at Week 12, the primary efficacy endpoint [for the definitions, see Section 10].

[34] CY was intravenously administered at 15 mg/kg (up to 1.2 g) at the start of treatment and Weeks 2, 4, 8, and 12, and then AZA was orally administered at 2 mg/kg/day between Weeks 14 and 24.
[35] RTX was intravenously administered at 375 mg/m^2 at the start of treatment and Weeks 1, 2, and 3.
[36] If any of the following (a) to (d) is met: (a) Worsened eGFR values were observed for more than 3 consecutive days, and the investigator assessed that the renal function would continue worsening without additional therapeutic intervention; (b) the eGFR value decreased from baseline by more than 10 mL/min during the treatment or follow-up period; (c) symptoms on the non-renal major items on the BVAS were continued or newly developed; and (d) rescue treatment with GC was considered most beneficial for the patient by a physician.
[37] Methylprednisolone 500 mg was intravenously administered once daily for 3 days, and then GC was orally administered according to the local standard of care treatment.
[38] Disease stage (newly diagnosed or relapsed), ANCA type (anti-MPO or anti-PR3 antibody positive), and base treatment (CY or RTX) were used as stratification factors.

Table 38. Proportion of patients achieving disease response at Week 12 (ITT population, LOCF)

	Avacopan 10 mg	Avacopan 30 mg	Placebo
Proportion of patients achieving disease response	91.7 (11/12)	80.0 (12/15)	84.6 (11/13)
Difference from placebo [90% CI]	7.1 [-14.0, 28.1]	-4.6 [-28.3, 19.0]	

% (Number of patients), Patients receiving rescue treatment were handled as non-responders

During the whole study period, adverse events occurred in 92.3% (12 of 13) of patients in the avacopan 10 mg group, 93.8% (15 of 16) of patients in the avacopan 30 mg group, and 100% (13 of 13) of patients in the placebo group. Table 39 shows the major adverse events.

No deaths occurred.

Serious adverse events occurred in 15.4% (2 of 13) of patients in the avacopan 10 mg group, 25.0% (4 of 16) of patients in the avacopan 30 mg group, and 23.1% (3 of 13) of patients in the placebo group. A causal relationship to the study drug could not be ruled out for the events reported by 1 patient (abscess limb/perirectal abscess) in the avacopan 10 mg group and 3 patients (atrial fibrillation, sepsis, and urinary tract infection in 1 patient each) in the avacopan 30 mg group.

Adverse events leading to discontinuation occurred in 7.7% (1 of 13) of patients in the avacopan 10 mg group, 18.8% (3/16) of patients in the avacopan 30 mg group, and 15.4% (2 of 13) of patients in the placebo group.

Adverse drug reactions occurred in 38.5% (5 of 13) of patients in the avacopan 10 mg group, 25.0% (4 of 16) of patients in the avacopan 30 mg group, and 38.5% (5 of 13) of patients in the placebo group.

Table 39. Adverse events reported by ≥2 patients in any group (whole period, safety analysis population)

Term	Avacopan 10 mg (n = 13)	Avacopan 30 mg (n = 16)	Placebo (n = 13)
Hypertension	3 (23.1)	4 (25.0)	4 (30.8)
Nasopharyngitis	3 (23.1)	0	0
Oedema peripheral	2 (15.4)	4 (25.0)	1 (7.7)
Nausea	2 (15.4)	2 (12.5)	1 (7.7)
Fatigue	2 (15.4)	1 (6.3)	3 (23.1)
Infusion related reaction	2 (15.4)	1 (6.3)	0
Myalgia	1 (7.7)	3 (18.8)	1 (7.7)
Headache	1 (7.7)	2 (12.5)	2 (15.4)
Fall	1 (7.7)	2 (12.5)	2 (15.4)
Ecchymosis	1 (7.7)	2 (12.5)	1 (7.7)
Insomnia	1 (7.7)	2 (12.5)	0
Dizziness	0	3 (18.8)	0
Back pain	0	2 (12.5)	2 (15.4)
Oropharyngeal pain	0	2 (12.5)	1 (7.7)
Arthralgia	0	2 (12.5)	0
Diarrhoea	0	2 (12.5)	0
Flatulence	0	2 (12.5)	0
Blood creatinine increased	0	2 (12.5)	0
Tachycardia	0	2 (12.5)	0
Cough	0	0	3 (23.1)
Scab	0	0	2 (15.4)
Weight increased	0	0	2 (15.4)
Sinus headache	0	0	2 (15.4)
Epistaxis	0	0	2 (15.4)
Paranasal sinus discomfort	0	0	2 (15.4)

Number of patients (%)

7.2 Global phase III study (CTD 5.3.5.1.3, Study CL010_168 [March 2017 to November 2019])

A randomized, double-blind, parallel-group study was conducted to evaluate the superiority of avacopan to a tapering prednisone regimen and safety in patients with MPA or patients with GPA (target sample size, 300 patients [150 per group][39]) requiring treatment with CY or RTX using the tapering prednisone regimen as the control in 18 countries or regions including Japan, Germany, and US. Table 40 shows the main inclusion criteria for this study.

Table 40. Main inclusion criteria

1. Diagnosis of MPA or GPA, consistent with Chapel Hill Consensus Conference definitions (revised in 2012)
2. Newly-diagnosed or relapsed disease requiring treatment with CY or RTX
3. Anti-MPO or anti-PR3 antibody positive
4. At least 1 major item, at least 3 non-major items, or at least 2 renal items of proteinuria and hematuria on the BVAS version 3 are met.
5. eGFR ≥15 mL/min/1.73 m^2
6. Aged ≥12 years

This study consisted of the 52-week treatment period and 8-week follow-up period. Avacopan 30 mg was orally administered twice daily for 52 weeks or prednisone was orally administered according to the predetermined tapering regimen in which its dose was started at 60 mg/day (for patients aged ≥18 years and weighing ≥55 kg), 45 mg/day (for patients aged ≥18 years and weighing <55 kg or patients aged <18 years and weighing >37 kg), or 30 mg/day (for patients aged <18 years and weighing ≤37 kg) and then gradually reduced to 0 mg over a period of 20 weeks. In the avacopan group, patients who had

[39] On the hypothesis that the expected proportion of patients achieving sustained remission at Week 52, the primary endpoint, was 63% in the avacopan group and 45% in the prednisone group, a sample size of 150 patients per group (300 patients in 2 groups) was estimated to provide 85% power at one-sided significance level of 2.5%.

been receiving GC, if applicable, were allowed to continue this prior treatment but had to discontinue it by Week 4 of avacopan treatment.[40] Throughout the study period, a regimen of CY followed by AZA[41] or RTX[42] was concomitantly used. Furthermore, rescue treatment with GC[43] or immunosuppressive drugs was allowed for a relapsed disease [For the definitions, see Section 10].

Of 331 randomized patients[44] (166 in the avacopan group, 165 in the prednisone group), 330 patients (166 in the avacopan group, 164 in the prednisone group) excluding 1 patient who did not receive the study drug were included in the ITT population and safety analysis population, and the ITT population was used as the efficacy analysis population.

Discontinuation occurred in 9.0% (15 of 166) of patients in the avacopan group and 9.1% (15 of 164) of patients in the prednisone group, and main reasons for discontinuation were consent withdrawal (3.6% [6 of 166] of patients in the avacopan group, 1.8% [3 of 164] of patients in the prednisone group) and adverse events (1.8% [3 of 166] of patients in the avacopan group, 3.6% [6 of 164] of patients in the prednisone group).

In the ITT population, the Japanese subgroup comprised 21 patients (11 in the avacopan group, 10 in the prednisone group), and discontinuation occurred in 1 patient each of the avacopan group and prednisone group (decided by a physician for both).

Table 41 shows results on the proportion of patients achieving sustained remission at Week 52, the primary efficacy endpoint[45] [for the definitions, see Section 10]. Comparison between the avacopan group and prednisone group revealed a statistically significant difference, demonstrating superiority of avacopan to the tapering prednisone regimen. Table 42 shows results in the Japanese subgroup.

Table 41. Proportion of patients achieving sustained remission at Week 52 (ITT population, non-responder imputation [NRI])

	Avacopan	Prednisone
Proportion of patients achieving sustained remission	65.7 (109/166)	54.9 (90/164)
Difference from prednisone [95% CI][a)] *P* value[b)]	12.5 [2.6, 22.3] 0.0066	

% (Number of patients)

a) Confidence interval determined according to summary score estimates on the stratification factors (base treatment, ANCA type, and disease stage) (*Categorical data analysis*. John Wiley & Sons; 2013. p231) and the Miettinen-Nurminen method

b) Wald test in summary score estimates on stratification factors (base treatment, ANCA type, and disease stage) at a one-sided significance level of 2.5%

40) Consequently, 75.3% (125 of 166) of patients in the avacopan group continued the prior treatment with GC and received it concomitantly by Week 4.

41) CY was intravenously administered at 15 mg/kg (up to 1.2 g) at the start of treatment and Weeks 2, 4, 7, 10, and 13; or CY was orally administered at 2 mg/kg/day (up to 200 mg) for 14 weeks, and then from Week 15 onwards, AZA up to 2 mg/kg/day, mycophenolate mofetil up to 2 g/day, or mycophenolate sodium up to 1440 mg/day was orally administered until end of the study.

42) RTX was intravenously administered at 375 mg/m^2 weekly for 4 weeks.

43) Methylprednisolone was intravenously administered at 0.5 to 1 mg/day for 3 days; or GC was orally administered on a tapering regimen according to the patient's condition.

44) Base treatment (RTX, intravenous CY or oral CY), ANCA type (anti-MPO or anti-PR3 antibody positive), disease stage (newly diagnosed or relapsed) were used as stratification factors.

45) In [redacted], the primary endpoint was defined as the proportion of patients achieving remission at Week 26, and 72.3% (120/166) of patients in the avacopan group and 70.1% (115 of 164) of patients in the prednisone group achieved remission, demonstrating non-inferiority of avacopan to prednisone.

Table 42. Proportion of patients achieving sustained remission at Week 52 (ITT population, Japanese subgroup, NRI)

	Avacopan	Prednisone
Proportion of patients achieving sustained remission	72.7 (8/11)	40.0 (4/10)
Difference from prednisone [95% CI][a)]	32.7 [-7.5, 72.9]	

% (Number of patients)
a) Confidence interval according to the Wald method

During the whole study period, adverse events occurred in 98.8% (164 of 166) of patients in the avacopan group and 98.2% (161 of 164) of patients in the prednisone group. Table 43 shows major events.

Deaths occurred in 2 patients in the avacopan group (pneumonia and granulomatosis with polyangiitis in 1 patient each) and 4 patients in the prednisone group (diarrhoea/vomiting/fungal infection, infectious pleural effusion, acute myocardial infarction, and death in 1 patient each). A causal relationship to the study drug could not be ruled out for the event reported by 1 patient (diarrhoea/vomiting/fungal infection) in the prednisone group.

Serious adverse events occurred in 42.2% (70 of 166) of patients in the avacopan group and 45.1% (74 of 164) of patients in the prednisone group. A causal relationship to the study drug could not be ruled out for the events reported by 20 patients (pneumonia in 2 patients; and angioedema, abdominal pain upper, liver function test increased, hepatic function abnormal/agranulocytosis, urosepsis/urinary tract infection, interstitial lung disease, arthralgia, hepatocellular injury, bronchopneumopathy, hepatitis/hepatitis cholestatic, skin necrosis, drug hypersensitivity, post procedural sepsis, atrioventricular block first degree, hepatic enzyme increased, Campylobacter gastroenteritis, hepatitis B, and hepatic function abnormal in 1 patient each) in the avacopan group and 25 patients (transaminases increased; purpura/thrombocytopenia, deep vein thrombosis, gastrointestinal disorder, diarrhoea/vomiting/fungal infection, diarrhoea/dehydration, pneumonia bacterial, herpes zoster, agranulocytosis/pneumonia, duodenitis, lymphopenia, pneumonia cytomegaloviral, urinary tract infection/depression, arthralgia/myalgia/nervous system disorder, lower respiratory tract infection, anti-neutrophil cytoplasmic antibody positive vasculitis, pyrexia, pneumonia, vomiting/abdominal pain upper, anaemia, respiratory tract infection viral, sepsis, pneumonia/bacteraemia/meningitis, pneumonia bacterial, and hepatic enzyme increased in 1 patient each) in the prednisone group.

Adverse events leading to discontinuation occurred in 16.3% (27 of 166) of patients in the avacopan group and 17.1% (28 of 164) of patients in the prednisone group.

Adverse drug reactions occurred in 60.2% (100 of 166) of patients in the avacopan group and 62.8% (103 of 164) of patients in the prednisone group.

Table 43. Adverse events reported by ≥5.0% of patients in any group (whole period, safety analysis population)

Term	Avacopan (n = 166)	Prednisone (n = 164)	Term	Avacopan (n = 166)	Prednisone (n = 164)
Nausea	39 (23.5)	34 (20.7)	Urinary tract infection	12 (7.2)	23 (14.0)
Oedema peripheral	35 (21.1)	40 (24.4)	Hypercholesterolaemia	12 (7.2)	20 (12.2)
Headache	34 (20.5)	23 (14.0)	Leukopenia	12 (7.2)	14 (8.5)
Arthralgia	31 (18.7)	36 (22.0)	Constipation	11 (6.6)	11 (6.7)
Hypertension	30 (18.1)	29 (17.7)	Pneumonia	11 (6.6)	11 (6.7)
Anti-neutrophil cytoplasmic antibody positive vasculitis	26 (15.7)	34 (20.7)	Abdominal pain upper	11 (6.6)	10 (6.1)
Cough	26 (15.7)	26 (15.9)	Dizziness	11 (6.6)	10 (6.1)
Nasopharyngitis	25 (15.1)	30 (18.3)	Sinusitis	10 (6.0)	12 (7.3)
Diarrhoea	25 (15.1)	24 (14.6)	Pruritus	10 (6.0)	10 (6.1)
Vomiting	25 (15.1)	21 (12.8)	Blood creatinine increased	10 (6.0)	8 (4.9)
Upper respiratory tract infection	24 (14.5)	24 (14.6)	Paraesthesia	9 (5.4)	7 (4.3)
Rash	19 (11.4)	13 (7.9)	Dyspnoea	8 (4.8)	11 (6.7)
Muscle spasms	18 (10.8)	37 (22.6)	Alopecia	7 (4.2)	12 (7.3)
Fatigue	17 (10.2)	15 (9.1)	Increased tendency to bruise	7 (4.2)	10 (6.1)
Myalgia	16 (9.6)	22 (13.4)	Lymphopenia	6 (3.6)	18 (11.0)
Back pain	16 (9.6)	22 (13.4)	Oropharyngeal pain	6 (3.6)	12 (7.3)
Pyrexia	15 (9.0)	19 (11.6)	Bronchitis	5 (3.0)	10 (6.1)
Epistaxis	14 (8.4)	21 (12.8)	Dyspepsia	5 (3.0)	10 (6.1)
Insomnia	13 (7.8)	25 (15.2)	Cushingoid	3 (1.8)	9 (5.5)
Anaemia	13 (7.8)	18 (11.0)	Tremor	2 (1.2)	10 (6.1)
Pain in extremity	13 (7.8)	13 (7.9)	Weight increased	1 (0.6)	17 (10.4)

Number of patients (%)

In the Japanese subgroup during the whole study period, adverse events occurred in 100% (11 of 11) of patients in the avacopan group and 100% (10 of 10) of patients in the prednisone group. Table 44 shows major events.

No deaths occurred.

Serious adverse events occurred in 36.4% (4 of 11) of patients in the avacopan group (pancreatitis acute/pancreatic carcinoma metastatic, hepatitis B, hepatic enzyme increased, and hepatic function abnormal in 1 patient each) and 50.0% (5 of 10) of patients in the prednisone group (pneumonia/bacteraemia/meningitis, interstitial lung disease/pneumonia bacterial, diarrhoea/rectal prolapse, hepatic enzyme increased/granulomatosis with polyangiitis, and hepatic enzyme increased/herpes zoster/large intestine polyp in 1 patient each). A causal relationship to the study drug could not be ruled out for the events reported by 2 patients (hepatitis B and hepatic function abnormal in 1 patient each) in the avacopan group and 3 patients (pneumonia/bacteraemia/meningitis, pneumonia bacterial, and hepatic enzyme increased in 1 patient each) in the prednisone group.

Adverse events leading to discontinuation occurred in 27.3% (3 of 11) of patients in the avacopan group and 30.0% (3 of 10) of patients in the prednisone group.

Adverse drug reactions occurred in 81.8% (9 of 11) of patients in the avacopan group and 70.0% (7 of 10) of patients in the prednisone group.

Table 44. Adverse events reported by ≥2 patients in either group (whole period, safety analysis population, Japanese subgroup)

Term	Avacopan (n = 11)	Prednisone (n = 10)	Term	Avacopan (n = 11)	Prednisone (n = 10)
Hypertension	4 (36.4)	6 (60.0)	Blood creatinine increased	2 (18.2)	0
Hepatic enzyme increased	3 (27.3)	3 (30.0)	Decreased appetite	2 (18.2)	0
White blood cell count decreased	3 (27.3)	0	Nephrogenic anaemia	2 (18.2)	0
Diarrhoea	2 (18.2)	2 (20.0)	Hypogammaglobulinaemia	2 (18.2)	0
Vomiting	2 (18.2)	2 (20.0)	Hepatic function abnormal	2 (18.2)	0
Constipation	2 (18.2)	1 (10.0)	Urinary tract infection	1 (9.1)	2 (20.0)
Stomatitis	2 (18.2)	1 (10.0)	Hypokalaemia	1 (9.1)	2 (20.0)
Pruritus generalised	2 (18.2)	1 (10.0)	Dental caries	0	2 (20.0)
Rash generalised	2 (18.2)	1 (10.0)	Arthralgia	0	2 (20.0)
Lymphocyte count decreased	2 (18.2)	1 (10.0)	Muscle spasms	0	2 (20.0)
Anaemia	2 (18.2)	1 (10.0)	Haemorrhage subcutaneous	0	2 (20.0)
Otitis media	2 (18.2)	0	Headache	0	2 (20.0)
Cytomegalovirus infection	2 (18.2)	0	Blood cholesterol increased	0	2 (20.0)
Oedema peripheral	2 (18.2)	0	Insomnia	0	2 (20.0)

Number of patients (%)

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan of avacopan:

In Japan, diagnoses of MPA and GPA are made using the clinical diagnostic criteria established by the MHLW on the basis of the Chapel Hill Consensus Conference definitions (revised in 2012), an internationally accepted classification system of vasculitis, and thus there are no fundamental differences in diagnosis of MPA or GPA between Japan and overseas. Japanese and foreign clinical practice guidelines recommend similar strategies for treatment of MPA and GPA in terms of the following points: (a) Treatment of MPA and GPA should basically comprise a combination of GCs and immunosuppressive drugs; (b) the standard remission induction therapy should use high dose GC and CY or RTX in combination; (c) the standard remission maintenance therapy should use low dose GC and AZA in combination; (d) it is desirable to use GC on a tapering regimen until the therapeutic goal is achieved and then continue GC at the minimum dose (discontinue where possible) (Japanese Clinical Practice Guideline, *Rheumatology.* 2014;53:2306-9). In addition, because no clinically meaningful ethnic differences were observed in the pharmacokinetics of avacopan [see Section 6.R], the applicant considered it possible to evaluate the efficacy and safety of avacopan in Japanese patients with MPA or GPA by conducting a global study (Study CL010_168) including Japan and then constructing clinical data package.

- Efficacy endpoints in the phase III study

The therapeutic goals of MPA and GPA are defined as remission induction and sustained remission, and for the goals, emphasis is placed on prevention or alleviation of a relapsed disease, which would cause accumulation of organ dysfunctions at an increased mortality risk, and early suppression of inflammation for improved long-term prognosis (Japanese Clinical Practice Guideline). In view of the above therapeutic goals and efficacy endpoints in clinical studies of the other drugs in patients with MPA and GPA (*N Engl J Med.* 2010;363:221-32, *Medicine.* 2007;86:269-77, etc.), the proportion of patients achieving sustained remission at Week 52 was established as the primary endpoint in Study CL010_168,

and the proportion of patients achieving remission at Week 26 was also established as the endpoint. These endpoints allowed the study to evaluate the efficacy of avacopan for both goals of remission induction and sustained remission.

Remission and sustained remission were defined as shown below [for the details, see Section 10] according to BVAS internationally accepted as a disease activity indicator of systemic vasculitis and use status of GCs; based on the definition of remission widely used in clinical studies in patients with MPA or GPA (*N Engl J Med.* 2010;363:221-32, *Medicine.* 2007;86:269-77, etc.); and by tightening the requirement for the dose of GC in the definition of remission recommended for clinical studies in patients with systemic vasculitis by the European Alliance of Associations for Rheumatology "BVAS of 0 and dose of GC is ≤7.5 mg/day prednisolone equivalent" (*Ann Rheum Dis.* 2007;66:605-17). BVAS of 0 indicates a condition where systemic symptoms and lesions in organs have disappeared and neither new development nor worsening has occurred for 4 weeks.

- Remission at Week 26 is defined as achieving BVAS of 0 and not taking GCs for treatment of ANCA-associated vasculitis for the last 4 weeks.
- Sustained remission at Week 52 is defined as achieving remission at both Weeks 26 and 52 along with no relapses between Weeks 26 and 52 and not taking GCs for treatment of ANCA-associated vasculitis for the last 4 weeks.

● Dosage regimen in the phase III study

In the phase III study, avacopan 30 mg was orally administered twice daily. This regimen was determined in view of results from the foreign phase II study (Study CL003_168) in patients with MPA, GPA, or renal limited vasculitis requiring treatment with CY or RTX, which evaluated the efficacy and safety of avacopan 10 mg and 30 mg administered concomitantly with high dose prednisone on a tapering regimen and immunosuppressive drugs. In this study, the proportion of patients achieving disease response at Week 12, the primary efficacy endpoint, did not differ among dose groups (Table 38), but results on the other endpoints such as the proportion of patients achieving BVAS of 0 at Week 4 and change in eGFR in the subgroup of patients having renal vasculitis at baseline indicated that improvement in the 30 mg group tended to be greater than that in the 10 mg group,[46)] and there are no clear differences in safety between 10 mg and 30 mg.

● Study population, comparator, and concomitant drugs in the phase III study

In view of the previously mentioned strategies for treatment of MPA and GPA, the phase III study included patients with MPA or GPA who had newly diagnosed or relapsed disease requiring CY or RTX, being eligible for remission induction, and met at least 1 major item, at least 3 non-major items, or at least 2 renal items of proteinuria and hematuria on BVAS. In this study where immunosuppressive drugs were concomitantly used, the efficacy and safety of avacopan were evaluated using a tapering GC regimen as the control.

[46)] The proportion of patients achieving BVAS of 0 at Week 4 (ITT population) was 8.3% (1 of 12) of patients in the avacopan 10 mg group, 33.3% (5 of 15) of patients in the avacopan 30 mg group, and 15.4% (2 of 13) of patients in the placebo group; a change in eGFR from baseline to Week 12 (mean ± SD [number of patients]) (subgroup of patients having renal vasculitis at baseline) was 1.3 ± 9.8 (8 patients) in the avacopan 10 mg group, 6.2 ± 22.2 (10 patients) in the avacopan 30 mg group, and 2.0 ± 10.7 (9 patients) in the placebo group; and the renal response was obtained in 40.0% (2 of 5) of patients in the avacopan 10 mg group, 62.5% (5 of 8) of patients in the avacopan 30 mg group, 16.7% (1 of 6) of patients in the placebo group.

Although prednisone, a GC unapproved in Japan, was used in Study CL010_168 as a comparator, the applicant considered it acceptable to evaluate the efficacy and safety of avacopan in Japanese patients with MPA or GPA based on results from this study (using prednisone, unapproved in Japan, as the comparator) for the following reasons: Prednisone is a prodrug of prednisolone, a GC widely used in Japan, and immediately metabolized into prednisolone after administration; and both GC potency and equivalent (mg) of prednisone are the same as those of prednisolone (*Japanese Journal of Clinical Immunology.* 2011;34:464-75).

For the concomitant immunosuppressive drug, the protocol allowed use of either a regimen of CY followed by AZA or RTX in each patient for the following reasons:

- As immunosuppressive drugs used concomitantly with high dose GC on a tapering regimen in the remission induction therapy, CY and RTX are recommended comparably in the foreign clinical practice guideline (*Ann Rheum Dis.* 2016;75:1583-94). In Japan, a recommendation level of CY is higher than that of RTX, but RTX may be used in patients considered eligible by physicians with adequate knowledge and experience in the treatment of ANCA-associated vasculitis (Japanese Clinical Practice Guideline). In addition, a randomized clinical study in patients with ANCA-associated vasculitis comparing the efficacy between CY and RTX showed that results on any of the evaluation indicators of death, renal functions, and relapse did not differ between these drugs (*Ann Rheum Dis.* 2015;74:1178-82).

Intravenous CY was concomitantly used until Week 13 and oral CY until Week 14, and AZA or other immunosuppressive drugs were orally administered from Week 15 onwards, in view of the increased risk of hypogonadism and secondary malignant tumor by the prolonged treatment, which lead to a recommendation to use CY within a period not exceeding 6 months (Japanese Clinical Practice Guideline). For patients concomitantly receiving RTX, on the other hand, the currently approved dosage regimen of RTX in foreign countries specifies regimens for remission maintenance therapy, but when Study CL010_168 was initiated, only the regimen of "Intravenous administration at 375 mg/m^2 weekly for up to 4 weeks" was approved, and thus the protocol of this study did not specify the second cycle of RTX for remission maintenance or concomitant use of the other immunosuppressive drugs in the latter half of the treatment period to ensure evaluation of an effect of avacopan on sustained remission without concomitant immunosuppressive drugs.

● Primary analysis population

On the basis of the similarities between MPA and GPA shown below, and from a viewpoint of the pharmacological effect of avacopan, which suppresses neutrophil activation by inhibiting binding of C5a to C5aR, avacopan is expected to be effective in the treatment of both MPA and GPA. The applicant therefore considered it acceptable to evaluate the efficacy and safety of avacopan in both patients with MPA and patients with GPA together, and the primary analysis was performed on data in the overall population comprising both subgroups by disease in Study CL010_168.

- MPA and GPA are major disease types of ANCA-associated vasculitis, which is classified as small-vessel vasculitis according to Chapel Hill Consensus Conference definitions (revised in 2012), and both are also characterized by production of autoantibodies against the neutrophil-expressed antigens MPO and PR3, with complement activation and C5a production involved in pathogenesis.

- MPA and GPA share clinical symptoms and pathological conditions in many points. For instance, both are associated with various symptoms ranging from cutaneous symptoms and glomerulonephritis to life-threatening pulmonary hemorrhage and are especially likely to damage the kidney packed with small vessels, causing potentially serious diseases.
- As previously mentioned, strategies for treatment of MPA and GPA do not differ and use common indicators for evaluation of disease activity.
- Generally, prognosis of MPA is poorer than that of GPA, but the concerned difference is considered to have a limited impact on Study CL010_168, which is primarily intended to evaluate the effectiveness in achieving remission induction and sustained remission, therapeutic goals of MPA and GPA.

PMDA's view:
The efficacy and safety of avacopan in Japanese patients with MPA or GPA are evaluable based on results from the global phase III study (Study CL010_168), in which the efficacy endpoints, dosage regimens, study population, and comparator were specified as presented above. The efficacy and safety in patients with each disease should be evaluated based on results from a subgroup analysis by disease (MPA or GPA), but in view of the similarities of symptoms and pathological conditions between MPA and GPA as well as the limited number of patients, the population comprising patients with MPA or GPA together was used in the primary analysis, which is understandable. The protocol that allowed concomitant use of either a regimen of CY followed by AZA or RTX in each patient is also understandable, but PMDA will evaluate the efficacy of avacopan in the treatment of MPA and GPA based on results separately in the subgroup receiving a regimen of CY followed by AZA and subgroup receiving RTX, in light of the plan that did not allow only patients receiving RTX concomitantly to use immunosuppressive drugs in the latter half of the treatment period [see Section 7.R.2].

7.R.2 Efficacy

The applicant's explanation about the efficacy of avacopan in the treatment of MPA and GPA:

● Proportion of patients achieving remission and proportion of patients achieving sustained remission

In Study CL010_168, the proportion of patients achieving remission at Week 26 in the avacopan group was similar to that in the prednisone group (Table 45), and in terms of the proportion of patients achieving sustained remission at Week 52, the primary efficacy endpoint, superiority of avacopan to prednisone was demonstrated (Table 41). Table 45 shows the proportion of patients achieving remission at Week 26 and proportion of patients achieving sustained remission at Week 52 in the subgroups by disease (disease subgroups, MPA and GPA). In both disease subgroups, the proportion of patients achieving remission at Week 26 in the avacopan group was similar to that in the prednisone group, and the proportion of patients achieving sustained remission at Week 52 in the avacopan group tended to be higher than that in the prednisone group.

Table 45. Proportion of patients achieving remission and proportion of patients achieving sustained remission by disease (Study CL010_168, ITT population, NRI)

Endpoint	Population	Avacopan	Prednisone	Difference between groups [95% CI]
Proportion of patients achieving remission at Week 26	Overall population	72.3 (120/166)	70.1 (115/164)	3.4 [-6.0, 12.8] a)
	Patients with MPA	73.3 (55/75)	67.6 (50/74)	5.8 [-8.9, 20.4] b)
	Patients with GPA	71.4 (65/91)	72.2 (65/90)	-0.8 [-13.9, 12.3] b)
Proportion of patients achieving sustained remission at Week 52	Overall population	65.7 (109/166)	54.9 (90/164)	12.5 [2.6, 22.3] a)
	Patients with MPA	70.7 (53/75)	51.4 (38/74)	19.3 [4.0, 34.7] b)
	Patients with GPA	61.5 (56/91)	57.8 (52/90)	3.8 [-10.5, 18.0] b)

% (Number of patients)

a) Confidence interval determined according to summary score estimates on the stratification factors (base treatment, ANCA type, and disease stage) (*Categorical data analysis*. John Wiley & Sons; 2013. p231) and the Miettinen-Nurminen method

b) Confidence interval according to the Wald method

- Efficacy by organ system affected

Table 46 and Table 47 show changes over time in BVAS total score and in BVAS score for each of the organ systems affected in the disease subgroups (MPA and GPA). In either disease subgroup, the BVAS total scores showed a trend toward a greater improvement in the avacopan group than in the prednisone group; and the BVAS scores for some of the organ systems affected also showed a trend toward a greater improvement in the avacopan group than in the prednisone group, suggesting that avacopan would be effective in the treatment of both MPA and GPA irrespective of the organ systems affected. The concerned improving trend was noted as early as at Week 10 and maintained up to Week 52.

Table 46. Changes over time in BVAS in patients with MPA (Study CL010_168, ITT population, observed cases [OC])

Variable		Group	Baseline	Week 10	Week 16	Week 26	Week 52
BVAS total score		Avacopan					
		Prednisone					
By organ system affected	General	Avacopan					
		Prednisone					
	Cutaneous	Avacopan					
		Prednisone					
	Mucous membranes/eyes	Avacopan					
		Prednisone					
	Ear, nose, and throat (ENT)	Avacopan					
		Prednisone					
	Chest	Avacopan					
		Prednisone					
	Cardiovascular	Avacopan					
		Prednisone					
	Abdominal	Avacopan					
		Prednisone					
	Renal	Avacopan					
		Prednisone					
	Nervous system	Avacopan					
		Prednisone					

Mean ± SD (Number of patients)

Table 47. Changes over time in BVAS in patients with GPA (Study CL010_168, ITT population, OC)

Variable		Group	Baseline	Week 10	Week 16	Week 26	Week 52
BVAS total score		Avacopan	[redacted]				
		Prednisone					
By organ system affected	General	Avacopan					
		Prednisone					
	Cutaneous	Avacopan					
		Prednisone					
	Mucous membranes/eyes	Avacopan					
		Prednisone					
	Ear, nose, and throat (ENT)	Avacopan					
		Prednisone					
	Chest	Avacopan					
		Prednisone					
	Cardiovascular	Avacopan					
		Prednisone					
	Abdominal	Avacopan					
		Prednisone					
	Renal	Avacopan					
		Prednisone					
	Nervous system	Avacopan					
		Prednisone					

Mean ± SD (Number of patients)

Table 48 shows changes in eGFR from baseline in the population of patients with a renal disease indicated by BVAS at baseline (renal disease population) in the disease subgroups (MPA and GPA) in Study CL010_168. In both subgroups, the improvement in the avacopan group was greater than that in the prednisone group.

Table 48. Changes in eGFR (mL/min/1.73 m^2) from baseline in disease subgroups (Study CL010_168, renal disease population, OC)

Disease	MPA		GPA	
Group	Avacopan	Prednisone	Avacopan	Prednisone
Baseline	32.1 ± 15.8 (67)	37.3 ± 21.0 (71)	57.6 ± 31.3 (64)	54.8 ± 30.6 (63)
Week 26	40.3 ± 17.7 (63)	43.1 ± 20.8 (66)	63.3 ± 28.3 (58)	55.6 ± 24.3 (61)
Change from baseline[a)]	8.2 [5.9, 10.5]	4.6 [2.3, 6.8]	3.4 [0.0, 6.9]	0.8 [-2.7, 4.2]
Week 52	45.0 ± 18.9 (63)	44.2 ± 19.3 (65)	62.4 ± 26.0 (56)	57.3 ± 23.1 (60)
Change from baseline[a)]	11.9 [9.6, 14.2]	5.4 [3.1, 7.7]	2.6 [-0.9, 6.1]	2.4 [−1.1, 5.8]

Mean ± SD (Number of patients), Change expressed as least squares mean [95% CI]

a) Mixed model for repeated measures (MMRM) using dose group, evaluation timepoint, and interaction between dose group and evaluation timepoint as factors and baseline as a covariate

- Proportion of patients experiencing relapse and time to relapse

Of patients achieving remission at Week 26 in Study CL010_168, 7.5% (9 of 120) of patients in the avacopan group and 12.2% (14 of 115) of patients in the prednisone group experienced relapse of ANCA-associated vasculitis [for the definitions, see Section 10]. Table 49 shows the number of patients who experienced relapse at a given timepoint after achieving BVAS of 0 and time from BVAS of 0 to relapse in this study, and Figure 3 shows the Kaplan-Meier curves. Time to relapse was longer in the avacopan group than in the prednisone group.

Table 49. Number of patients who experienced relapse after achieving BVAS of 0 and time from BVAS of 0 to relapse (Study CL010_168, population of patients achieving BVAS of 0)

	Avacopan (n = 158)	Prednisone (n = 157)
Number of patients who experienced relapse after achieving BVAS of 0 (%)	16 (10.1)	33 (21.0)
Median from BVAS of 0 to relapse (days) [95% CI][a)]	NE [NE]	NE [NE]
Hazard ratio [95% CI][a)]	0.46 [0.25, 0.84]	

NE, Not estimated
a) Kaplan-Meier method

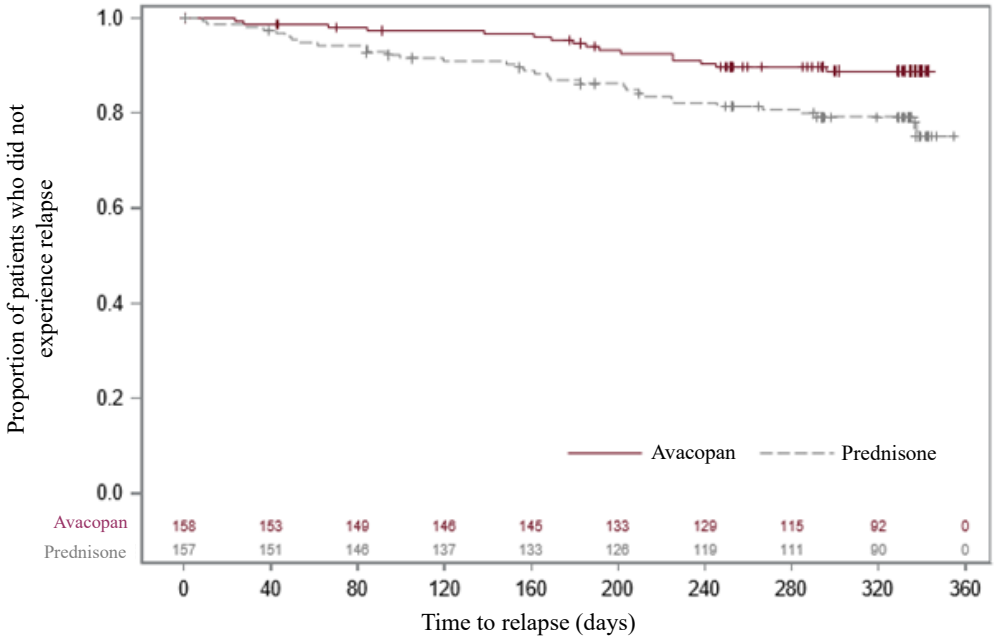

Figure 3. Kaplan-Meier curves using the first relapse of ANCA-associated vasculitis as an event (ITT population)

- Efficacy in Japanese patients with MPA or GPA

The proportion of patients achieving sustained remission at Week 52, the primary efficacy endpoint in Study CL010_168, tended to be higher in the avacopan group than in the prednisone group in the Japanese subgroup as observed in the overall population (Table 42). Table 50 shows the proportion of patients achieving remission at Week 26 and proportion of patients achieving sustained remission at Week 52 in the Japanese subgroup. Although the results should be carefully interpreted because of the limited sample size of Japanese patients, values on both endpoints tended to be higher in the avacopan group than in the placebo group. In both disease types in the Japanese subgroup, the proportion of patients achieving remission at Week 26 did not tend to be measurably lower in the avacopan group than in the prednisone group, and the proportion of patients achieving sustained remission at Week 52 tended to be higher in the avacopan group than in the placebo group.

Table 50. Proportion of patients achieving remission and proportion of patients achieving sustained remission in disease types (Study CL010_168, Japanese subgroup, NRI)

Endpoint	Population	Avacopan	Prednisone	Difference between groups [95% CI][a)]
Proportion of patients achieving remission at Week 26	Overall Japanese	81.8 (9/11)	70.0 (7/10)	11.8 [-24.6, 48.2]
	Patients with MPA	71.4 (5/7)	77.8 (7/9)	-6.3 [-49.5, 36.8]
	Patients with GPA	100 (4/4)	0 (0/1)	100 [100, 100]
Proportion of patients achieving sustained remission at Week 52	Overall Japanese	72.7 (8/11)	40.0 (4/10)	32.7 [-7.5, 72.9]
	Patients with MPA	71.4 (5/7)	44.4 (4/9)	27.0 [-19.6, 73.6]
	Patients with GPA	75.0 (3/4)	0 (0/1)	75.0 [32.6, 100]

% (Number of patients)
a) Confidence interval according to the Wald method

In Study CL010_168, patient characteristics that tended to differ between the Japanese subgroup and overall population were age (mean 72.7 years in the Japanese subgroup, mean 60.9 years in the overall population), sex (proportion of females; 71.4%, 43.5%), BMI (mean 20.9 kg/m^2, mean 26.8 kg/m^2), ANCA type (proportion of patients positive for anti-MPO antibody; 95.2%, 57.0%), disease type (proportion of patients with MPA; 76.2%, 45.2%), eGFR at baseline (mean 38.8 mL/min/1.73 m^2, mean 51.8 mL/min/1.73 m^2), and proportion of patients with vasculitis complicated by interstitial lung disease (57.1%, 7.0%). Table 51 shows the proportion of patients achieving remission at Week 26 and proportion of patients achieving sustained remission at Week 52 in subgroups formed by each of the above characteristics and race in Study CL010_168. Although the results should be carefully interpreted because of the limited sample size of some subgroups, values on these endpoints did not tend to differ clearly between any of the subgroups and overall population. The patient characteristics are unlikely to affect the efficacy evaluation. The efficacy of avacopan in Japanese patients with MPA or GPA is evaluable based on results in the overall population.

Table 51. Proportion of patients achieving remission at Week 26 and proportion of patients achieving sustained remission at Week 52 by patient characteristic (Study CL010_168, ITT population, NRI)

Patient characteristic		Proportion of patients achieving remission at Week 26		Proportion of patients achieving sustained remission at Week 52	
		Avacopan	Prednisone	Avacopan	Prednisone
Age	<65 years	72.5 (58/80)	70.0 (63/90)	66.3 (53/80)	54.4 (49/90)
	≥65 years	72.1 (62/86)	70.3 (52/74)	65.1 (56/86)	55.4 (41/74)
Sex	Male	74.5 (73/98)	73.9 (65/88)	68.4 (67/98)	56.8 (50/88)
	Female	69.1 (47/68)	65.8 (50/76)	61.8 (42/68)	52.6 (40/76)
BMI	<30 kg/m^2	72.1 (93/129)	68.3 (82/120)	67.4 (87/129)	54.2 (65/120)
	≥30 kg/m^2	72.2 (26/36)	74.4 (32/43)	58.3 (21/36)	55.8 (24/43)
ANCA type	Anti-PR3 antibody positive	70.8 (51/72)	71.4 (50/70)	59.7 (43/72)	57.1 (40/70)
	Anti-MPO antibody positive	73.4 (69/94)	69.1 (65/94)	70.2 (66/94)	53.2 (50/94)
Disease type	MPA	73.3 (55/75)	67.6 (50/74)	70.7 (53/75)	51.4 (38/74)
	GPA	71.4 (65/91)	72.2 (65/90)	61.5 (56/91)	57.8 (52/90)
eGFR at baseline	<30 mL/min/1.73 m^2	69.2 (36/52)	68.8 (33/48)	67.3 (35/52)	60.4 (29/48)
	30-59 mL/min/1.73 m^2	80.4 (45/56)	70.2 (40/57)	71.4 (40/56)	54.4 (31/57)
	>59 mL/min/1.73 m^2	65.5 (36/55)	72.4 (42/58)	56.4 (31/55)	51.7 (30/58)
Complicated by interstitial lung disease	Yes	72.7 (8/11)	91.7 (11/12)	63.6 (7/11)	66.7 (8/12)
	No	72.3 (112/155)	68.4 (104/152)	65.8 (102/155)	53.9 (82/152)
Race	Asian	76.5 (13/17)	66.7 (10/15)	70.6 (12/17)	46.7 (7/15)
	Caucasian	71.7 (99/138)	70.0 (98/140)	65.9 (91/138)	55.0 (77/140)
	Others	72.7 (8/11)	77.8 (7/9)	54.5 (6/11)	66.7 (6/9)

% (Number of patients)

The above results indicated that the efficacy of avacopan is expected in Japanese patients with MPA or GPA, although Study CL010_168 included only the limited number of Japanese patients.

● Efficacy by concomitant immunosuppressive drug

Table 52 shows analysis results on the efficacy in subgroups formed by concomitant immunosuppressive drug (CY/AZA or RTX) in Study CL010_168. The proportion of patients achieving remission at Week 26 in the avacopan group was similar to that in the prednisone group in both subgroups. The proportion of patients achieving sustained remission at Week 52 was higher in the avacopan group than in the prednisone group in the concomitant RTX subgroup but showed no difference between the avacopan group and prednisone group in the concomitant CY/AZA subgroup, indicating a different trend between these subgroups. The concerned trend, however, was potentially caused by a difference in proportion of patients using immunosuppressive drugs for rescue treatment at Week 26 onward, which was lower in the avacopan group than in the prednisone group in the concomitant CY/AZA subgroup,[47] apparently leading to the narrowed difference in proportion of patients achieving sustained remission between the groups. On the secondary endpoints, on the other hand, results in the concomitant CY/AZA and concomitant RTX subgroups showed similar trends (Table 53). Avacopan can be effective even in patients concomitantly receiving CY/AZA.

Table 52. Proportion of patients achieving remission at Week 26 and proportion of patients achieving sustained remission at Week 52 by concomitant immunosuppressive drug (Study CL010_168, ITT population, NRI)

Concomitant drug	Proportion of patients achieving remission at Week 26		Proportion of patients achieving sustained remission at Week 52	
	Avacopan	Prednisone	Avacopan	Prednisone
CY/AZA	62.7 (37/59)	59.6 (34/57)	55.9 (33/59)	52.6 (30/57)
RTX	77.6 (83/107)	75.7 (81/107)	71.0 (76/107)	56.1 (60/107)

% (Number of patients)

Table 53. Results on secondary endpoints by concomitant immunosuppressive drug (Study CL010_168, ITT population, OC)

Endpoint	CY/AZA		RTX	
	Avacopan	Prednisone	Avacopan	Prednisone
Proportion of patients who experienced relapse	13.0 (7/54)	22.6 (12/53)	8.7 (9/104)	20.2 (21/104)
Proportion of patients achieving BVAS of 0 at Week 4	66.1 (73/107)	68.4 (39/57)	58.9 (63/107)	68.2 73/107)
Change in eGFR from baseline to Week 52	10.9 ± 19.5 (43)	6.3 ± 19.6 (46)	5.9 ± 15.2 (76)	3.2 ± 13.9 (79)
Change in UACR from baseline to Week 4 (%)[a)]	-38.1 [-50.4, -22.8] (47)	-6.3 [-25.7, 18.2] (50)	-43.4 [-53.8, -30.6] (74)	8.3 [-13.9, 36.3] (74)
Change in urinary MCP-1: Creatinine ratio from baseline to Week 52 (%)[a)]	-75.5 [-80.9, -68.5] (39)	-73.2 [-81.2, -62.0] (41)	-71.3 [-77.2, -63.9] (67)	-68.0 [-74.2, -60.3] (67)
Change in VDI from baseline to Week 52	1.73 ± 1.59 (51)	1.65 ± 1.04 (51)	1.06 ± 1.09 (99)	1.05 ± 1.01 (100)
GTI-CWS at Week 26	45.6 ± 45.5 (52)	64.4 ± 58.2 (51)	36.8 ± 36.6 (102)	52.9 ± 49.7 (102)
GTI-AIS at Week 26	12.2 ± 45.6 (52)	32.6 ± 47.8 (51)	11.7 ± 34.6 (102)	19.8 ± 43.5 (102)
Change in SF-36 PCS from baseline to Week 52	3.4 ± 11.4 (50)	3.2 ± 10.3 (49)	6.3 ± 10.7 (97)	3.6 ± 11.4 (95)
Change in SF-36 MCS from baseline to Week 52	6.4 ± 12.9 (50)	5.9 ± 13.3 (49)	7.1 ± 11.9 (98)	6.5 ± 13.6 (95)
Change in EQ-5D-5L VAS from baseline to Week 52	11.8 ± 20.2 (51)	7.1 ± 20.8 (50)	13.9 ± 19.2 (98)	10.0 ± 24.1 (96)

% (Number of patients) or mean ± SD (Number of patients)
a) Geometric mean [95% CI] (Number of patients)

PMDA's view:

In Study CL010_168 in patients with MPA or GPA requiring CY or RTX, results on the proportion of patients achieving sustained remission at Week 52, the primary endpoint, demonstrated superiority of avacopan to the prednisone tapering regimen, and furthermore results on the other endpoints including

[47] Proportion of patients using immunosuppressive drugs for rescue treatment at Week 26 onward: 6.8% (4 of 59) of patients in the avacopan group and 14.0% (8 of 57) of patients in the prednisone group in the concomitant CY/AZA subgroup; and 15.0% (16 of 107) of patients in the avacopan group and 18.7% (20 of 107) of patients in the prednisone group in the concomitant RTX subgroup

the proportion of patients achieving remission, symptoms by organ system affected, and relapse showed that avacopan is comparable to or better than the prednisone tapering regimen. The above findings demonstrated the efficacy of avacopan in the treatment of MPA and GPA in achieving both remission induction and sustained remission. In the Japanese subgroup in Study CL010_168, of which sample size is limited, though, the results on the proportion of patients achieving sustained remission at Week 52, the primary endpoint, and other multiple endpoints do not show any trend clearly different from that in the overall population. Avacopan can be effective in Japanese patients with MPA or GPA.

With respect to the efficacy in subgroups formed by concomitant immunosuppressive drug, the result on the proportion of patients achieving sustained remission at Week 52 in the concomitant CY/AZA subgroup tended to be lower than that in the concomitant RTX subgroup, but even in the concomitant CY/AZA subgroup, results on multiple endpoints are better than in the standard therapy with GC. The above findings indicated that the efficacy of avacopan is expected irrespective of the type of concomitant immunosuppressive drugs.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.3 Safety

The applicant's explanation about the safety of avacopan based on pooled safety data from 3 clinical studies of avacopan in patients with ANCA-associated vasculitis (Studies CL002_168, CL003_168, and CL010_168) (3-study pooled data):

Table 54 shows a summary of the safety of avacopan based on the 3-study pooled data. Deaths occurred in 0.8% (2 of 239) of patients in the avacopan group (pneumonia and granulomatosis with polyangiitis in 1 patient each) and 2.0% (4 of 200) of patients in the prednisone group (diarrhoea/vomiting/fungal infection, infectious pleural effusion, acute myocardial infarction, and death in 1 patient each). A causal relationship to the study drug could not be ruled out for the event in 1 patient (diarrhoea/vomiting/fungal infection) in the prednisone group. The Japanese subgroup and overall population did not show any clearly different trends, although the comparison had limitations owing to the small sample size of this subgroup.

Table 54. Summary of the safety of avacopan (3-study pooled data, safety analysis population)

Disease		ANCA-associated vasculitis[a)]		By disease			
				MPA		GPA	
Dose group		Avacopan	Prednisone	Avacopan	Prednisone	Avacopan	Prednisone
Overall population	Number of patients	239	200	101	87	134	109
	Total exposure period (person-years)	212.3	195.7	93.5	85.7	117.0	108.7
	Adverse event	233 (97.5) 1328.5	195 (97.5) 1626.5	100 (99.0) 2205.6	85 (97.7) 2248.1	129 (96.3) 1013.5	107 (98.2) 1306.6
	Serious adverse event	94 (39.3) 61.6	82 (41.0) 60.1	45 (44.6) 71.5	46 (52.9) 88.6	48 (35.8) 54.6	35 (32.1) 41.9
	Death	2 (0.8) 0.9	4 (2.0) 2.0	1 (1.0) 1.1	3 (3.4) 3.5	1 (0.7) 0.9	1 (0.9) 0.9
	Adverse event leading to discontinuation	35 (14.6) 18.2	32 (16.0) 18.0	20 (19.8) 24.5	17 (19.5) 22.4	15 (11.2) 13.8	15 (13.8) 14.9
	Adverse drug reaction	168 (70.3) 175.7	137 (68.5) 159.3	68 (67.3) 156.7	60 (69.0) 170.3	96 (71.6) 184.7	74 (67.9) 145.9
Japanese subgroup	Number of patients	11	10	7	9	4	1
	Total exposure period (person-years)	12.3	10.9	8.1	9.7	4.2	1.2
	Adverse event	11 (100) 6277.7	10 (100) 2898.8	7 (100) 9469.4	9 (100) 2883.6	4 (100) 3948.6	1 (100) 3043.8
	Serious adverse event	4 (36.4) 42.6	5 (50.0) 76.2	2 (28.6) 28.8	4 (44.4) 61.7	2 (50.0) 82.2	1 (100) 1304.5
	Death	0	0	0	0	0	0
	Adverse event leading to discontinuation	3 (27.3) 30.2	3 (30.0) 35.4	2 (28.6) 33.1	2 (22.2) 23.8	1 (25.0) 25.6	1 (100) 1304.5
	Adverse drug reaction	9 (81.8) 185.7	7 (70.0) 174.3	6 (85.7) 234.4	7 (77.8) 244.2	3 (75.0) 131.2	0

Top, Number of patients (%); Bottom, Number of patients with events per 100 person-years adjusted according to the exposure period[b)]

a) The overall population includes patients with MPA or GPA, and 8 patients with renal limited vasculitis or other diseases (4 in the avacopan group, 4 in the prednisone group).

b) Time to onset of the first event (for patients without events, treatment period) was tabulated.

Table 55 shows major adverse events in the 3-study pooled data. There were no events of which the incidence in the avacopan group clearly exceeded that in the prednisone group in the populations of patients with ANCA-associated vasculitis and of patients with GPA. In the population of patients with MPA, headache more frequently occurred in the avacopan group than in the prednisone group, but no serious events were reported. The tolerability was considered acceptable.

Table 55. Adverse events reported by ≥5.0% of patients in the avacopan group in the population of patients with ANCA-associated vasculitis (3-study pooled data, safety analysis population)

Disease	ANCA-associated vasculitis[a)]		By disease			
			MPA		GPA	
Dose group	Avacopan	Prednisone	Avacopan	Prednisone	Avacopan	Prednisone
Number of patients	239	200	101	87	134	109
Total exposure period (person-years)	212.3	195.7	93.5	85.7	117.0	108.7
Nausea	55 (23.0) 31.7	41 (20.5) 25.4	23 (22.8) 30.5	15 (17.2) 20.3	30 (22.4) 30.9	25 (22.9) 28.8
Hypertension	45 (18.8) 24.3	35 (17.5) 20.9	21 (20.8) 26.6	19 (21.8) 26.8	23 (17.2) 22.0	16 (14.7) 16.8
Oedema peripheral	44 (18.4) 24.6	45 (22.5) 28.0	23 (22.8) 30.2	23 (26.4) 33.1	21 (15.7) 20.8	20 (18.3) 22.1
Headache	44 (18.4) 24.7	28 (14.0) 15.9	26 (25.7) 35.6	11 (12.6) 13.8	17 (12.7) 16.5	16 (14.7) 16.7
Arthralgia	41 (17.2) 21.7	38 (19.0) 22.1	16 (15.8) 18.8	14 (16.1) 17.9	25 (18.7) 24.6	24 (22.0) 25.9
Nasopharyngitis	37 (15.5) 19.2	35 (17.5) 20.4	20 (19.8) 25.0	21 (24.1) 29.4	16 (11.9) 14.4	14 (12.8) 14.2
Vomiting	36 (15.1) 19.1	22 (11.0) 12.1	18 (17.8) 22.3	9 (10.3) 11.3	15 (11.2) 13.9	13 (11.9) 13.0
Diarrhoea	33 (13.8) 17.6	27 (13.5) 15.3	18 (17.8) 22.6	17 (19.5) 23.3	15 (11.2) 14.2	10 (9.2) 9.7
Cough	31 (13.0) 16.0	31 (15.5) 17.8	15 (14.9) 18.0	10 (11.5) 12.8	15 (11.2) 13.8	21 (19.3) 22.1
Anti-neutrophil cytoplasmic antibody positive vasculitis	27 (11.3) 13.8	34 (17.0) 19.5	13 (12.9) 15.4	18 (20.7) 24.0	14 (10.4) 12.8	16 (14.7) 16.3
Upper respiratory tract infection	27 (11.3) 13.8	25 (12.5) 13.8	9 (8.9) 10.4	8 (9.2) 9.8	17 (12.7) 15.9	17 (15.6) 17.2
Fatigue	24 (10.0) 12.3	21 (10.5) 11.5	11 (10.9) 13.1	9 (10.3) 11.3	13 (9.7) 11.9	11 (10.1) 10.9
Rash	23 (9.6) 11.7	14 (7.0) 7.6	14 (13.9) 17.0	5 (5.7) 6.0	8 (6.0) 7.1	9 (8.3) 8.9
Epistaxis	21 (8.8) 10.5	25 (12.5) 14.3	2 (2.0) 2.2	8 (9.2) 10.3	17 (12.7) 15.8	16 (14.7) 16.8
Myalgia	21 (8.8) 10.5	24 (12.0) 13.2	8 (7.9) 8.9	9 (10.3) 11.0	13 (9.7) 12.0	15 (13.8) 15.3
Muscle spasms	20 (8.4) 10.3	43 (21.5) 27.3	16 (15.8) 20.2	20 (23.0) 28.6	4 (3.0) 3.5	22 (20.2) 25.4
Back pain	20 (8.4) 10.0	29 (14.5) 15.9	12 (11.9) 14.0	18 (20.7) 23.0	8 (6.0) 7.1	11 (10.1) 10.7
Insomnia	19 (7.9) 9.5	26 (13.0) 15.3	7 (6.9) 7.8	14 (16.1) 19.8	11 (8.2) 10.2	12 (11.0) 12.2
Pyrexia	18 (7.5) 9.1	22 (11.0) 12.1	9 (8.9) 10.4	12 (13.8) 15.5	9 (6.7) 8.3	9 (8.3) 8.7
Pain in extremity	17 (7.1) 8.4	13 (6.5) 6.9	9 (8.9) 10.0	8 (9.2) 10.0	7 (5.2) 6.3	5 (4.6) 4.7
Constipation	16 (6.7) 8.0	16 (8.0) 8.7	7 (6.9) 8.0	6 (6.9) 7.5	8 (6.0) 7.3	9 (8.3) 8.8
Abdominal pain upper	16 (6.7) 7.9	12 (6.0) 6.4	8 (7.9) 9.2	5 (5.7) 6.1	7 (5.2) 6.2	7 (6.4) 6.8
Urinary tract infection	15 (6.3) 7.4	24 (12.0) 13.3	11 (10.9) 12.8	12 (13.8) 15.5	4 (3.0) 3.5	12 (11.0) 11.8
Paraesthesia	15 (6.3) 7.4	10 (5.0) 5.3	8 (7.9) 9.1	4 (4.6) 4.8	7 (5.2) 6.2	5 (4.6) 4.8
Hypercholesterolaemia	14 (5.9) 7.0	21 (10.5) 11.9	9 (8.9) 10.5	8 (9.2) 10.3	5 (3.7) 4.4	13 (11.9) 13.4
Anaemia	14 (5.9) 7.0	20 (10.0) 11.0	9 (8.9) 10.5	12 (13.8) 15.5	5 (3.7) 4.4	8 (7.3) 7.8
Dizziness	14 (5.9) 7.0	12 (6.0) 6.5	9 (8.9) 10.6	4 (4.6) 4.8	5 (3.7) 4.4	8 (7.3) 7.9
Blood creatinine increased	14 (5.9) 6.9	10 (5.0) 5.3	9 (8.9) 10.3	4 (4.6) 4.8	5 (3.7) 4.4	6 (5.5) 5.7
Leukopenia	12 (5.0) 5.9	14 (7.0) 7.5	7 (6.9) 8.0	10 (11.5) 12.8	5 (3.7) 4.4	4 (3.7) 3.7

Top, Number of patients (%); Bottom, Number of patients with events per 100 person-years adjusted according to the exposure period[b)]

a) Included patients with MPA or GPA, and 8 patients with renal limited vasculitis or other diseases (4 in the avacopan group, 4 in the prednisone group).

b) Time to onset of the first event (for patients without events, treatment period) was tabulated.

Concerning adverse events potentially related to avacopan, the following events were investigated intensively in view of the pharmacological effect of avacopan and pathological characteristics in patients with MPA or GPA.

7.R.3.1 Infections

The applicant's explanation about the incidence of infections associated with avacopan:
Table 56 shows the incidence of infections based on the 3-study pooled data. The incidence of any event in the dose groups was almost similar. Serious infections occurred in 12.1% (29 of 239) of patients in the avacopan group and 14.0% (28 of 200) of patients in the prednisone group. A causal relationship to the study drug could not be ruled out for the events in 9 patients in the avacopan group (pneumonia in 2 patients; abscess limb/perirectal abscess, sepsis, urinary tract infection, urosepsis/urinary tract infection, post procedural sepsis, Campylobacter gastroenteritis, and hepatitis B in 1 patient each) and 13 patients in the prednisone group (pneumonia in 3 patients; pneumonia bacterial in 2 patients; fungal infection, herpes zoster, pneumonia cytomegaloviral, urinary tract infection, lower respiratory tract infection, respiratory tract infection viral, sepsis, and pneumonia/bacteraemia/meningitis in 1 patient each). Although tuberculosis was found in 2 patients in the avacopan group, both events were latent tuberculosis identified by the screening result, and the causal relationship to the study drug was denied. Hepatitis B occurred in 1 patient in each group. A causal relationship to the study drug was denied for hepatitis B in the prednisone group, but hepatitis B in the avacopan group was reactivated hepatitis B developed in the follow-up period, and the causal relationship to the study drug could not be ruled out. The Japanese subgroup and overall population did not show any clearly different trend for the incidence of infections, although the comparison had limitations owing to the small sample size of this subgroup.

Because serious infections occurred in patients receiving avacopan as described above, the package insert will provide a cautionary statement that patients should carefully monitored during treatment with avacopan and, if the concerned event occurs, appropriate measures should be taken. In addition, although Pneumocystis infection was not reported in the clinical studies, the package insert will provide a cautionary statement that appropriate prophylactic measures against Pneumocystis pneumonia should be considered when using avacopan, taking into account that avacopan has not been used under the situation where prophylactic administration against Pneumocystis infection is not performed. Concerning Meningococcal infection reported by patients receiving an anti-C5 antibody preparation, the applicant considers it unnecessary to raise special caution because no such infection occurred in the clinical studies of avacopan; and avacopan does not have any impact on C5b-9, which is involved in protective functions against infections caused by capsule forming bacteria such as *Neisseria meningitidis*.

Table 56. Incidence of infections (3-study pooled data, safety analysis population)

Disease		ANCA-associated vasculitis[a)]		By disease			
				MPA		GPA	
Dose group		Avacopan	Prednisone	Avacopan	Prednisone	Avacopan	Prednisone
Overall population	Number of patients	239	200	101	87	134	109
	Total exposure period (person-years)	212.3	195.7	93.5	85.7	117.0	108.7
	Infections	151 (63.2) 139.1	139 (69.5) 148.5	69 (68.3) 164.3	67 (77.0) 189.0	79 (59.0) 120.4	70 (64.2) 121.8
	Serious infection	29 (12.1) 14.9	28 (14.0) 15.6	20 (19.8) 24.8	19 (21.8) 25.7	8 (6.0) 7.1	8 (7.3) 7.7
	Pneumonia	20 (8.4) 9.9	24 (12.0) 13.0	13 (12.9) 15.2	11 (12.6) 13.5	7 (5.2) 6.1	11 (10.1) 10.7
	Tuberculosis	2 (0.8) 0.9	0	0	0	2 (1.5) 1.7	0
	Opportunistic infection[b)]	18 (10.8) 10.6	27 (16.5) 16.4	14 (18.7) 18.7	17 (23.0) 24.0	4 (4.4) 4.2	10 (11.1) 10.6
	Deep fungal infection	0	0	0	0	0	0
	Pneumocystis pneumonia	0	0	0	0	0	0
	Hepatitis B	1 (0.4) 0.5	1 (0.5) 0.5	1 (1.0) 1.1	0	0	0
	Hepatitis C	0	0	0	0	0	0
	Meningococcal infection (including sepsis)	0	0	0	0	0	0
Japanese subgroup	Number of patients	11	10	7	9	4	1
	Total exposure period (person-years)	12.3	10.9	8.1	9.7	4.2	1.2
	Infections	9 (81.8) 191.9	6 (60.0) 113.7	6 (85.7) 340.8	6 (66.7) 145.4	3 (75.0) 102.4	0
	Serious infection	1 (9.1) 8.2	3 (30.0) 33.0	1 (14.3) 12.5	3 (33.3) 37.7	0	0
	Pneumonia	2 (18.2) 18.4	2 (20.0) 19.9	2 (28.6) 29.8	2 (22.2) 22.4	0	0
	Tuberculosis	0	0	0	0	0	0
	Opportunistic infection	2 (18.2) 18.0	2 (20.0) 21.2	2 (28.6) 28.7	2 (22.2) 24.1	0	0
	Deep fungal infection	0	0	0	0	0	0
	Pneumocystis pneumonia	0	0	0	0	0	0
	Hepatitis B	1 (9.1) 8.2	0	1 (14.3) 12.5	0	0	0
	Hepatitis C	0	0	0	0	0	0
	Meningococcal infection (including sepsis)	0	0	0	0	0	0

Top, Number of patients (%); Bottom, Number of patients with events per 100 person-years adjusted according to the exposure period[c)]

a) The overall population includes patients with MPA or GPA, and 8 patients with renal limited vasculitis or other diseases (4 in the avacopan group, 4 in the prednisone group).

b) Data only from Study CL010_168 were tabulated. The number of patients/total exposure period in each group is as follows: 166 patients with MPA and GPA per 180.0 person-years in the avacopan group, 164 patients with MPA and GPA per 180.1 person-years in the prednisone group, 75 patients with MPA per 82.5 person-years in the avacopan group, 74 patients with MPA per 80.2 person-years in the prednisone group, 91 patients with GPA per 97.5 person-years in the avacopan group, and 90 patients with GPA per 99.9 person-years in the prednisone group.

c) Time to onset of the first event (for patients without events, treatment period) was tabulated.

7.R.3.2 Hepatic dysfunction

The applicant's explanation about the incidence of hepatic dysfunction associated with avacopan:
Table 57 shows the incidence of hepatic dysfunction based on the 3-study pooled data. The incidence of any event in the dose groups was almost similar in the populations of patients with ANCA-associated vasculitis and of patients with GPA, but in the population of patients with MPA, the incidence of all hepatic dysfunction and serious hepatic dysfunction in the avacopan group tended to be higher than those in the prednisone group. Serious hepatic dysfunction occurred in 4.2% (10 of 239) of patients in the avacopan group and 3.0% (6 of 200) of patients in the prednisone group. A causal relationship to the study drug could not be ruled out for the events in 7 patients in the avacopan group (hepatic enzyme increased and hepatic function abnormal in 2 patients each; liver function test increased, hepatocellular injury, and hepatitis cholestatic in 1 patient each) and 2 patients in the prednisone group (transaminases increased and hepatic enzyme increased in 1 patient each). The Japanese subgroup and overall population did not show any clearly different trend for the incidence of hepatic dysfunction, although the comparison had limitations owing to the small sample size of this subgroup.

Most of the serious hepatic dysfunctions reported in the clinical studies of avacopan occurred in patients with other underlying factors potentially causing hepatic dysfunction (concomitant drugs, alcohol, and viral disease), and thus their causal relationships to avacopan remain unclear. As presented above, however, the serious hepatic dysfunctions for which the causal relationship to the study drug could not be ruled out occurred more frequently in the avacopan group than in the prednisone group. In view of this finding, the package insert will provide a cautionary statement that a hepatic function test should be periodically performed at baseline and during treatment with avacopan, patients should be carefully monitored, and if the concerned event occurs, appropriate measures should be taken.

Table 57. Incidence of hepatic dysfunction (3-study pooled data, safety analysis population)

Disease		ANCA-associated vasculitis[a)]		By disease			
				MPA		GPA	
Dose group		Avacopan	Prednisone	Avacopan	Prednisone	Avacopan	Prednisone
Overall population	Number of patients	239	200	101	87	134	109
	Total exposure period (person-years)	212.3	195.7	93.5	85.7	117.0	108.7
	Hepatic dysfunction	28 (11.7) 14.7	22 (11.0) 12.3	13 (12.9) 15.8	7 (8.0) 8.7	15 (11.2) 14.0	14 (12.8) 14.4
	Serious hepatic dysfunction	10 (4.2) 4.9	6 (3.0) 3.2	6 (5.9) 6.8	3 (3.4) 3.6	4 (3.0) 3.5	3 (2.8) 2.8
	Hepatic enzyme increased	6 (2.5) 2.9	7 (3.5) 3.7	4 (4.0) 4.4	2 (2.3) 2.4	2 (1.5) 1.7	5 (4.6) 4.8
	Hepatic function abnormal	3 (1.3) 1.4	0	2 (2.0) 2.2	0	1 (0.7) 0.9	0
	Alanine aminotransferase increased	8 (3.3) 3.9	7 (3.5) 3.7	2 (2.0) 2.2	1 (1.1) 1.2	6 (4.5) 5.3	6 (5.5) 5.8
	Blood bilirubin increased	3 (1.3) 1.4	1 (0.5) 0.5	0	0	3 (2.2) 2.6	1 (0.9) 0.9
	Liver function test increased	3 (1.3) 1.4	1 (0.5) 0.5	1 (1.0) 1.1	0	2 (1.5) 1.7	1 (0.9) 0.9
	Aspartate aminotransferase increased	5 (2.1) 2.4	4 (2.0) 2.1	2 (2.0) 2.2	1 (1.1) 1.2	3 (2.2) 2.6	3 (2.8) 2.8
	Transaminases increased	2 (0.8) 1.0	4 (2.0) 2.1	2 (2.0) 2.2	1 (1.1) 1.2	0	2 (1.8) 1.9
	Drug-induced liver injury	1 (0.4) 0.5	0	0	0	1 (0.7) 0.9	0
Japanese subgroup	Number of patients	11	10	7	9	4	1
	Total exposure period (person-years)	12.3	10.9	8.1	9.7	4.2	1.2
	Hepatic dysfunction	5 (45.5) 67.4	4 (40.0) 54.3	4 (57.1) 91.9	3 (33.3) 41.2	1 (25.0) 32.6	1 (100.0) 1304.5
	Serious hepatic dysfunction	2 (18.2) 19.8	2 (20.0) 23.1	1 (14.3) 14.2	1 (11.1) 11.6	1 (25.0) 32.6	1 (100.0) 1304.5
	Hepatic enzyme increased	3 (27.3) 31.7	3 (30.0) 37.4	2 (28.6) 31.2	2 (22.2) 25.2	1 (25.0) 32.6	1 (100.0) 1304.5
	Hepatic function abnormal	2 (18.2) 19.6	0	2 (28.6) 33.1	0	0	0
	Alanine aminotransferase increased	0	0	0	0	0	0
	Blood bilirubin increased	0	0	0	0	0	0
	Liver function test increased	0	0	0	0	0	0
	Aspartate aminotransferase increased	0	0	0	0	0	0
	Transaminases increased	0	0	0	0	0	0
	Drug-induced liver injury	0	0	0	0	0	0

Top, Number of patients (%); Bottom, Number of patients with events per 100 person-years adjusted according to the exposure period[b)]

a) The overall population includes patients with MPA or GPA, and 8 patients with renal limited vasculitis or other diseases (4 in the avacopan group, 4 in the prednisone group).

b) Time to onset of the first event (for patients without events, treatment period) was tabulated.

PMDA's view on the safety of avacopan based on the above review in Sections 7.R.3.1 and 7.R.3.2:

The submitted clinical study results do not suggest critical concerns in terms of the safety of avacopan in patients with MPA or GPA, and the observed adverse events are manageable. Concerning the infections and hepatic dysfunctions, a certain number of serious events for which a causal relationship to avacopan could not be ruled out occurred in the clinical studies, and thus the package insert should

include cautionary statements about the risk of the concerned events associated with avacopan, and attention should be continuously paid to the incidences of these events. Taking into account that the number of Japanese patients with MPA or GPA included in the clinical studies was limited, the applicant should accumulate safety information on avacopan through post-marketing surveillance, etc. and provide the obtained information to healthcare professionals as appropriate.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.4 Clinical positioning

The applicant's explanation about clinical positioning of avacopan expected in the treatment of MPA and GPA:

The therapeutic goals of MPA and GPA are defined as remission induction and sustained remission, and for the goals, emphasis is placed on prevention or alleviation of a relapsed disease, which would cause accumulation of organ dysfunctions at an increased mortality risk (Japanese Clinical Practice Guideline, *Rheumatology.* 2014;53:2306-9, *Am J Kidney Dis.* 2019;7:124-37). The Japanese Clinical Practice Guideline recommends high dose GC on a tapering regimen concomitantly with CY as the standard remission induction therapy, which is the initial treatment, but also allows high dose GC on a tapering regimen concomitantly with RTX to be used in patients considered eligible for RTX by physicians with adequate knowledge and experience in the treatment of ANCA-associated vasculitis. The guideline also mentions GC monotherapy as a treatment option for patients who are elderly, have renal impairment requiring dialysis, are at a high risk of adverse drug reactions such as opportunistic infections, or have a limited disease without severely affected organs. As the standard remission maintenance therapy, a combination of low dose GC and AZA is recommended. For the high dose GC, the tapering regimen is indicated because it has a risk of infections, osteonecrosis, and psychiatric disorders. In addition, even at a medium to low dose of GC, the prolonged use has a high risk of osteoporosis, cataract and glaucoma, and hyperglycemia and diabetes mellitus, and thus the guideline instructs that GC should be kept at the minimum necessary dose or, if possible, should be discontinued after the therapeutic goal is achieved (Japanese Clinical Practice Guideline).

With the above strategies for treatment of MPA and GPA taken into account, Study CL010_168 was conducted in patients with MPA or GPA requiring CY or RTX to evaluate the efficacy and safety of avacopan by comparing those of the high dose prednisone on a tapering regimen in the patients receiving a regimen of CY followed by AZA or RTX concomitantly. The study showed that the proportion of patients achieving remission at Week 26 in the avacopan group was similar to that in the prednisone group, and in terms of the proportion of patients achieving sustained remission at Week 52, the primary efficacy endpoint, superiority of avacopan to prednisone was demonstrated (Table 45).

Study CL010_168 included only patients positive for ANCA, and there is no information about the efficacy and safety of avacopan in patients negative for ANCA, but in view of the reports below, similar efficacy and safety of avacopan in patients with MPA or GPA can be obtained irrespective of the ANCA status. The applicant, however, plans to collect information on the ANCA status as a patient characteristic through the post-marketing surveillance and thereby continuously evaluate the efficacy and safety in patients negative for ANCA.

- Recently, the presence of ANCA negative ANCA-associated vasculitis (a condition that serologically tests negative for ANCA but meets the other definitions of ANCA-associated vasculitis) is reported; for instance, in patients who have clinical presentation of anti-MPO antibody positive ANCA-associated vasculitis but test negative for ANCA, a ceruloplasmin degradation product at 50 kDa is suggested to bind to ANCA in serum, potentially causing a false negative result for ANCA in a laboratory test (Japanese Clinical Practice Guideline).

In view of the above finding, avacopan can be used irrespective of ANCA as a new option in the treatment of MPA and GPA in achieving remission induction and sustained remission. In the treatment of MPA and GPA, however, drugs must be selected according to the individual patient's condition including severity of vasculitis, age, and complications and timing of use. Considering that eligibility for avacopan and concomitant drugs will be determined according to the individual patient's condition by physicians conversant in the treatment of this disease, the package insert will provide a cautionary statement that avacopan should be used by physicians with adequate knowledge and experience in the treatment of MPA and GPA.

PMDA's view:
In view of the protocol of Study CL010_168 and its results, and the efficacy and safety profiles of avacopan available up to now, in the therapeutic strategies of MPA and GPA, avacopan is positioned as equivalent of high dose GC for remission induction and as equivalent of low dose GC for remission maintenance, allowing reduction of the dose or treatment duration of GC, which potentially causes critical adverse drug reactions, and thus serves as a new treatment option which is expected to prevent relapse. In view of treatment of MPA and GPA which accompanies various concomitant drugs such as immunosuppressive drugs and GC, physicians conversant in the treatment of MPA and GPA should use avacopan after understanding patient populations in clinical studies and clinical study results also covering information about concomitant drugs, carefully weighing the expected benefit against the risk in individual patients, and assessing eligibility for avacopan and choice of concomitant drugs. Study CL010_168 did not evaluate the efficacy and safety in ANCA negative patients, but in view of the applicant's explanation about the presence of patients who test false negative for ANCA in a laboratory test and no fundamental differences in clinical characteristics and the treatment plan between ANCA positive and negative patients, PMDA considers it hardly necessary to limit avacopan to ANCA positive patients.

Future discussions about a new strategy for treatment of MPA and GPA and positioning of avacopan at relevant academic societies are desired, covering not only clinical study results available up to now but also information obtained through post-marketing surveillance.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.5 Indications

PMDA considers that the proposed indications of avacopan as "microscopic polyangiitis, granulomatosis with polyangiitis" is acceptable based on the submitted data and review in Sections 7.R.2, 7.R.3, and 7.R.4.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.6 Dosage and administration

PMDA considers that the proposed dosage and administration of avacopan for the treatment of MPA and GPA as oral administration of 30 mg twice daily is acceptable based on the submitted data and review in Sections 7.R.1, 7.R.2, and 7.R.3.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.7 Post-marketing safety measures

The applicant plans to conduct a specified use-results survey to investigate the safety and efficacy of avacopan including its long-term treatment in post-marketing clinical use.

PMDA's view:

As reviewed in Section 7.R.3, data on avacopan available up to now have not suggested critical safety concerns, and the safety of avacopan in patients with MPA or GPA is acceptable. The safety and efficacy of long-term treatment with avacopan in Japanese patients with MPA or GPA, however, should be continuously investigated through post-marketing surveillance because the clinical studies did not provide information about the efficacy and safety of avacopan in ANCA negative patients and included the limited number of Japanese patients with MPA or GPA.

In addition, a cautionary statement that avacopan should be used by physicians conversant in the treatment of MPA and GPA should be provided to healthcare professionals.

The above conclusion of PMDA will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.3) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that avacopan has efficacy in the treatment of MPA and GPA, and that avacopan has acceptable safety in view of its benefits. Avacopan is clinically meaningful because it offers a new treatment option for patients with MPA or GPA. The safety of avacopan in Japanese patients with MPA or GPA in clinical use should be further evaluated in post-marketing surveillance.

PMDA has concluded that avacopan may be approved if avacopan is not considered to have any particular problems based on comments from the Expert Discussion.

10. Others

The efficacy evaluation methods and definition of endpoints in the clinical studies of avacopan are as shown below.

<table>
<tr><th>Item</th><th>Definition</th></tr>
<tr><td colspan="2">Common in all the studies</td></tr>
<tr><td>BVAS</td><td>An indicator representative of disease activity of systemic vasculitis and a total score obtained by scoring 56 symptoms and signs in 9 organ systems including the general condition and adding the score in each system (ranging from 0 to 63. A higher score indicates higher disease activity, and BVAS of 0 indicates the absence of disease activity).

Evaluation items in BVAS version 3
<table>
<tr><th rowspan="2">Organ system</th><th rowspan="2">Evaluation items</th><th colspan="2">Maximum scores</th></tr>
<tr><th>Persistent[a)]</th><th>New/worse[b)]</th></tr>
<tr><td>General</td><td>Myalgia , arthralgia/arthritis, fever ≥38.0°C, weight loss ≥2 kg</td><td>2</td><td>3</td></tr>
<tr><td>Cutaneous</td><td>Infarct, purpura, ulcer, gangrene, other skin vasculitis</td><td>3</td><td>6</td></tr>
<tr><td>Mucous membranes/ eyes</td><td>Mouth ulcers/oral granuloma, genital ulcers, sialadenitis or dacryoadenitis, proptosis, episcleritis/scleritis, conjunctivitis/blepharitis/keratitis, blurred vision, sudden visual loss, uveitis, retinal changes (vasculitis/thrombosis/exudate/haemorrhage)</td><td>3</td><td>6</td></tr>
<tr><td>Ear, nose, and throat</td><td>Epistaxis/crusts/intranasal ulcers/granulomata, paranasal sinus involvement, subglottic stenosis, conductive hearing loss, sensorineural hearing loss</td><td>3</td><td>6</td></tr>
<tr><td>Chest</td><td>Wheeze, nodules or cavities, pleural effusion/pleurisy, infiltrate, endobronchial pseudotumor/ulcerative lesions, massive haemoptysis/alveolar haemorrhage, respiratory failure</td><td>3</td><td>6</td></tr>
<tr><td>Cardiovascular</td><td>Loss of pulses, valvular heart disease, pericarditis, ischaemic cardiac pain, cardiomyopathy, congestive cardiac failure</td><td>3</td><td>6</td></tr>
<tr><td>Abdominal</td><td>Peritonitis, bloody diarrhoea, ischaemic abdominal pain</td><td>4</td><td>9</td></tr>
<tr><td>Renal</td><td>Hypertension (Diastolic >95 mm Hg), proteinuria (>1+ or >0.2 g/day), haematuria (>1+ or >10 red blood cells/hpf), SCr elevation (≥1.4 mg/dL), SCr increased (>30%) or CCr decreased (>25%)</td><td>6</td><td>12</td></tr>
<tr><td>Nervous system</td><td>Headache, meningitis, organic confusion, seizures, stroke, spinal cord lesion, cranial nerve palsy, sensory peripheral neuropathy, motor mononeuritis multiplex</td><td>6</td><td>9</td></tr>
</table>
hpf, High power field or 400-fold magnified field; SCr, Serum creatinine value; CCr, Creatinine clearance
a) Present in the prior 4 weeks or before
b) Newly develop within 4 weeks</td></tr>
<tr><td colspan="2">Phase II studies (Studies CL002_168 and CL003_168)</td></tr>
<tr><td>Proportion of patients achieving disease response</td><td>Proportion of patients in whom BVAS decreased from baseline by ≥50% and no worsening occurred in any item</td></tr>
<tr><td colspan="2">Phase III study (Study CL010_168)</td></tr>
<tr><td>Remission</td><td>Meeting all of the following conditions:
• Achieving BVAS of 0
• Not taking GCs for treatment of ANCA-associated vasculitis for the last 4 weeks
• Keeping BVAS ≤0·for the last 4 weeks (if assessed at an unscheduled visit)</td></tr>
<tr><td>Proportion of patients achieving remission</td><td>Proportion of patients who have achieved remission</td></tr>
</table>

Item	Definition
Sustained remission	Meeting all of the following conditions: • Achieving remission at Weeks 26 and 52 • Not taking GCs for treatment of ANCA-associated vasculitis for the last 4 weeks • Not experiencing relapse between Weeks 26 and 52
Proportion of patients achieving sustained remission	Proportion of patients who have achieved sustained remission
Relapse	After achieved remission, on BVAS, at least 1 major item, at least 3 non-major items, or at least 1 non-major item at 2 consecutive scheduled visits are met.
EQ-5D-5L VAS	General scale of healthcare-related QOL used to assess QOL overall comprising 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Patients are asked to answer questions related to any of the 5 dimensions, and from their answers, the score is calculated using a conversion table (ranging from 0 to 100. A higher score indicates better QOL).
GTI	Assessment scale of toxicity associated with GCs comprising 13 items (BMI, glucose tolerance, blood pressure, lipids, bone density, steroid myopathy, skin toxicity, neuropsychiatric toxicity, infection, endocrine, gastrointestinal, musculoskeletal, and ocular symptoms). These items are assessed by comparing the baseline state, and the score is calculated using relative weighing factors specified for each item.
GTI-CWS	Score representing cumulative toxicity over time
GTI-AIS	Score representing improvement and worsening of toxicity over time
SF-36	Non-disease specific scale of healthcare-related QOL comprising 36 items. Patients are asked to answer questions related to any of these items, and the score is calculated from the answers.
SF-36 MCS	Summary score of mental QOL-related questions in SF-36 (ranging from 0 to 100. A higher score indicates a better mental condition.)
SF-36 PCS	Summary score of physical QOL-related questions in SF-36 (ranging from 0 to 100. A higher score indicates a better physical condition.)
VDI	Scale intended to assess organ damage that occurred since the onset of vasculitis, comprising 64 items in 11 organs (musculoskeletal; skin/mucous membranes; ocular; ear, nose, and throat; pulmonary; cardiovascular; peripheral vascular disease; gastrointestinal; renal; neuropsychiatric; and other). The total score is obtained by checking the patient's symptoms against 64 items and adding the number of applicable items for each organ.

Review Report (2)

August 26, 2021

Product Submitted for Approval

Brand Name	Tavneos Capsules 10 mg
Non-proprietary Name	Avacopan
Applicant	Kissei Pharmaceutical Co., Ltd.
Date of Application	February 26, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008, dated December 25, 2008).

1.1 Efficacy, clinical positioning, indications, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the efficacy, clinical positioning, indications, and dosage and administration of avacopan presented in the Review Report (1) and also raised the comments described below.

- In the treatment of MPA and GPA in Japan, GC is less likely to be discontinued before Week 20. However, the study treatments specified in Study CL010_168 were not largely different from routine clinical practice in Japan, given that the use of GC and immunosuppressive drugs is allowed at relapse. The results of Study CL010_168 indicates that the efficacy of avacopan is expected in the treatment of Japanese patients with MPA or GPA.
- Information about the efficacy and safety of avacopan monotherapy (including treatment with transient concomitant use of GC) covering remission induction should be collected after the market launch in view of the following points: Study CL010_168 did not evaluate the efficacy of avacopan used for remission induction in patients not receiving immunosuppressive drugs concomitantly, and 75.3% (125 of 166) of patients in the avacopan group continued receiving GC concomitantly from the prior treatment to Week 4; and many of the elderly and other patients who cannot use immunosuppressive drugs receive GC alone in the treatment of MPA and GPA in Japan. Furthermore, the proportion of patients achieving sustained remission at Week 52 in the avacopan group tended to be lower in the population of patients receiving CY concomitantly and achieving remission induction than in the population of patients receiving RTX concomitantly and achieving remission induction. Information about the effects of concomitant drugs on the efficacy of avacopan, therefore, should be collected after the market launch.

- Avacopan is expected to be positioned as a therapeutic drug similar to GC. However, high dose GC may be more appropriate for remission induction than avacopan in some patients, taking into account that the use of avacopan is limited in patients with the most severe conditions such as severe renal impairment requiring dialysis at the onset of MPA and GPA or serious alveolar haemorrhage.

1.2 Safety and risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the safety and post-marketing investigations of avacopan in the Review Report (1) and raised comments concerning the efficacy and safety of avacopan monotherapy as well as effects of concomitant drugs on the efficacy of avacopan, presented in the previous sections, as information or issues to be collected continuously after the market launch so that the usage of avacopan can be discussed at relevant academic societies.

In view of the discussions presented in Section "7.R.7 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for avacopan should include the safety and efficacy specifications presented in Table 58; and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Table 59. PMDA requested that the applicant investigate the issues above during post-marketing surveillance.

Table 58. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hepatic dysfunction • Serious infections	• Not applicable	• Not applicable
Efficacy specification		
• Not applicable		

Table 59. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey	• Not applicable	• Disseminate data gathered during early post-marketing phase vigilance

The applicant's explanation:

As presented in Table 60, the applicant will conduct a specified use-results survey in patients with MPA or GPA, with the target sample size of 250 and observation period of 2 years to evaluate the long-term safety and efficacy of avacopan in clinical use, using the safety specifications of hepatic dysfunction and serious infections. In addition, the applicant will collect information from ANCA negative patients, who have not been included in the clinical studies, patients who start avacopan without receiving immunosuppressive drugs concomitantly, and patients receiving avacopan monotherapy (including treatment with transient concomitant use of GC), in whom evaluation was limited in the clinical studies, to at least a certain extent; and further evaluate the safety and efficacy including the effects of concomitant drugs.

Table 60. Outline of specified use-results survey (draft)

Objective	To collect and evaluate information about the long-term safety and efficacy in clinical use
Survey method	Survey of consecutive patients
Patient population	Patients with MPA or GPA
Observation period	2 years
Planned sample size	250 patients (227 included in safety analysis) Including ≥50 patients who have achieved remission induction
Main survey items	• Safety specifications: Hepatic dysfunction and serious infections • Patient characteristics (body weight, age, disease activity, duration of disease, medical history, complications, etc.) • Use status of avacopan • Prior treatment for primary disease • Concomitant drugs and therapies • Laboratory tests • Adverse events • Efficacy evaluation

PMDA accepted these measures and considers that the applicant should disseminate the collected information to healthcare professionals in an appropriate and prompt manner.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following approval condition. Because the product is designated as an orphan drug, the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indications

Microscopic polyangiitis and granulomatosis with polyangiitis

Dosage and Administration

The usual adult dosage is 30 mg of avacopan orally administered twice daily after breakfast and dinner.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

AIS	Aggregate improvement score
ALT	Alanine aminotransferase
Ames test	Bacterial reverse mutation test
ANCA	Anti-neutrophil cytoplasmic antibody
AST	Aspartate aminotransferase
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area under the plasma concentration-time curve from time zero to 't' (where t = the final time of detection)
AUC_{tau}	Area under the plasma concentration-time curve over a dosing interval
Avacopan	Avacopan
AZA	Azathioprine
BCRP	Breast cancer resistance protein
BVAS	Birmingham vasculitis activity score
C3a	Complement 3a
C3aR	Complement 3a receptor
C5a	Complement 5a
C5aR	Complement 5a receptor
C5b-9	Complement 5b, 6, 7, 8, and 9 complex
Caco-2	Human colorectal adenocarcinoma cell line
CL	Total clearance
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CWS	Cumulative worsening score
CY	Cyclophosphamide
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
eGFR	Estimated glomerular filtration rate
GC	Glucocorticoid
GPA	Granulomatosis with polyangiitis
GTI	Glucocorticoid toxicity index
HEK293	Human embryonic kidney 293 cell
hERG	Human *ether-a-go-go-related gene*
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
ICH Q1E guideline	Guideline on Evaluation for Stability Data (PFSB/ELD Notification No. 0603004, dated June 3, 2003)
Ig	Immunoglobulin
ITT	Intent to treat
Japanese Clinical Practice Guideline	Guidelines for the Management of ANCA-associated Vasculitis 2017 edited by Research Group for Intractable Vasculitis, Research Group for Intractable Kidney Diseases, and Research Group for Diffuse Lung Diseases, the Policy Research Project for Intractable Diseases (Intractable Diseases Policy Research Project) funded by Health and Labour and Welfare Sciences Research Grants
KLH	Keyhole limpet hemocyanin
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LOCF	Last observation carried forward
MATE	Multidrug and toxin extrusion protein
MCP	Monocyte chemoattractant protein

MCS	Mental component summary
MDCK	Madin-Darby canine kidney cell
MDR1	Multi drug resistance associated protein
MF	Master file
MMRM	Mixed model for repeated measures
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
mRNA	Messenger ribonucleic acid
NMR	Nuclear magnetic resonance spectroscopy
NRI	Non-responder imputation
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OC	Observed cases
OCT	Organic cation transporter
PBS	Phosphate buffered saline
PCS	Physical component summary
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PR3	Protease 3
PTP	Press through packaging
QOL	Quality of life
QTc	Corrected QT interval
RH	Relative humidity
RTX	Rituximab (Genetical Recombination)
SD	Sprague dawley
SF-36	Medical outcome short form 36-item health survey
$t_{1/2}$	Elimination half-life
Tavneos	Tavneos Capsules 10 mg
t_{max}	Time to reach maximum concentration
UACR	Urinary albumin-creatinine ratio
VAS	Visual analog scale
VDI	Vasculitis damage index
Vd_{ss}	Volume of distribution at steady state
V_z/F	Apparent volume of distribution of the drug